MANUAL OF NUTRITIONAL THERAPEUTICS

Fifth Edition

MANUAL OF NUTRITIONAL THERAPEUTICS

Fifth Edition

David H. Alpers, M.D.
William B. Kountz Professor of Geriatrics in Medicine
Assistant Director, Center for Human Nutrition
Washington University School of Medicine
St. Louis, Missouri

William F. Stenson, M.D.
Professor of Medicine
Washington University School of Medicine
St. Louis, Missouri

Beth E. Taylor, R.D., C.N.S.D.
Nutrition Support Specialist, Surgical Intensive Care Unit
Barnes-Jewish Hospital
St. Louis, Missouri

Dennis M. Bier, M.D.
Professor of Pediatrics
Baylor College of Medicine
Director USDA/ARS Children's Nutrition Research Center
Houston, Texas

Wolters Kluwer Health | Lippincott Williams & Wilkins

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: *Charles W. Mitchell*
Managing Editor: *Sirkka E. Howes*
Project Manager: *Bridgett Dougherty*
Marketing Manager: *Angela Panetta*
Manufacturing Manager: *Kathleen Brown*
Design Coordinator: *Stephen Druding*
Production Services: *International Typesetting & Composition*

Fifth Edition © 2008
Fourth edition, © 2002

Lippincott Williams & Wilkins, a Wolters Kluwer business
530 Walnut Street
Philadelphia, PA 19106 USA
LWW.com

Printed in the United States

Library of Congress Cataloging-in-Publication Data

Manual of nutritional therapeutics / David H. Alpers . . . [et al.]. -- 5th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-0-7817-6841-2
ISBN-10: 0-7817-6841-1
1. Diet therapy--Handbooks, manuals, etc. 2. Nutrition--Handbooks, manuals, etc. I. Alpers, David H.
[DNLM: 1. Diet Therapy--Handbooks. 2. Nutrition Physiology--Handbooks. WB 39 A456m 2008]
RM217.2.A47 2008
615.8'54--dc22

2007041346

---

10 9 8 7 6 5 4 3 2 1

To our fathers, who taught us both respect for knowledge and concern for the individual.

PREFACE

MANUAL OF NUTRITIONAL THERAPEUTICS, 5TH EDITION

The information on nutritional topics that is useful for health care workers continues to increase at a steady pace. This manual was conceived as a source of information for physicians, nurses, dietitians, and other health professionals in various disciplines, and for students at all levels. The continued use of this manual has supported the need for such an information source, filtered by the authors to focus on the information we find useful for the practice of medicine and surgery. We assume that the health care worker has knowledge of the underlying diseases that might benefit from nutritional intervention. Thus, this edition of the *Manual of Nutritional Therapeutics,* like its predecessors, is not intended to be a textbook of nutrition. It should be used to obtain the information that is needed in managing the nutritional needs of adults, adolescents, and older children. We have tried to be practical and to provide explanations for the recommendations provided. In many cases, new systematic reviews of an increasing number of randomized, controlled clinical trials have provided a much more solid evidence base for these recommendations.

The chapters on individual nutrient components—Section II and Chapter 12 on diets—have retained their form subdivided by sections that deal with many different individual nutrients and/or diets. The original outline form has been modified for many of the other chapters to better fit the more narrative needs of those chapters. We have added a dietitian to this edition, Beth Taylor, consultant to the Center for Human Nutrition, Washington University School of Medicine, who had assisted in reviewing chapters from previous editions. As a result of this added expertise and viewpoint, the chapters in Section III (Therapeutic Nutrition) have been completely revised. The information is as current as possible given the lag time involved in publishing a book. But, nutrient preparations can change rapidly, or are replaced by other products, so the reader should always check the local availability of any given preparation. URLs for many web sites containing nutritional information are included, not only for convenience and to update information not included in the manual, but also to provide sources of information that the authors use and trust.

The authors are gratified by the reception the book has enjoyed, and hope that its readers, old and new, will derive as much benefit from it as we, the authors, have received in revising it. We are grateful to our colleagues at Lippincott Williams & Wilkins for editorial support and advice. Especially we thank our spouses and families for their support in allowing us the time needed to create the 5th edition of this book.

David H. Alpers, M.D.
William F. Stenson, M.D.
Beth E. Taylor, R.D., C.N.S.D.
Dennis M. Bier, M.D.

CONTENTS

I: GENERAL CONCEPTS OF NUTRITION

II: INDIVIDUAL NUTRIENT COMPONENTS

III: THERAPEUTIC NUTRITION

IV: NUTRITIONAL MANAGEMENT OF SPECIFIC DISEASES

APPENDIXES

General Concepts of Nutrition

1

APPROACH TO NUTRIENT DEFICIENCY

1

The medical use of nutrients to rectify states of deficiency depends on an appropriate knowledge base. This chapter outlines some general areas that involve both macronutrients (energy, protein, lipids) and micronutrients (vitamins, minerals). The subjects covered include (a) definitions of the nutrient requirement, (b) the concept of dietary goals and guidelines, along with food composition and preparation, (c) the identification of individual nutrient deficiency, (d) the medical use of nutrition support, and (e) the interaction of other medical therapies (drugs) with components of nutritional therapy. Subsequent chapters expand on many of these topics in more detail, and the reader is referred to these chapters when appropriate. This discussion is not meant to include all possible variants on these themes but rather highlights some common examples.

DEFINITIONS OF NUTRIENT SUFFICIENCY

Recommended Dietary Allowance

The recommended dietary allowance (RDA) for many years was the most widely publicized of the definitions of nutrient sufficiency in the United States. It was based on available scientific knowledge and deliberation by experts, and was approved by the Food and Nutrition Board of the National Academy of Sciences Committee on Dietary Allowances. The RDA outlined the levels of intake of essential nutrients judged to be adequate to meet the known nutritional needs of practically all healthy persons. The RDA is currently defined as the average daily dietary nutrient level sufficient to meet the requirement of nearly all (97% to 98%) healthy individuals in a particular gender and life stage group, and so exceeded the requirements of most persons. It is important to remember that the RDA cannot be relied on for a precise estimate of the needs of patients with medical illness, particularly if malabsorption is present. The RDA was revised most recently in 1989. Values quite similar to the RDA have been developed for the basal requirements of the inhabitants of many other countries (1,2).

Nonetheless, these guidelines have been deemed insufficient for many reasons. New understanding has been acquired of nutrient requirements and of the role of food components in reducing the risk for chronic diseases (e.g., cancer, heart disease, osteoporosis) and preventing classic deficiency syndromes. RDAs were previously developed with only the latter goal in mind. Moreover, RDAs were formerly based on the assumption that all nutrients are derived from natural foods; currently, however, dietary tablets, fortified foods, and food supplements are important sources of some nutrients. Thus, the governments of the United States and Canada together have formulated the dietary reference intake (Appendix B).

Dietary Reference Intake

Dietary reference intake (DRI) is now a collective term that includes the estimated average requirement (EAR), RDA, adequate intake (AI), and tolerable upper intake level (UL). The DRI is newly developed and has replaced the periodically revised RDA. It is the undertaking of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences (www.nas.edu), in collaboration with Health Canada. It is being developed for 12 life stages, and 12 volumes have appeared thus far, six covering the nutrients themselves: calcium, vitamin D, magnesium, and phosphorus (3); the B vitamins niacin, biotin, and choline (4); antioxidant micronutrients, including vitamins C and E, selenium, and carotenoids (5); vitamins A and K, iron, zinc, and trace minerals (6); water, potassium, chloride, and sulfate (7); and energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (8). Other volumes cover guiding principles of nutrition labeling and fortification, applications in dietary planning, applications in dietary assessment, proposed definition of dietary fiber, proposed definition and plan for review of dietary antioxidants and related compounds, and risk assessment method for establishing upper intake levels for nutrients.

The EAR is the daily intake value estimated to meet the requirements of 50% of persons in a normal life stage and gender group. It is used to set the RDA and plan recommendations for intake in various groups. The RDA is the intake level sufficient to meet the daily requirements of most people in a specific life stage and gender group and is set at two standard deviations above the EAR. This estimate also includes a coefficient of variation of 10% if the data do not permit the calculation of standard deviations. If not enough data are available to calculate an EAR, AI is used. AI is based on approximations of average nutrient intake by an age- or gender-defined subgroup. The tolerable UL is the maximum amount of a daily nutrient intake that is unlikely to pose a health threat for persons within an age and gender subgroup. This term was deemed important because so many nutrients are now ingested from supplements at levels far exceeding those possible in the diet. Compromises within the DRI recommendation must be made, both because these values are often not precisely known and because the new recommendation may be used to prevent onset of disease (e.g., fracture risk) rather than clinical deficiency (rickets). Table 1-1 outlines some of the suggested population-based reference intakes that have been recommended to prevent cancer and heart disease, and those levels recommended by the World Health Organization and the Commission of the European Community for young, healthy adults.

Daily Reference Values

The RDAs were standards set by the U.S. Food and Drug Administration (FDA) in 1973 for purposes of food labeling. *Daily value* and *percent daily value* are the new reference terms on the nutrition label. The term *daily value* encompasses two sets of reference values: daily reference values (DRVs) and the old reference daily intakes (RDIs), now called *dietary reference intakes* (DRI). DRVs are provided for total and saturated fat, cholesterol, total carbohydrates, dietary fiber, sodium, potassium, and protein. They are based on current nutritional recommendations for adults and children aged 4 or older. RDIs are the same as the current U.S. RDAs for 19 vitamins and minerals. The terms DRV and RDI do not appear on the nutrition label. What do appear are daily values, reflecting DRVs and RDIs for a 2,000-cal reference diet (Table 1-2). (See Appendix B for further details.)

TABLE 1-1. Population Reference Intakes/Guidelines of Dietary Constituents for Prevention of Chronic Diseases in Adults, Ages 20 to 50

	WCRF[a]	NAS[b]	WHO[c]	AHA[d]	PRI/goal[e]
Constituent macronutrients					
CHO (% kcal)	55–75	>55	55–75	55–60	45–55
Starch (%)	50–70	—	50–70	55–60	—
Sugar, nonmilk (%)	<10	—	<10	Low	10
Nonsoluble fiber (g/day)	20–35	—	16–24	20–25	39
Fats (% kcal)	15–30	<30	15–30	≤30	20–30
Polyunsaturated	2–10	≤10	3–7	≤10	2.5
Monosaturated	3–10	—	—	≤15	—
Saturated	0–10	<10	<10	8–10	10
Cholesterol (mg/day)	100–130	<300	<300	<300	—
Protein (% kcal)	9–12	—	10–15	—	—
Vegetable	6–12	—	—	—	—
Animal	0–3	—	—	—	—
Alcohol (% kcal)	<2	<2 oz	—	<2 oz	—
Micronutrients					
Carotenoids (mg/day)	9–18	—	—	—	—
Vitamin C (mg/day)	175–400	—	30	—	40–45
Folate (μg/day)	250–450	—	200	—	200
Vitamin D (μg/day)	0 (sun)–10	—	2.5	—	0–15
Vitamin E (mg/day)	4–7	—	—	—	<4
Calcium (mg/day)	500–750	—	400–500	—	700
Selenium (μg/day)	75–125	—	30–40	—	55
Iodine (μg/day)	125–150	—	120–150	—	130
Iron (mg/day)	15–25	—	16	—	9–21
Potassium (g/day)	1.6–3.2	—	—	—	3.1
Sodium (g/day)	<4	<4	<4	<6	0.58–3.5
Zinc (mg/day)	11–13	—	7.1–9.5	—	7.1–9.5

[a] WCRF, World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, and the Prevention of Cancer: A Global Perspective, 1997*. Provides estimates of probable range of dietary constituents consumed as a result of following recommendations of the report.
[b] NAS, National Academy of Sciences Food and Nutrition Board, 1989 recommendations for individuals.
[c] WHO, World Health Organization, 1990.
[d] AHA, American Heart Association, dietary guidelines for healthy American adults. Krauss RM, et al. *Circulation* 1996;94:1795.
[e] PRI/goal, population reference intake ranges (female–male) for young European adults (ages 19 to 50), Commission of the European Community. Report of the Scientific Commission for Food (31st Series): Nutrient and energy intakes, 1993, or ultimate European goals (James WPT. Healthy nutrition, European series 24. Copenhagen: WHO Regional Office for Europe: 1988).

Reference Weights

Reference weights and heights are used when the average values provided by age and life stage categories are not appropriate and more specific information is needed. Because overweight and obesity are so prevalent, the older reference values based on the Third National Health and Nutrition Examination Survey (NHANES III) in the United States have been updated (8). Table 1-3 shows the old and new body mass index (BMI) calculated from available reference data for children and young adults.

Estimated Adequate Intake for Healthy Persons

For some nutrients (Na, Cl, K), the daily requirements appear to be much lower than the content in an average U.S. diet. Thus, the concept of RDA is replaced by that of an adequate intake (Table 1-4). For other nutrients also the information is insufficient for EAR to be calculated and actual recommendations to be made. These nutrients include vitamin K, biotin, calcium, chromium, fluoride, and manganese. Adequate intake is also used to

TABLE 1-2. Daily Values for Adults and Children Age 4 or Older

Food component	Daily value[a]	Percentage of total caloric intake
Total fat	65 g[b]	30
Saturated fat	20 g[b]	10
Cholesterol	300 mg	—
Sodium	2,400 mg	—
Potassium	3,500 mg	—
Chloride	3,400 mg	—
Total carbohydrate	300 g[b]	60
Dietary fiber	25 g[c]	—
Protein	50 g[b]	10
Vitamin A	5,000 IU	—
Vitamin C	60 mg	—
Calcium	1 g	—
Iron	18 mg	—
Vitamin D	400 IU	—
Vitamin E	30 IU	—
Vitamin K	80 μg	—
Thiamine	1.5 mg	—
Riboflavin	1.7 mg	—
Niacin	20 mg	—
Vitamin B_6	2.0 mg	—
Folate	0.4 mg	—
Vitamin B_{12}	6.0 mg	—
Biotin	0.3 mg	—
Pantothenic acid	10 mg	—
Phosphorus	1 g	—
Chromium	120 μg	—
Iodine	150 μg	—
Magnesium	400 mg	—
Manganese	2 mg	—
Selenium	70 μg	—
Zinc	15 mg	—
Copper	2.0 mg	—

[a] Based on daily reference values and reference daily intakes.
[b] Daily value based on a 2,000-cal reference diet.
[c] Daily value based on 12.5 g/1,000 cal.
From FDA/CFSAN www.cfsan.fda.gov

TABLE 1-3. New Reference Body Mass Index for Children and Adults in the United States

Male (y)	Median BMI (kg/m^2)	Female (y)	Median BMI (kg/m^2)
4–8	15.3	4–8	15.3
9–13	17.2	9–13	17.4
14–18	20.5	14–18	20.4
19–30[a]	22.5	19–30	21.5

[a] Because no evidence indicates that weights should change with aging, provided that activity is maintained, the reference weights of this group are applicable to all adults.
Data are taken from male and female median body mass index (BMI) from the Centers for Disease Control and Prevention/National Center for Health Statistics growth charts, adapted from *Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification*, Washington, DC: National Academies Press, 2003:75.

TABLE 1-4. Estimated Adequate Intakes (AI) for Healthy Persons for Sodium, Chloride, and Potassium

Age	Weight (kg)	Weight (lb)	Sodium (g/day)	Chloride (g/day)	Potassium (g/day)
Up to 6 months	4.5	10	0.12	0.18	0.4
7–12 months	8.9	20	0.37	0.57	0.7
1–3 years			1.0	1.5	3.0
4–8 years			1.2	1.9	3.8
9–13 years			1.5400	2.3	4.5
14–18 years			1.5	2.3	4.7
18–50 years	70	154	1.5	2.3	4.7
51–70 years			1.3	2.0	4.7
>70 years			1.3	1.8	4.7

Data from the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, Washington, DC: National Academies Press: (i) *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate,* 2005; (ii) *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty acids, Cholesterol, Protein, and Amino Acids,* 2005.

TABLE 1-5. Vitamin and Mineral Toxicity

Nutrient	Symptoms of toxicity	Minimal intake
Vitamin B_1	Headache, irritability, insomnia	?, probably >50 mg/d
	Fast heart rate, weakness, occasional severe allergic reaction (anaphylaxis)	
Vitamin B_2	Yellow-orange color of urine	Safe up to 10 mg/day
Vitamin B_6	Peripheral sensory neuropathy (numbness)	2–6 g/day
Niacin	Flushing, burning of hands and face	>1 g/day
	Nausea, vomiting, diarrhea, abnormal heart rhythm, exacerbation of gout, rash, itching, glucose intolerance, abnormal liver blood chemistries	>3 g/day
Folate	Convulsions if on phenytoin (Dilantin)	>40 mg
	In pregnancy can compete with Zn and Fe for absorption, rare allergy (rash, itching, fever, wheezing)	
Vitamin B_{12}	None	
Vitamin C	False-positive sugar in urine, false low sugar in blood, false-negative test for blood in stool, diarrhea	2–6 g/day
	Dental erosions, increased oxalate, kidney stones, interference with anticoagulation from warfarin (Coumadin)	4–9 g/day
Biotin	None	
Pantothenic acid	Diarrhea	10–20 mg/day
Vitamin A	Nausea, vomiting, skin desquamation	50,000–100,000 IU/day
	Fatigue, hair loss, bone pain, anorexia, irritability	Chronic ingestion
	Vomiting, bulging fontanelles, growth failure, optic atrophy, sixth nerve palsy	>4,000 IU/kg/day
	Newborn microcephaly, dilated ventricles	15,000 IU/day if taken between 14 and 40 days of gestation

(*continued*)

TABLE 1-5. Vitamin and Mineral Toxicity (*Continued*)

Nutrient	Symptoms of toxicity	Minimal intake
Vitamin D	Increased calcium in blood and urine, nausea, anorexia, itching, increased urine, thirst, abdominal pain, constipation, bone pain, kidney stones, weight loss, pancreatitis, hypertension, abnormal heart rhythm	>1,000 IU/day in nongrowing adults, depends on Ca intake
Vitamin E	? Any symptoms, occasional weakness, fatigue, hypertension, nausea, increased effect of warfarin (Coumadin)	800–900 IU/day
Vitamin K	Jaundice in newborn	>10 mg/day to infant or pregnant mother
Na	Edema	If retaining sodium (heart, liver disease)
	Confusion	If very excessive intake
K	Weakness, confusion, abnormal heart rhythm	If renal function low and 50–100 mEq/day in supplements, drugs
Ca	Nausea, vomiting, weakness, constipation, dry mouth, increased urine, abnormal heart rhythm, kidney stones	Especially if vitamin D >400 IU/day and supplement >1–2 g/day
Mg	Nausea, vomiting, hypertension, drowsiness	If renal function low and Mg given IV
P	Symptoms not related to low calcium	Only in renal failure
Fe	Nausea, vomiting, diarrhea, abdominal pain	>20 mg/kg/day
Zn	Copper deficiency (anemia), ? decreased immune function, nausea, vomiting, rash, dehydration, gastric ulceration	>450 mg/day
Cu	Nausea, vomiting, diarrhea, cramps	>15 mg/day
I	Decreased thyroid function	>2,000 μg/day
F	Spine and muscle pain, weakness	20–80 mg/day
Mn	None	Up to 10 mg/day
Cr	None recognized	
Se	Hair and nail loss, skin lesions, tooth decay	>5 mg/day
	Nausea, vomiting, fatigue, hair loss, diarrhea, irritability	>20 mg/day

estimate the needs of children for most nutrients (see Appendix B for details). Many vitamins and minerals have been reported to cause toxicity when taken in excess (Table 1-5). This concern is the major reason for the new UL recommendations (Appendix B). Most cases of nutrient toxicity are associated with supplementation, not food intake. Estimated toxic levels range from as low as five times (selenium) to 25 to 50 times (folate, vitamins C and E) the recommended dietary intake. The best-documented toxicities from nutrients involve vitamins A, B_3 (niacin), B_6, and D, iron, and selenium. Besides direct toxicity, significant problems can arise when high doses of some nutrients interact with other nutrients. For example, high doses of calcium can interfere with iron absorption, high doses of zinc can impair copper absorption, and high doses of vitamin E can impair vitamin K action.

DIETARY GUIDELINES AND PROPERTIES OF AVAILABLE FOODS FOR HEALTHY PERSONS

Guidelines

Based in part on the nutritional assessments listed above, guidelines have been developed for average normal persons and to prevent chronic diseases (Table 1-1 and Table 1-6;

TABLE 1-6. *Dietary Guidelines for Americans, 2005*: Key Recommendations

Category	Recommendation
Adequate nutrients	Consume a variety of nutrient-dense foods and beverages with basic food groups while choosing foods that limit intake of saturated and trans fats, cholesterol, added sugars, salt, and alcohol
	Meet recommended intakes within energy needs by adopting a balanced eating pattern, e.g., the USDA Food Guide (pyramid)
Weight management	Maintain weight in a healthy range
	To prevent gradual weight gain over time, make small decreases in food and beverage calories and increase physical activity
Physical activity	Engage in regular physical activity and reduce sedentary activities
	To reduce the risk of chronic disease in adulthood engage in at least 30 minutes of moderate-intensity activity above the usual on most days of the week
	For most people, greater health benefits can be obtained by physical activity of more vigorous intensity or longer duration
	Include cardiovascular conditioning, stretching exercises for flexibility, and resistance exercises or calisthenics for muscle strength
Food groups encouraged	Consume within energy needs 2 cups of fruit and 2½ cups of vegetables for a reference 2,000-kcal intake
	Choose from all 5 vegetable groups (dark green, orange, legumes, starchy vegetables, others) several times a week
	Consume 3 or more ounces of whole grain products/day; at least half of the grains should come from whole grains
	Consume 3 cups/day of fat-free or low fat milk or milk products
Fats	Consume 10% of calories from saturated fatty acids and <300 mg of cholesterol; keep *trans* fatty acid intake as low as possible
	Keep total fat intake between 20% and 35% of calories, with most coming from sources of polyunsaturated or monounsaturated fatty acids, such as fish, nuts, and vegetable oils
	Choose lean, low-fat, or fat-free products
Carbohydrates	Choose fiber-rich fruits, vegetables, and whole grains often
	Choose and prepare foods with little added sugars or caloric sweetener
Sodium and potassium	Consume <2.3 g (~1 tsp of salt) of sodium/day
	Consume and prepare foods with little salt, but use potassium-rich foods, such as fruits and vegetables
Alcoholic beverages	Consume sensibly and in moderation, up to 1 drink/day for women and 2 drinks/day for men
	Alcohol should not be consumed by those who cannot restrict intake, by pregnant or lactating women, or those who might become pregnant, or by those engaged in activities that require attention or coordination, such as driving or operating machinery
Food safety	To avoid microbial foodborne illness, clean hands and food contact surfaces, fruits, and vegetables, but do not rinse meat or poultry.
	Cook foods at a safe temperature, chill perishable food promptly, and avoid raw milk, eggs, raw or undercooked meat and poultry

Modified from *Dietary Guidelines for Americans,* 2005 (www.health.gov/dietaryguidelines/dga2005).

see also Chapter 2). These guidelines generally advise that a normal weight be achieved and maintained. In addition, total fat intake should be limited to about 30% of calories, cholesterol intake decreased, intake of complex carbohydrates and fiber increased, excess intake of salt avoided, and alcohol ingested only in moderation.

The *U.S. Dietary Guidelines for Americans*, 2005 (9) emerged from a scientific analysis conducted by the Dietary Guidelines Advisory Committee (DGAC) appointed by the U.S. Department of Health and Human Services and the U.S. Department of Agriculture (USDA) (www.health.govdietary guidelines/dga2005/report/). An example of a recommended eating pattern can be found in the USDA Food Guide (www.usda.gov/cnpp/pyramid.html). The recommendations in the Dietary Guidelines are for Americans over age 2, and are

TABLE 1-7. Selected Food Composition Guides

Authors	Title	Year, edition	Publisher
Pennington JAT, Spenger J	*Bowes & Church, Food Values of Portions Commonly Used*	2004, 18th	Lippincott Williams & Wilkins
	Diet AnalysisPlus Win/Mac	2006	Wadsworth/Thomson
McNance and Widdowson	*The Composition of Foods*	2002, 6th	Royal Society of Chemistry
Senser F, Scherz H, Souci SW,	*Food Composition and Nutrition Tables*	2000, 6th	CRC Press
USDA, Human Nutrition Information Service	*Nutritive Value of Foods (Home & Garden Bull No.72 (HG-72 in pdf)*	October 2002	U.S. Government Printing Office www.ars.usda.gov
USDA	*USDA National Nutrient Database for Standard Reference*	2005, release 8	www.ars.usda.gov/services/
American Dietetic Association	*Manual of Clinical Dietetics*	2000, 6th	American Dietetic Association
Nelson J, Moxness KE, Gastineau CF, Jenson MD	*Mayo Clinic Diet Manual*	1994, 7th	Mosby–Year Book
Duyff RL	*ADA Complete Food and Nutrition Guide*	2002, 2nd	American Dietetic Association
Hands ES	*Food Finder*	1995, 3rd	ESHA Research, Inc.

written to be flexible enough to include food preferences for different racial, ethnic, and vegetarian groups. The key recommendations (Table 1-6) have been limited to those that reflect generally agreed upon scientific evidence. Thus, they are not quite as specific as earlier versions of the Dietary Guidelines. These recommendations are made less specific as many of the common ideas in nutrition have been shown to lack strong evidence in their support. Nonetheless, these guidelines are the best current wisdom of the nutritional leadership in the United States.

Food Composition

Practical application of the dietary guidelines is based on knowledge of food composition. Many guides are available, some of which are listed in Table 1-7. These sources differ in the type of information offered. All cover most vitamins and minerals and macronutrients (water, proteins, lipids, and carbohydrate, including total or crude fiber). McNance and Widdowson (Table 1-7) also cover total dietary fiber, oligosaccharides, selenium, manganese, iodine, nonstarch polysaccharides, and fatty acids for every food. All these sources list the nutrient contents of foods by different food groups (fats and oils, meats, nuts, legumes). Each book can be valuable depending on the clinical need.

The USDA produces a regularly updated Home & Garden bulletin of the *Nutritive Value of Foods*. More details can be found in the USDA *National Database for Standard Reference-release 18*, available on the internet at www.ars.usda.gov/services/. Table 1-8 lists some general sources of information on nutrition available on the internet.

Food Processing

The data included in the *Nutritive Value of Foods* document the differences in the composition of raw and processed foods, but the enormous variety of changes that occur during processing cannot be covered. Foods are affected by the type of processing (freezing, canning, concentration), the length of the processing procedure, during which nutrients can be lost or inactivated, and the effects of storage. The factors most likely to render nutrients unstable in food are heating, oxidation, and pH (Table 1-9).

TABLE 1-8. Nutrition-related Internet Sites

Organization	Internet address
American Council on Science and Health (consumer education consortium)	*www.acsh.org/nutrition/index.html*
American Dietetic Association	*www.eatright.org*
American Heart Association	*www.americanheart.org*
American Society for Nutrition	*www.asnutrition.org*
American Society for Parenteral and Enteral Nutrition	*www.clinnutr.org*
Council for Responsible Nutrition (trade organization for supplement industry)	*www.crnusa.org*
Department of Agriculture/Agriculture Research Service	*www.ars.usda.gov*
Dietary Guidelines for Americans, 2005	*www.health.gov/dietaryguidelines/dga2005/*
Food and Drug Administration	*www.fda.gov*
Food and Nutrition Information Center/Dietary Reference Intakes	*www.nal.usda.gov/fnic/text/000105.html*
FDA, Center for Food Safety and Applied Nutrition	*www.cfsan.fda.gov*
FDA, *Report Adverse Effects of Supplements*	*www.fda.gov/medwatch/*
Healthcare professionals	*report/hcp.htm*
Consumers	*report/consumer/consumer.htm*
International Food Information Council	*ificinfo.health.org*
National Center for Complementary and Alternative Medicine	*nccam.nih.gov*
National Health Information Center	*nhic-nt.health.org*
National Products Alert Database, University of Illinois	*pcog8.pmmp.uic.edu/mcp/nap1.html*
Office of Dietary Supplements	*dietary-supplements.info.nih.gov*
Office of Disease Prevention & Health Promotion	*odphp.osophs.dhhs.gov*
USDA, Dietary Guidelines Advisory Commission	*www.usda.gov/dgac*
United States Pharmacopeia	*www.usp.org*
World Health Organization/Food & Agriculture Organization	*www.fao.org*

Most processed foods are usually less stable than dry foods because of a lesser degree of oxidation and the possibility of microbial contamination. Fresh produce must be kept moist to prevent wilting and loss of nutrients through cell damage. In modern practice, the characteristics of a controlled environment maintained to retard ripening (as for apples, pears, tomatoes) can play a major role in nutrient stability. The percentage of nutrients lost can be significant, and also varies for enriched versus unenriched foods. Examples are given in Table 1-10.

Other specific examples of the effects of food processing are provided in Chapters 6 and 7 in the sections on individual vitamins and minerals. For the most part, water-soluble vitamins and minerals are lost when foods are boiled and are better preserved when foods are broiled, sautéed, or steamed.

Food Supplements, Fortifiers, and Additives

A particular nutrient can be added to the diet of a population in several ways. These include (a) providing supplements containing the nutrient, (b) fortifying food samples with the nutrient, and (c) increasing the intake of foods rich in the nutrient. The benefit of supplements is that only appropriate groups are targeted. The consumption of table foods is more natural and conducive to a good diet, but if the nutrient is needed in doses close to or exceeding the upper limit of the DRI (e.g., folic acid to prevent neural tube defects), diet alone may be inadequate. The advantage of fortification is that the nutrient reaches many more people. Although supplements, fortifiers, and additives are defined separately, it is sometimes difficult to distinguish between them, as all are added to foods (Table 1-11). In fact, the USDA brochure on food additives (10) categorizes food additives as outlined in Table 1-11 and defines them broadly

TABLE 1-9. Factors Rendering Nutrients Unstable (U) in Foods or Having Little Effect (S)

Nutrients	Heat	Oxygen or air	Light	pH			Moisture[a]
				Acid	Neutral	Alkaline	
Vitamins							
Vitamin A or carotenes	U	U	U	U	S	S	U
Ascorbate (C)	U	U	U	S	U	U	U
Biotin	U	S	S	S	S	S	—
Choline	S	U	S	S	S	S	—
Cobalamin (B_{12})	S	U	U	S	S	S	—
Vitamin D	U	U	U	S	S	U	U
Folic acid	U	U	U	U	U	S	—
Inositol	U	S	S	S	S	S	—
Vitamin K	S	S	U	U	S	U	—
Niacin	S	S	S	S	S	S	—
Pantothenate	U	S	S	S	S	U	—
Pyridoxine (B_6)	U	S	U	S	S	S	—
Riboflavin	U	S	U	S	S	U	U
Thiamine	U	U	S	S	U	U	U
Tocopherols (E)	U	U	U	S	S	S	U
Amino acids							
Isoleucine	S	S	S	S	S	S	—
Leucine	S	S	S	S	S	S	—
Lysine	U	S	S	S	S	S	—
Methionine	S	S	S	S	S	S	—
Phenylalanine	S	S	S	S	S	S	—
Threonine	U	S	S	U	S	U	—
Tryptophan	S	S	U	U	S	S	—
Valine	S	S	S	S	S	S	—
Fatty acids polyunsaturated	S[b]	U	U	S	S	U	

[a] Moist processed foods are always less stable than dry because of greater risk of oxidation, effects of heat, and possibilities for microbial growth. In fresh produce, however, adequate moisture to prevent wilting is important in nutrient stability.
[b] If not excessive, such as when dripped on hot coals.
Modified from Harris RS, Karmas E. *Nutritional Evaluation of Food Processing,* 2nd ed. Westport, CT: AVI, 1975.

as "any substance the intended use of which results or may reasonably be expected to result—directly or indirectly—in its becoming a component or otherwise affecting the characteristics of any food." By this definition, a nutrient fortifier is considered an additive. However, each category is regulated differently and should be considered separately.

Food/Nutrient Supplements

The FDA first regulated supplements as foods "for special dietary use" (1938), and vitamins, minerals, and other dietary substances were included. In 1994, the Dietary Supplement Health and Education Act (DSHEA) became law and provided for some regulation of supplements, while prohibiting their regulation as drugs or food additives. A dietary supplement was defined as a product intended to supplement the diet that contains a vitamin, mineral, herb, amino acid, a substance meant to increase the total dietary intake, or any metabolites, constituents, or combinations of the above. Like conventional foods, they are not subject to premarket approval by the FDA and are exempt from food additive regulations. In other words, clinical studies are not required to demonstrate their efficacy, safety, or possible interactions. Safety issues are handled by

TABLE 1-10. Retention of Nutrients in Cooked Vegetables[a]

	Ascorbic acid (%)	Thiamine (%)	Riboflavin (%)	Niacin (%)	Vitamin B_6 (%)	Folacin (%)	Vitamin A (%)
Potatoes							
Prepared from raw							
Baked in skin	80	85	95	95	95	90	—
Boiled in skin	75	80	95	95	95	90	—
Boiled without skin	75	80	95	95	95	75	—
Fried	80	80	95	95	95	75	—
Hashed-brown[b]	25	40	85	80	—	65	—
Mashed	75	80	95	95	95	75	—
Scalloped and au gratin	80	80	95	95	95	75	—
Prepared from frozen							
French fried, heated	50	75	95	95	95	75	—
Baked, stuffed, heated	80	85	95	95	95	80	—
Hashed-brown	80	80	95	95	95	80	—
Other vegetables[c]							
Prepared from raw, drained							
Greens, dark and leafy	60	85	95	90	90	65	95
Roots, bulbs, other vegetables of high starch and/or sugar content[d]	70	85	95	95	95	70	90
Other[e,f]	80	85	95	90	90	70	90
Prepared from frozen, drained							
Greens, dark and leafy[c]	60	90	95	90	90	55	95
Roots, bulbs, other vegetables of high starch and/or sugar content[d]	70	90	95	95	95	70	90
Other[e,f]	80	90	95	90	90	70	90

[a] Percent true retention = nutrient content per gram of cooked food × grams of food after cooking/nutrient content per gram of raw food × grams of food before cooking × 100.
[b] Potatoes were pared, boiled, and held overnight before hash-browning.
[c] Cooked in small or moderate amount of water until tender.
[d] Vegetables such as beets, carrots, green peas, lima beans, onions, parsnips, rutabagas, salsify, turnips, summer and winter squash, and other immature seeds of the legume group.
[e] Vegetables such as asparagus, bean sprouts, broccoli, brussels sprouts, cabbage, cauliflower, eggplant, kohlrabi, okra, and sweet peppers.
[f] Because of limited data, values are based on nutrient retention data from other cooked plant products.
From *Composition of Foods—Raw, Processed, Prepared, 1990 Supplement*. Washington, DC: U.S. Department of Agriculture, Human Nutrition Information Service, Agriculture Handbook No. 8, 1990.

TABLE 1-11. Common Food Additives

Additive function	Nutrient type	Nutrient form	Foods likely used
Maintain nutrition	B vitamins	Thiamine, riboflavin, niacin, pyridoxine, folate, B_{12}	Cereals, pasta, flour, breads, corn meals, rice
	Fat-soluble vitamins	Vitamins A, D	Milk, milk products
	Minerals	FeEDTA, Zn oxide	Cereals, breads
		Ca citrate, carbonate	Juices, flour, cereal
		iodide	Salt, premature infant formulas
Enhance flavor, desirability	Sweeteners	Aspartame, saccharine, acesulfame K, sucralose, fructose, sugar alcohols, honey, cane juice, molasses	Beverages, yogurt, gelatin desserts, candies, chewing gum
	Fat substitute	Egg white/milk protein blend (Simplesse)	Frozen desserts
		Sucrose-triglyceride (Olestra)	Potato/corn chips
	Glutamates	MSG	Soups
	Stimulants	Caffeine	Soft drinks
Maintain palatability	Preservatives	Ascorbate, BHA, BHT, benzoates, Na nitrite, Na sulfite, propionic acid	Bread, cheese, meat, frozen/dried fruit, margarine, chips
Control pH	Acids/bases	$NaHCO_3$, citric acid, phosphoric acid, tartrazine	Soft drinks, cakes, chocolates, butter
Improve consistency	Bulk agents	Lecithin, mono- and di-glycerides, pectin, carrageenan, guar gum, alginates	Baked goods, salad dressing, ice cream, processed cheese

EDTA, ethylenediamine-tetraacetic acid; MSG, monosodium glutamate; BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene.

public warnings or recalls. Because the law separated supplements from additives, ingredients on the market before 1994 were considered safe. Supplements introduced after 1994 must be accompanied by evidence that the ingredient is "reasonably expected to be safe." Hundreds of supplements have not been approved (11); individual micronutrient supplements are discussed in Chapters 6 and 7, and other types of nutrient supplements in Chapters 8 and 12.

Nutrient Fortification

The addition of nutrients during processing to improve the nutritional qualities of foods is initiated legislatively and regulated by the FDA. The most common nutrients in the United States that are regulated as additives are thiamine, niacin, riboflavin, iron (all in fortified flour since the 1950s), and folate (in cereal grain products and ready-to-eat cereals since 1998) (Table 1-12). The increased intake of these nutrients, documented in the 1997 report *Nutrient Content of the U.S. Food Supply* (U.S. Department of Agriculture Center for Nutrition Policy and Promotion), is a consequence of the fortification of grains. The increased intake of vitamins A and C and carotene is the result of the consumption of larger amounts of fruits and vegetables. These changes reflect a shift from animal fat to vegetable oils and other plant products. Increased intake of calcium and phosphorus is largely a consequence of greater cheese consumption.

TABLE 1-12. FDA-recommended Fortification Levels Based on a Caloric Standard

Nutrient	U.S. RDA	Level of nutrients per 100 kcal
Vitamin A, IU	5,000	250
Vitamin C, mg	60	3
Thiamine, mg	1.5	0.075
Riboflavin, mg	1.7	0.085
Niacin, mg	20	1.0
Calcium, g	1	0.05
Iron, mg	18	0.9
Vitamin D, IU	400	20[a]
Vitamin E, IU	30	1.5
Vitamin B_6, mg	2.0	0.1
Folic acid, mg	0.4	0.02
Vitamin B_{12}, μg	6	0.3
Phosphorus, g	1	0.05
Iodine, μg	150	7.5[a]
Magnesium, mg	400	20
Zinc, mg	15	0.75
Copper, mg	2.0	0.1
Biotin, mg	0.03	0.015
Pantothenic acid, mg	10	0.5

IU, international unit; RDA, recommended daily allowance.
[a] Optional.
Data from Miller SA, Stephenson MF. Food fortification. *Bibl Nutr Dieta.* 1987;40:82.

Food fortification also prevents the deficiency of nutrients whose major dietary contribution is from only selected foods (e.g., iron or vitamin D), exemplified by the principles used in iron fortification (U.S. Department of Agriculture, *Food Technology,* April 1989). A need for the nutrient must be demonstrated in a defined population (e.g., vitamin D in milk for infants and the elderly), use of the product must not lead to toxicity, the vehicle to which nutrients are added must be appropriate (e.g., addition of iron to cereal to prevent deficiency in children), and use of the product must not be confusing to consumers. Although the amount of added nutrient can vary widely when analyzed, and there is a risk of overconsumption of some nutrients in certain subgroups, there is yet not much evidence to substantiate this risk (12). Analysis of nutrient intake in the NHANES IV survey will determine if the wide availability of nutrients in supplements has lead to overconsumption.

Food Additives

Additives are becoming nearly ubiquitous in processed foods. Although some of these substances have no nutrient value *per se,* they carry the potential for toxicity and thus can affect the acceptance or availability of a prepared food to which they have been added. The original Food and Agriculture Organization (FAO)/World Health Organization (WHO) definition of an additive (1955) was "non-nutritive substances added intentionally to food, generally in small quantities, to improve its appearance, flavor, texture, or storage properties." Now the definition of the Codex Alimentarius (sponsored by WHO) includes "any substance not normally consumed as a food by itself and not normally used as a typical ingredient of the food, whether or not it has nutritive value, the intentional addition of which to food for a technological purpose in the manufacturing, processing, preparation, treatment, packing, packaging, transport, or holding of such food results . . . in it or its by-products becoming a component of . . . such foods."

The use of additives is governed by the Food and Drug Act of 1906, which prevented the manufacture of adulterated foods; the Food, Drug, and Cosmetic Act of 1938, which allowed the government to remove adulterated foods from the market but did not regulate food additives; and by the Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act of 1958. This amendment required that a new preservative or new use or amount of preservative be approved by the FDA before use, and that the compound be safe for humans. The preservative may not be used to make a product appear other (e.g., fresher) than it is. This is the rationale for not allowing sulfites to be added to meats. The additive must also be of food grade. Nearly 3,000 additives are used in food processing. Most recently, the Food Additives Amendment (Delaney clause) has provided that "no additive shall be deemed to be safe if it is found to produce cancer in man or animal."

Additives are used (a) to improve nutritional value (vitamin D in milk, vitamin A in margarine, iodine in table salt, B vitamins and iron in refined breads and cereals); (b) to make food more appealing (colors, flavor enhancers, and sweeteners, most often sugar, salt, and corn syrup or their substitutes); (c) to maintain palatability and freshness (sodium nitrates to protect cured foods, vitamin C to prevent uncooked fruit from browning); (d) to control pH (in baking mixes, soft drinks), and (e) to improve consistency or aid in processing (carrageenan to give consistency to peanut butter, leavening agents to make baked goods rise) (Table 1-11).

Two major categories are exempt from testing and approval. About 700 additives are "generally recognized as safe" (GRAS) because past experience indicates that they have no known harmful effects. "Prior sanctioned substances," approved for use in food before 1958, also are exempt. New evidence can reopen testing on an additive, however. Most recently, butylated hydroxyanisole (BHA) and sulfites have been reviewed and approval continued (Food and Drug Administration, June 1998).

Similar regulations have been applied by the Joint Expert Committee for Food Additives of the FAO/WHO. Additives are classified for safety by acceptable daily intake (ADI) from 0 mg/kg to some upper limit (World Health Organization, 1987). The ADI is calculated by dividing the highest dose with no observable adverse effect in animals by a safety factor, usually 100. This improved approach to safety factor determination has been validated in a number of cases, including BHA, saccharine, and the coloring agent erythrosine (13).

SIGNS AND SYMPTOMS OF NUTRIENT DEFICIENCY

General Assessment

A person's nutritional status can be altered by any illness that affects nutrient intake, absorption, or utilization, and it should be a part of any general medical examination or evaluation for a medical disorder. The assessment comprises a history, physical examination, and laboratory tests. Many of the details of these components are covered in subsequent chapters, but the general outline is considered here.

Nutritional History

The history should be focused on identifying possible causes of altered nutrient intake or absorption and of increased losses or requirements (Table 1-13).

Special attention should be paid to changes in body weight (see Chapters 5 and 15), alcohol intake, causes of nutrient loss (bleeding, diarrhea), intercurrent illness, and medication that might affect intake or nutrient losses. Key questions should become a routine part of the history, including the following: (a) Has the patient's weight changed recently? By how much and how rapidly? (b) Has the patient's appetite changed? (c) Is the appetite change caused by altered taste or smell, problems with chewing or swallowing, poorly fitting dentures, or depression? (d) Who prepares meals for the patient, and has that changed recently? (e) Who shops and pays for food? (f) Are symptoms of gastrointestinal disease present? (g) Does the patient consume alcohol, medications, or dietary supplements or herbal remedies? (h) Is the patient on a restricted diet of any sort? Decreased or altered

TABLE 1-13. Nutritional History Screen

Mechanism of deficiency	If history of	Suspect deficiency of
Inadequate intake	■ All foods, ask about alcoholism, weight loss, poverty, dental disease, AIDS, taste changes	Calories, protein, thiamine, niacin, folate, pyridoxine, riboflavin
	■ Fruit, vegetables, grains	Vitamin C, thiamine, niacin, folate, dietary fiber
	■ Meat, dairy products, eggs	Protein, vitamin B_{12}
	■ Food idiosyncrasies, allergy	Lactose
Inadequate absorption	■ Drugs (especially antacids, anticonvulsants, cholestyramine, laxatives, neomycin, alcohol)	Selected vitamins and minerals
	■ Malabsorption (diarrhea, weight loss, steatorrhea)	Vitamins A, D, and K, calories, protein, iron, calcium, magnesium, zinc
	■ AIDS	Vitamin B_{12}
	■ Surgery e.g.	
	Gastrectomy	Vitamin B_{12}, iron
	Resection of small intestine	Vitamin B_{12}, bile salts (if >100 cm of distal ileum), all others (if jejunal)
Increased losses	■ Alcohol abuse	Magnesium, zinc, phosphorus
	■ Blood loss	Iron
	■ Diabetes, poorly controlled	Calories
	■ Diarrhea	Protein, zinc, electrolytes
	■ Draining abscesses, wounds	Protein
	■ Peritoneal dialysis or hemodialysis	Protein, water-soluble vitamins, zinc
	■ Drugs (especially diuretics, laxatives)	Potassium, magnesium
Increased requirements	■ Fever	Calories
	■ Hyperthyroidism	Calories
	■ Increased physiologic demands (infancy, adolescence, pregnancy, lactation)	Various nutrients
	■ Surgery, trauma, burns, infection	Calories, protein

taste is a common symptom that often is overlooked or incompletely assessed. Many common causes are not related to nutrient status, such as menopause, depression, or poor dental hygiene. Deficiencies of vitamin A, vitamin B_{12}, and perhaps zinc may also alter taste. Medications are among the most common causes of decreased or altered taste, especially chloride salts, which are secreted by salivary glands and drugs with anticholinergic effects, which produce xerostomia (see list of drugs in Table 1-14).

Physical Examination

Tissues that proliferate rapidly (skin, oral and gastrointestinal mucosa, hair, bone marrow) are most likely to manifest signs of nutrient deficiency. Some are accessible to the physical examination, some (gastrointestinal mucosa) are manifested by history (diarrhea), and others (bone marrow failure) present indirectly. The examination can be approached in one of four ways: assessment of the physical findings to identify the nutrient deficiency, a search for relevant signs of nutrient deficiency suspected from the history, oral examination (a neglected area of the physical examination), or, in selected cases, anthropomorphic measurements.

Dehydration. Deficiencies of Na, Cl, and H_2O lead to dehydration (see also discussion of sodium in Chapter 7). In adult patients, the manifestations of dehydration (including sunken eyeballs, mucosal xerosis, low blood pressure, and mental confusion) are less striking and specific than in children and infants. One or none may be present in any individual case.

TABLE 1-14. Common Drug-induced Oral Manifestations

Candidiasis
Antibiotics
Antineoplastics
Corticosteroids
Immunosuppressives
Steroid inhalers

Contact hypersensitivity
Iodine, mouthwashes, cosmetics, antiseptic lozenges, chewing gum, food additives
Menthol, toothpastes (esp. those containing cinnamon-aldehyde, formalin, and herbal components), dental materials (amalgam, steel wires, acrylic components)
Thymol
Topical analgesics
Topical antibiotics

Erythema multiforme
Anticonvulsants
Antimalarials
Barbiturates
Busulfan
Chlorpropamide, estrogens/progestins, ginseng, gold compounds, iodine mouthwashes
Isoniazid
Meprobamate
Minoxidil
Penicillins
Phenolphthalein
Phenylbutazone, phenytoin, Propylthiouracil, rifampicin
Salicylates
Sulfonamides
Tetracyclines, tolbutamide, verapamil

Fixed drug eruptions
Barbiturates, gold, indomethacin, lidocaine, penicillamine, salicylates
Chlordiazepoxide
Sulfonamides
Tetracyclines

Gingival hyperplasia
Cotrimoxazole, cyclosporine, erythromycin, ketoconazole, lamotrigine, lithium
Nifedipine, phenobarbital
Phenytoin sodium, sertraline, sodium valproate, topiramate, vigabatrin

Hairy/black tongue
Antibiotics, antidepressants
Corticosteroids, griseofulvin, lansoprazole
Sodium peroxide, tobacco, tetracyclines

Intraoral bleeding, petechiae, purpura
Antiarrhythmics
Phenylbutazone
Potassium chloride
Sulfonamides
Thiocyanate
Thiouracil
Warfarin sodium

Ulcerations, mucositis, stomatitis, glossitis
ACE inhibitors, antiarrhythmics, antibiotics
Antineoplastics, antidepressants, atorvastatin
Aspirin
D-Penicillamine, gabapentin, ganciclovir
Gold salts, interferons
Lamotrigine
Lithium
Meprobamate
Mercurial diuretics
Methotrexate
Methyldopa
NSAIDs
Phenylbutazone
Potassium chloride
Propranolol, propylthiouracil, protease inhibitors, proton pump inhibitors
Spironolactone
Thiazide diuretics
Tolbutamide, zidovudine

Xerostomia
Anorexiants
Antiarrhythmics
Antibiotics (broad-spectrum)
Anticholinergics
Anticoagulants
Anticonvulsants
Antidepressants
Antidiarrheals
Antihistamines, anti-HIV protease inhibitors
Antihypertensives
Antinauseants
Antineoplastics
Antiparkinsonism agents
Antispasmodics
Aspirin
Benzodiazepines
Bronchodilators
CNS stimulants
Decongestants
Diuretics
Ganglion-blocking agents, omeprazole, tramadol

Salivary gland enlargement or pain
Antipsychotics, clonidine, H2 receptor antagonists
Iodides
Isoproterenol
Methyldopa
Hypnotics
Lithium
Monoamine oxidase inhibitors
Muscle relaxants
Narcotics, nitrofurantoin
NSAIDs
Sympathomimetics
Tranquilizers, warfarin

Sources: Chernoff R. *Geriatric Nutrition.* Gaithersburg, MD: Aspen Publishers, 1991; Abdollahi M, Radfar M, A review of drug-induced oral reactions. *J Contemp Dent Pract.* 2003;4:10.

Nutrient Deficiency. An important part of the physical examination is the search for signs of nutrient deficiency. Table 1-15 lists the most common signs and the nutrient deficiencies frequently associated with them. Table 1-16 lists physical examination findings according to the individual vitamin that is lacking.

Oral Mucosa. Because the oral mucosa regenerates rapidly, it can be a sensitive indicator of nutrient deficiency. Table 1-17 lists the oral manifestations commonly associated with individual nutrient deficiencies. Oral manifestations are not specific for nutrient deficiency,

TABLE 1-15. Signs and Symptoms of Nutritional Deficiency in Adult Patients

Sign or symptom	Possible nutrient deficiency
General	
Wasted, skinny (especially temporal muscles)	Protein–calorie
Abdomen	
Distension	Protein–calorie
Hepatomegaly	Protein–calorie
Extremities	
Edema	Protein, thiamine
Decubitus ulcers, poor wound healing	Protein, vitamin C, zinc
Bone tenderness	Vitamin D
Bone ache, joint pain	Vitamin C
Muscle wasting and weakness	Protein, calorie, vitamin D
Muscle tenderness, muscle pain	Thiamine
Skin	
Pallor	Folate, iron, vitamin B_{12}
Follicular hyperkeratosis	Vitamins A and C
Perifollicular petechiae (especially after raised venous pressure	Vitamin C
Flaking dermatitis, scaling	Protein, calories, niacin, riboflavin, zinc, vitamin A
Bruising, purpura	Vitamin C, vitamin K, essential fatty acids
Pigmentation changes, desquamation of semiexposed areas	Niacin, protein–calorie
Scrotal dermatosis	Riboflavin
Cellophane appearance	Protein (also corticosteroid use, aging)
Hair	
Sparse and thin	Protein, zinc, biotin
Easy to pull out	Protein
Corkscrew hairs, coiled hair	Vitamin C, vitamin A
Nails	
Spooning	Iron
Transverse lines	Protein
Eyes	
History of night blindness (especially impaired visual recovery after glare)	Vitamin A
Photophobia, blurring, conjunctival inflammation	Riboflavin, vitamin A
Mouth	
Glossitis (slick red tongue)	Riboflavin, niacin, folic acid, vitamin B_{12} protein
Gums—bleeding, receding, spongy, ulcers, hypertrophic	Vitamins C, A, and K; folic acid, niacin
Cheilosis (dry, cracking, ulcerated lips)	Riboflavin, pyridoxine, niacin
Angular stomatitis	Riboflavin, pyridoxine, niacin
Hypogeusia	Zinc, vitamin A, vitamin B_{12}
Tongue fissuring	Niacin
Burning, sore mouth and tongue	Vitamins B_{12} and B_6, niacin, vitamin C folic acid, iron
Leukoplakia	Vitamins A, B_{12}, and B complex; folic acid, niacin
Neck	
Goiter	Iodine
Parotid enlargement	Protein (also alcohol excess, starch chewing)

(*continued*)

TABLE 1-15. Signs and Symptoms of Nutritional Deficiency in Adult Patients (*Continued*)

Sign or symptom	Possible nutrient deficiency
Neurologic	
Tetany	Calcium, magnesium
Peripheral neuropathy (paresthesias)	Thiamine, pyridoxine
Loss of reflexes, wrist drop, foot drop (loss of vibratory and position sense)	Vitamin B_{12}, vitamin E
Dementia, disorientation	Niacin, vitamin B_{12}
Confabulation	Thiamine
Ophthalmoplegia	Thiamine, vitamin E
Depression	Biotin, folic acid, vitamin B_{12}

TABLE 1-16. Clinical Manifestations of Vitamin Deficiency States

Vitamin	Major causes of deficiency	Clinical deficiency symptoms
Thiamine	Inadequate intake, alcoholism	*Neurologic*—mental confusion, irritability, sensory loss and paresthesias (peripheral neuropathy), weakness, anorexia *Eyes*—ophthalmoplegia *Cardiac*—tachycardia, cardiomegaly, congestive heart failure *Other*—constipation, sudden death, muscle tenderness and pain
Riboflavin	Inadequate intake	*Skin*—nasolabial seborrhea, fissuring and redness around eyes and mouth, magenta tongue, genital dermatosis *Eyes*—corneal vascularization
Pyridoxine	Inadequate intake, old age, alcoholism	*Skin*—nasolabial seborrhea, glossitis, cheilosis *Neurologic*—paresthesias, peripheral neuropathy *Other*—anemia
Niacin	Inadequate intake, alcoholism, carcinoid syndrome	*Skin*—nasolabial seborrhea, fissuring eyelid corners, angular fissures around mouth, papillary atrophy, pellagrous dermatitis (sun-exposed areas), burning mouth or tongue *Neurologic*—mental confusion *Other*—diarrhea
Folic acid	Inadequate intake, alcoholism, malabsorption, pregnancy, hemolysis, drugs (anticonvulsants, sulfasalazine, methotrexate)	*Skin*—pallor *Oral*—glossitis, hyperpigmentation of tongue *Neurologic*—depression *Other*—diarrhea, anemia
Cobalamin (B_{12})	Malabsorption, pernicious anemia, vegetarian diets	*Skin*—hyperpigmentation, pallor *Oral*—glossitis *Neurologic*—ataxia, optic neuritis, paresthesias, peripheral neuropathy, mental disorders *Other*—anemia, anorexia, diarrhea

(*continued*)

TABLE 1-16. Clinical Manifestations of Vitamin Deficiency States (*Continued*)

Vitamin	Major causes of deficiency	Clinical deficiency symptoms
Vitamin C	Alcoholism, inadequate intake	*Skin*—petechiae, purpura, swollen bleeding gums, delayed wound healing, flaking dermatosis *Other*—bone pain, depression, anorexia
Biotin	Total parenteral nutrition (TPN)	*Skin*—pluckable sparse hair, pallor, seborrheic dermatitis *Neurologic*—depression *Other*—anemia, fatigue
Vitamin A	Fat malabsorption, alcoholism	*Eyes*—Bitot's spots, conjunctival and corneal xerosis (dryness), keratomalacia, poor dark adaptation *Skin*—follicular hyperkeratosis, xerosis *Hair*—coiled, keratinized
Vitamin D	Fat malabsorption, lack of sunlight, breast-fed newborn	*Bone*—bowlegs, beading of ribs, bone pain, epiphyseal deformities, vertebral fractures, muscle pain
Vitamin E	Premature infants, fat malabsorption, cystic fibrosis, chronic biliary obstruction	*Neurologic*—peripheral neuropathy, ophthalmoplegia
Vitamin K	Fat malabsorption, excessive warfarin dose	*Skin*—subcutaneous hemorrhage, ecchymoses

and the same conditions can be caused in particular by medication. Table 1-14 lists some of the more important drug-induced oral presentations.

Anthropomorphic Measurements. The most useful of these measurements include body weight and height, but the latter is overlooked in many cases by physicians. These measurements are important in estimating the general nutritional status by a comparison with weight guidelines (see Chapter 5), and height is also important in assessing energy needs and determining body mass index.

Laboratory Tests

When the history and physical examination findings suggest a deficiency, it is often appropriate to assess the status of individual nutrients by specific tests. One must be careful to use the proper test, depending on whether one is assessing total body stores or recent intake (Tables 1-18 and 1-19). Each of these tests is discussed in detail in Chapters 6 and 7.

Many of the tests listed in Tables 1-18 and 1-19 measure static nutrient content. Only few tests measure actual function and allow a direct assessment of nutrient status.

The Concept of Malnutrition

It is difficult to separate malnutrition that is correctable by the addition of nutrients from malnutrition that results from the underlying disease. In many cases these two causes overlap. When the nutritional deficiency is limited to specific micronutrients, these can be individually examined by appropriate tests (Tables 1-18 and 1-19, and Chapters 6 and 7). Deficiencies are more common in the elderly patient who often presents with insufficient dietary intake, poor appetite, muscle wasting, and weight loss. Common deficiencies in such patients include vitamins A, B_{12}, D, E, calcium, and zinc. When the deficiency is global, however, it may be more difficult to distinguish from the effects of the underlying disease and enhanced catabolic rate, as exemplified by the differences noted between starvation and cachexia (Table 1-20). While admitting that it is not possible to readily distinguish between starvation and disease-associated cachexia at the bedside, tools have been developed to assess malnutrition in the clinic and to use these to follow the course of the illness. One such test, the Mini Nutritional Assessment (MNA) has been designed for use in the elderly population, and has been translated into many languages and validated in many countries

TABLE 1-17. Nutritional Deficiencies and Related Oral Manifestations

Nutrient deficiency	Oral manifestations
Vitamin A	Candidiasis *Gingivae*—hypertrophy, inflammation *Oral mucosa*—keratosis, leukoplakia Periodontal disease
Vitamin B complex	*Lips*—angular cheilosis *Oral mucosa*—leukoplakia Periodontal disease *Tongue*—papillary hypertrophy, magenta color, fissuring, glossitis
Vitamin B_2 (riboflavin)	Filiform papillae—atrophic Fungiform papillae—enlarged *Lips*—shiny, red, angular cheilosis *Tongue*—magenta color, soreness
Vitamin B_3 (niacin)	*Lips*—angular cheilosis *Oral mucosa*—intense irritation/inflammation, red, painful, denuded, ulcerated, mucositis/stomatitis *Tongue*—glossitis; tip/borders—red, swollen, beefy; dorsum—smooth, dry Ulcerative gingivitis
Vitamin B_6 (pyridoxine)	*Oral mucosa*—burning/sore mouth *Lips*—angular cheilosis *Tongue*—glossitis, glossodynia
Vitamin B_{12} (cobalamin)	*Lips*—angular cheilosis Burning/sore mouth *Oral mucosa*—ulcerations (aphthous type), mucositis/stomatitis *Tongue*—beefy red, glossy, smooth, glossitis, glossodynia, loss of papillae
Vitamin C (megavitamin C withdrawal)	Burning/sore mouth Candidiasis *Gingivae*—friability, raggedness, swelling, redness Hemorrhagic tendency—petechiae, subperiosteal Periodontal disease *Teeth*—marked mobility, spontaneous exfoliation
Vitamin D	Periodontal disease
Vitamin K	*Gingivae*—bleeding
Folic acid	*Oral mucosa*—mucositis/stomatitis, ulcerations (aphthous type) Burning/sore mouth Candidiasis Filiform/fungiform papillae—atrophic *Gingivae*—inflammation *Lips*—angular cheilosis *Tongue*—glossitis; tip/borders—red swollen; dorsum—slick, bald, pale, or fiery red
Iron	Dental caries—increased susceptibility Filiform papillae—atrophic *Lips*—angular cheilosis, pallor *Oral mucosa*—pallor, sore mouth, ulcerations (aphthous type) Oral parethesias, burning *Tongue*—atrophic, pale; glossitis Xerostomia
Protein	*Oral mucosa*—fragility, burning sensation *Lips*—angular cheilosis Periodontal disease

Modified from Chernoff R. *Geriatric Nutrition.* Gaithersburg, MD: Aspen Publishers, 1991.

TABLE 1-18. Clinical Laboratory Tests for Detection of Vitamin Deficiency

		Reference range (units)[a]			
Vitamin	**Test**	**Fluid**	**Marginal**	**Deficient**	**Usefulness**
B_1	Transketolase ratio	RBC	1.16–1.24	>1.25	+ when severe
	Thiamine	Serum		<12.7 (nmol/L)	Direct measure
	Thiamine	Urine		<27 (μg/g creat.)	
B_2	GSH reductase ratio	Serum	1.20–1.40	>1.40	Body stores
	Riboflavin	Urine	27–79	<27 (μg/g creat.)	Recent intake
B_6	AST activity ratio	RBC	1.70–1.85	>1.85	Body stores
	Pyridoxal-5-PO_4	Plasma	20–30	<20 (nmol/L)	Stores, sensitive
	4-pyridoxic acid	Urine		<3.0 (μmol/day)	Recent intake
	Total vitamin B_6	Urine		<0.5 (μmol/day)	Recent intake
Niacin	N-methylnicotinamide	Urine	0.5–2.5	<0.5 (mg/g creat.)	Recent intake
	2-pyridone	Urine	2.0–3.9	<2.0 (mg/g creat.)	Recent intake
Folate	Folic acid	Plasma	3.0–5.9	<3.0 (ng/mL)	Stores + intake
	Folic acid	RBC	140–159	<140 (ng/mL)	Body stores
Folate or B_{12}	Homocysteine	Plasma	12–15	>15 (μmol/L)	Function
	Cobalamin	Serum	150–200	<150 (pg/mL)	Body stores
	Methylmalonic acid	Serum		>376 (nmol/L)	Function
	Holotranscobalamin II	Serum	40–60	>60 (pg/mL)	Stores, sensitive
C	Ascorbic acid	Serum	11–23	<11 (μmol/L)	Recent intake
	Ascorbic acid	WBC	10–20	<10 (μg/108 cells)	Stores
A	Retinol	Plasma	10–19	<10 (μg/dL)	Stores + intake
	Retinol-binding protein	Plasma		<50 (mg/L)	Function
D	25-OH vitamin D	Serum	12–25	<12 (nmol/L)	Body stores
	1,25-$(OH)_2$ vitamin D	Serum	48–65	<48 (pmol/L)	Function
E	α-tocopherol	Serum	5.0–7.0	<5 (μg/mL)	Body stores
	α-tocopherol/total lipid	Serum	0.8–1.0	<0.8	Stores preferred
	H_2O_2 hemolysis	RBC	10–20	>20 (%)	Function
K	Prothrombin time	Plasma	1.5–2.0	>2.0 (sec. over function control)	Function
	Phylloquinone			<0.35 (nmol/L)	Recent intake

[a] Check local laboratory for variations from ranges.
GSH, glutathione; AST, aspartate amino transferase.

around the world. It is composed of simple measurements and questions and can be completed in 10 to 15 minutes (Table 1-21) (14). It utilizes the BMI and mid-arm circumference measurements described in Chapter 5, and can be used along with the Subjective Global Assessment (SGA, see Chapter 5) for predicting mortality and hospital costs.

DIET THERAPY

Diets are used for many purposes, only some of them therapeutic. Some diets are recommended to prevent the onset of chronic diseases, such as atherosclerosis or obesity (see Chapters 13 and 14). The data regarding the efficacy of such diets are incomplete. Other diets are used to manage medical illnesses, such as diabetes, hyperlipidemia, and renal disease (see Chapter 13). Still others are used for one specific aspect of overall management, such as the addition of calcium-containing foods for osteopenia (see Chapter 7). A few

TABLE 1-19. Clinical Laboratory Detection of Micronutrient Mineral Deficiency

Nutrient	Test	Method	Reference range (units)[a]	Usefulness
Iron	Iron (serum)	Colorimetric	50–200 (mg/dL)	Poor measure of body stores
	Total iron binding (serum)	Colorimetric	245–400 (mg/dL)	
	Iron-binding capacity (TIBC)	Calculation	15–50 (%)	Insensitive for iron status
	Transferrin (serum)	Immunoturbidimetric	200–400 (mg/dL)	Preferred over TIBC if available
	Ferritin (serum)	Immunoturbidimetric	18–300 (ng/mL)	Measures body stores: high specificity when low, poor sensitivity
Zn	Zinc (plasma)	Flame atomic absorption	20–130 (mg/dL)	Poor specificity for body stores
	Zinc tolerance test (plasma Zn)	Flame atomic absorption	> Twofold increase over baseline at 2 h	For malabsorption
Cu	Copper (serum)	Flame atomic absorption	55–175 (mg/dL)	Insensitive for body stores
	Ceruloplasmin (plasma)	Immunoturbidimetric	10–60 (mg/dL)	Independent of body stores
Selenium	Selenium (serum)	Fluorometry	100–340 (ng/mL)	Insensitive for body stores
	Glutathione peroxidase (plasma)	Spectrophotometric	455–800 (U/L)	More sensitive for body stores

[a] Check local laboratory for variation from ranges.

diets are used to eliminate or treat specific disorders, such as low-fat, low-lactose, low-sodium, or gluten-free diets (see Chapter 12).

Some diets are advertised commercially as providing nutritional remedies (usually unproven) for serious illness (most commonly cancer) and preventing cancer or obesity. One must keep in mind the strong placebo effect of all treatments, including diets. The greatest caution must be exercised in regard to unproven nutritional remedies for cancer because of the highly charged emotional situation in which these treatments are undertaken.

TABLE 1-20. Nutritional Alterations in Starvation and Cachexia

Variable	Starvation	Cachexia
Body weight	−1	0/−1
Body cell mass	−1	−3
Body fat	−3	−2
Caloric intake	−3	−3
Total energy expenditure	−2	−1
Resting energy expenditure	−3	+2
Protein synthesis	−3	+1/−1
Protein degradation	−3	+3
Serum insulin	−3	+3
Serum cortisol	0	+2

Adapted from Kotler DP. Cachexia. *Ann Intern Med.* 2000;133:622.

TABLE 1-21. Mini Nutritional Assessment (MNA)

Category	Criteria for points	Points
Anthropometric Assessment		
1. Body mass index (BMI) (kg/m^2)	<19 = 0, 19 to <21 = 1 21 to <23 = 2, ≥ 23 = 3	
2. Mid-arm circumference (MAC) cm	<21 = 0, 21 ≤ 22 = 0.5, >22 = 1.0	
3. Calf circumference (CC) in cm	<31 = 0 points, >31 = 1 point	
4. Weight loss during last 3 months	>3 kg (6.6 lb) = 0, does not know = 1 1-3 kg = 2, no weight loss = 3	
General Assessment		
5. Lives independently (not in nursing home or hospital)	no = 0 points, yes = 1 point	
6. Takes > 3 prescription drugs/day	yes = 0 points, no = 1 point	
7. Has suffered psychological stress or acute disease in past 3 months	yes = 0 points, no = 2 points	
8. Mobility	bed/chair bound = 0, able to get out of chair/bed but doesn't go out = 1, goes out = 2	
9. Neuropsychological problems	severe dementia = 0, mild dementia = 1 no psychological problems = 2	
10. Pressure sores or skin ulcers	yes = 0, no = 1	
Dietary Assessment		
11. How many full meals are eaten/day	1 meal = 0, 2 meals = 1, 3 meals = 3	
12. Selected consumption markers for protein intake	at least 1 serving of dairy products/d Y or N? ≥2 servings of legumes or eggs/week Y or N? meat, fish, or poultry every day Y or N? 0 or 1 Y = 0 points, 2 Y = 0.5, 3 Y = 1.0	
13. Consumes 2 or more servings of fruits or vegetables/day	no = 0, yes = 1	
14. Has food intake declined in past 3 months due to loss of appetite, or digestive, chewing, or swallowing difficulties?	severe loss of appetite = 0, moderate loss of appetite = 1, no loss of appetite = 2	
15. How much fluid is consumed/day	<3 cups = 0, 3-5 cups = 0.5, >5 cups = 1.0	
16. Mode of feeding	unable to eat without assistance = 0, self-fed with some difficulty = 1, self-fed easily = 2	
Self assessment		
17. Do they view themselves as having malnutrition problems?	major malnutrition = 0, does not know or moderate malnutrition = 1, no problem = 2	
18. In comparison with other people of the same age, how do they consider their health status	not as good−0, does not know = 0.5, as good = 1, better = 2	
	maximum 30 points	**Total**
Malnutrition Indicator Score	>24 points = well nourished 17–23.5 points = at risk of malnutrition <17 points = malnourished	

Adapted from Vellas B, Guigos Y, Garry PJ, et al. The Mini nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition.* 1999;15:116.

TABLE 1-22. Dietary Supplements That Affect Drug Action

Supplement	Drug	Effect
Vitamins		
Vitamin A	Alcohol	Hypervitaminosis A may enhance hepatotoxicity of alcohol.
	Isotretinoin	Additive toxic effects may result from combination therapy with vitamin A or other supplements containing vitamin A.
	Tetracycline	Combination therapy may enhance drug-induced intracranial hypertension (severe headache).
Vitamin D	Digoxin	Vitamin D-induced hypercalcemia may potentiate the effects of the drug and result in cardiac arrhythmias.
Vitamin E	Warfarin	May enhance anticoagulant response to warfarin.
	Aspirin	↑ anti-thrombotic effect
Vitamin K	Warfarin	Vitamin K in liquid food supplements may inhibit the hypoprothrombic effect of drug.
Ascorbic acid	Fluphenazine	Large doses may interfere with drug absorption and result in a return of manic behavior.
	Warfarin	Megadoses may decrease prothrombin time.
Folacin	Methotrexate	Folacin or its derivatives in vitamin preparations may alter responses to drug.
	Phenytoin	May decrease anticonvulsant action of drug.
Pyridoxine	Levodopa	Reverses antiparkinsonism effect of drug.
	Phenytoin	Large doses may reduce phenytoin levels.
	Hydralazine, isoniazid, penicillamine	May correct drug-induced peripheral neuropathy.
Dietary supplement		
Dong quai	Warfarin	Potentiate effect
Garlic supplement	Protease inhibitors	↓ efficacy
Ginseng	Oral hypoglycemics	↑ efficacy
Kava	Benzodiazepines	↑ sedation
Minerals		
Calcium, iron	Tetracycline	Concurrent use may decrease drug absorption.
Magnesium, zinc, iron	Penicillamine	Concurrent use may decrease drug effectiveness.

Modified from Pemberton CM. *Mayo Clinic Diet Manual,* 6th ed. Toronto: Decker, 1988.

The claims made for these diets can best be countered by promoting the diet recommended for cancer prevention (1) (see Chapter 15), which is very similar to that recommended for all healthy adults (Chapter 2). In both these diets, the primary goal is achieving and maintaining a normal weight.

Following a U.S. Court of Appeals decision (*Pearson v Shalala*), the FDA revoked the regulations codifying its policy not to allow health claims for four substances and their relationship to disease to appear on food labels. These claims are for dietary fiber and cancer, antioxidant vitamins and cancer, ω-3 fatty acids and coronary artery disease, and 0.8-mg folate supplements to reduce neural tube defects versus lower amounts of folate in conventional food. However, reversal of the FDA policy is not the equivalent of claims by the FDA regarding substance–disease relationships. Such claims must now be individually assessed.

DRUGS AND NUTRIENTS

Effects of Drugs on Micronutrient Metabolism

The clinical importance of many such effects is often not apparent because the drugs are used for only a limited time. Information on these multiple interactions is available from

TABLE 1-23. Examples of Drug-induced Alteration of Food Intake

Hypophagic drugs	Hyperphagic drugs	Drugs producing hypogeusia/dysgeusia
alcohol amphetamines cisplatin cocaine diethylpropion hydrochloride fenfluramine hydrochloride hydroxyurea methotrexate metformin phenmetrazine hydrochloride SSRIs	amitriptyline hydrochloride anabolic steroids benzodiazepines buclizine hydrochloride chlortetracycline cyproheptadine hydrochloride glucocorticoids phenothiazines reserpine sulfonylureas tricyclic antidepressants	amphetamines, acarbose, acetaminophen, ACE inhibitors, acetazolamide, acyclovir, antibiotics, antidepressants, beta-blockers, benzodiazepines, carbimazole, chlorhexidine, chlorpromazine, cisplatin, clofibrate, D-Penicillamine, dicyclomine, encainide, ethionamide, etidronate, 5-fluorouracil, gancyclovir, granisetron, gold salts, griseofulvin, isotretinoin, iansoprazole, levodopa, lithium carbonate, methimazole, methocarbamol, methylthiouracil, oxyfedrine, penicillin, pentamidine, phytonadione, propylthiouracil, quinidine, ranitidine, ritonavir, selegiline, statins, tamoxifen, topiramate, triptans, ursodiol, vitamins (high-dose)

SSRI, selective serotonin reuptake inhibitor.
Source (in part): Abdollahi M, Radfar M. A review of drug-induced oral reactions. *J Contemp Dent Pract.* 2003;4:1.

the NIH Clinical Center and the Drug-Nutrient Interaction Task Force (www.cc.nih.gov/patient_education/drug_nutrient/), and from books (15).

Effect of Vitamins and Minerals on Drug Action

Although large doses of micronutrients are usually required to produce a clinical effect, the mechanism by which some sources of vitamins (e.g. grapefruit juice) affect drug metabolism (decreasing the area under the curve following absorption) differs from that of nutrient provision (Table 1-22).

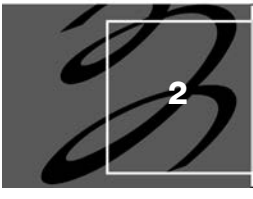
Drug-induced Alterations of Food Intake

Many drugs (including alcohol) decrease appetite, especially in persons with chronic illness. Some drugs, especially tricyclic antidepressants, increase appetite in depressed and also nondepressed persons. Amitriptyline is the most active of this group and causes weight gain, perhaps in part through hyperphagia. Drugs are the most common cause of dysgeusia. Most

chloride salts (or other halides) are secreted in saliva and may affect taste. Drugs with anticholinergic effects cause dry mouth and may affect appetite. Table 1-23 lists some drugs that commonly affect food intake.

References

1. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, and the Prevention of Cancer: A Global Perspective*. Washington, DC: WCRF/AICR, 1997.
2. World Health Organization. *Trace Elements in Human Nutrition and Health*. Prepared in collaboration with the Food and Agriculture Organization of the United Nations and the International Atomic Energy Agency. Geneva: WHO, 1996.
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. Washington, DC: National Academies Press, 1997.
4. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline*. Washington, DC: National Academies Press, 2000.
5. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Vitamin E, Vitamin C, Selenium, and Carotenoids*. Washington, DC: National Academies Press, 2000.
6. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academies Press, 2001.
7. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate*. Washington, DC: National Academies Press, 2005.
8. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academies Press, 2005.
9. *Dietary Guidelines for Americans*, 2005. *www.health.gov/dietaryguidelines/dga2005*
10. U.S. Department of Agriculture, Food and Drug Administration. *Food Additives*. Washington, DC: U.S. Government Printing Office, 1992.
11. Fletcher RJ, Bell IP, Lambert JP. Public health aspects of food fortification: a question of balance. *Proc Nutr Soc*. 2004;63:605.
12. Sarubin A. *The Health Professional's Guide to Popular Dietary Supplements*. 2nd ed. Chicago: The American Dietetic Association, 2003.
13. Pascal G. Safety assessment of food additives and flavoring substances. In: van der Heijden K, Younes M, Fishbein L, Miller S, eds. *International Food Safety Handbook*. New York: Marcel Dekker, 1999:239.
14. Vellas B, Guigos Y, Garry PJ, et al. The Mini nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition*. 1999;15:116.
15. Boulleta JI, Armenti VT. *Handbook of Drug-Nutrient Interactions*. Towata, NJ: Humana Press, 2004.



2 RECOMMENDATIONS FOR HEALTHY YOUNG ADULTS

INTRODUCTION

Despite the extensive array of volumes on nutrition, diet, and health displayed in bookstores that present diverse, and often conflicting, recommendations for healthy eating, virtually all expert scientific panels reporting guidelines for good nutritional practice have devised remarkably consistent dietary recommendations for healthy adults. Further, despite impressions generated by almost daily media reports of new dietary fads, the principles of healthy eating have not fundamentally changed over the last 50 years. The most widely

disseminated general recommendations for healthy adults are included in two reports. The first, which represents the combined recommendations of the U.S. Department of Agriculture and the U.S. Department of Health and Human Services, is called *Dietary Guidelines for Americans, 2005* (1); the second, *AHA Dietary Guidelines Revision 2000: A Statement for Health Care Professionals from the Nutrition Committee of the American Heart Association,* reflects the recommendations of the American Heart Association (2), recommendations followed by a companion set for prevention of cardiovascular disease in women (3).

Dietary Guidelines for Americans, 2005

Dietary Guidelines for Americans, 2005 (1) is presented in three levels of complexity. The simplest guidance is offered in the consumer brochure (1) and is based on three guiding principles: (a) Make smart choices from every food group, (b) find your balance between food and physical activity, and (c) get the most nutrition out of your calories.

A smart choices healthy eating plan includes emphasizing fruits, vegetables, whole grains, and fat-free or low-fat dairy milk products. The plan also includes lean meats, fish, poultry, beans, eggs, and nuts, and is low in saturated fats, *trans* fats, cholesterol, salt, and added sugars. Balancing food intake with physical activity requires being physically active for at least 30 minutes most days of the week, with the recognition that increasing the duration or intensity of physical activity can have even greater health benefits and may be needed to control weight. Getting the most nutrition from the calories one eats requires choosing the most nutritionally rich foods from each food group daily (1).

The most detailed recommendations are provided in the *Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2005* (1). This document represents the comprehensive 364-page report presented by the Advisory Committee to the Secretary of Health and Human Services and the Secretary of Agriculture, documenting the scientific evidence for the recommendations in the report. The entire document, a summary of the available data and their citations, can be downloaded at the URL provided in reference 1. The lengthy document is intended for nutrition and public health professionals interested in the research details that provide the basis for the Dietary Guidelines.

The third, intermediate document, titled *Dietary Guidelines for Americans, 2005* (1) (Table 2-1), offers its recommendations at a level of detail appropriate for most health care professionals and the educated consumer. This publication (1) presents detailed key recommendations for a healthy diet grouped under nine thematic categories (Table 2-1):

1. Adequate nutrients within calorie needs
2. Weight management
3. Physical activity
4. Food groups to encourage
5. Fats
6. Carbohydrates
7. Sodium and potassium
8. Alcoholic beverages
9. Food safety

The Guidelines include further key recommendations for specific population groups such as women of childbearing age, pregnant women, children and adolescents, and older adults (1).

1. **Adequate nutrients within calorie needs** encompasses two key recommendations. The first is to "consume a variety of nutrient-dense foods and beverages within and among the basic food groups while choosing foods that limit the intake of saturated, *trans* fats, cholesterol, added sugars, salt and alcohol." The second encourages "meeting recommended intakes within energy needs by adopting a balanced eating pattern such as the USDA Food Guide or the DASH (Dietary Appropaches to Stop Hypertension) Eating Plan" (4–6).
2. Key recommendations for **weight management** include recommendations that individuals "maintain body weight in a healthy range" by balancing "calories from food and beverages

TABLE 2-1. ***Dietary Guidelines for Americans, 2005:*** **Key Recommendations**

Adequate nutrients within calorie needs	■ Consume a variety of nutrient-dense foods and beverages within and among the basic food groups while choosing foods that limit the intake of saturated and *trans* fats, cholesterol, added sugars, salt, and alcohol. ■ Meet recommended intakes within energy needs by adopting a balanced eating pattern, such as the USDA Food Guide or the DASH eating plan.
Weight management	■ To maintain body weight in a health range, balance calories from foods and beverages with calories expended. ■ To prevent gradual weight gain over time, make small decreases in food and beverage calories and increase physical activity.
Physical activity	■ Engage in regular physical activity and reduce sedentary activities to promote health, psychological well-being, and a healthy body weight. ■ To reduce the risk of chronic disease in adulthood, engage in at least 30 min of moderate-intensity physical activity, above usual activity, at work or home on most days of the week. ■ For most people, greater health benefits can be obtained by engaging in physical activity of more vigorous intensity or longer duration. ■ To help manage body weight and prevent gradual unhealthy body weight gain in adulthood, engage in approximately 60 min of moderate- to vigorous intensity activity on most days of the week while not exceeding caloric intake requirements. ■ To sustain weight loss in adulthood, participate in at least 60 to 90 min of daily moderate-intensity physical activity while not exceeding caloric intake requirements. Some people may need to consult with a health care provider before participating in this level of activity. ■ Achieve physical fitness by including cardiovascular conditioning, stretching exercises for flexibility, and resistance exercises or calisthenics for muscle strength and endurance.
Food groups to encourage	■ Consume a sufficient amount of fruits and vegetables while staying within energy needs. Two cups of fruit and 2½ cups of vegetables per day are recommended for a reference 2,000-cal intake, with higher or lower amounts depending on the calorie level. ■ Choose a variety of fruits and vegetables each day. In particular, select from all five vegetable subgroups (dark green, orange, legumes, starchy vegetables, and other vegetables) several times a week. ■ Consume 3 or more ounce-equivalents of whole-grain products per day, with the rest of the recommended grains coming from enriched or whole-grain products. In general, at least half the grains should come from whole grains. ■ Consume 3 cups per day of fat-free or low-fat milk or equivalent milk products.
Fats	■ Consume less than 10% of calories from saturated fatty acids and less than 300 mg/day of cholesterol, and keep *trans* fatty acid consumption as low as possible. ■ Keep total fat intake between 20% and 35% of calories, with most fats coming from sources of polyunsaturated and monounsaturated fatty acids, such as fish, nuts, and vegetable oils. ■ When selecting and preparing meat, poultry, dry beans, and milk or milk products, make choices that are lean, low-fat, or fat-free. ■ Limit intake of fats and oils high in saturated or *trans* fatty acids, and choose products low in such fats and oils.
Carbohydrates	■ Choose fiber-rich fruits, vegetables, and whole grains often. ■ Choose and prepare foods and beverages with little added sugars or caloric sweeteners, such as amounts suggested by the USDA Food Guide and the DASH Eating Plan. ■ Reduce the incidence of dental caries by practicing good oral hygiene and consuming sugar- and starch-containing foods and beverages less frequently.

(*continued*)

TABLE 2-1. ***Dietary Guidelines for Americans, 2005:*** **Key Recommendations (*Continued*)**

Sodium and potassium	■ Consume less than 2,300 mg (approximately 1 tsp of salt) of sodium per day. ■ Choose and prepare foods with little salt. At the same time, consume potassium-rich foods, such as fruits and vegetables.
Alcoholic beverages	■ Those who choose to drink alcoholic beverages should do so sensibly and in moderation–defined as the consumption of up to one drink per day for women and up to two drinks per day for men. ■ Alcoholic beverages should not be consumed by some individuals, including those who cannot restrict their alcohol intake, women of childbearing age who may become pregnant, pregnant and lactating women, children and adolescents, individuals taking medications that can interact with alcohol, and those with specific medical conditions. ■ Alcoholic beverages should be avoided by individuals engaging in activities that require attention, skill, or coordination, such as driving or operating machinery.
Food safety	■ To avoid microbial foodborne illness: ▪ Clean hands, food contact surfaces, and fruits and vegetables. Meat and poultry should *not* be washed or rinsed. ▪ Separate raw, cooked, and ready-to-eat foods while shopping, preparing, or storing foods. ▪ Cook foods to a safe temperature to kill microorganisms. ▪ Chill (refrigerate) perishable food promptly and defrost food properly. ▪ Avoid raw (unpasteurized) milk or any products made from unpasteurized milk, raw or partially cooked eggs or foods containing raw eggs, raw or undercooked meat and poultry, unpasteurized juices, and raw sprouts.

with calories expended" and "prevent gradual weight gain over time" by making "small decreases in food and beverage calories and increase physical activity."

3. The principal **physical activity** guidance is to "engage in regular physical activity and reduce sedentary activities to promote health, psychological well-being, and a healthy body weight" and to "achieve physical fitness by including cardiovascular conditioning, stretching exercises for flexibility, and resistance exercises or calisthenics for muscle strength and endurance."
4. There are four key recommendations regarding **food groups to encourage.** First, individuals are encouraged to "consume a sufficient amount of fruits and vegetables while staying within energy needs." Secondly, individuals should "choose a variety of fruits and vegetables each day." In particular, they should "select from all five vegetable subgroups (dark green, orange, legumes, starchy vegetables and other vegetables) several times a week." Third, there should be a goal to "consume 3 or more ounce-equivalents of whole-grain products per day, with the rest of the recommended grains coming from enriched or whole-grain products. In general, at least half the grains should come from whole grains." Finally, individuals should strive to "consume 3 cups per day of fat-free or low-fat milk or equivalent milk products."
5. The **fats** guideline recommends that individuals consume "less than 10 percent of calories from saturated fatty acids and less than 300 mg/day of cholesterol, and keep *trans* fatty acid consumption as low as possible." Additionally, people should keep "total fat intake between 20 to 35 percent of calories with most fats coming from sources of polyunsaturated and monounsaturated fatty acids, such as fish, nuts and vegetable oils" and limit "intake of fats and oils high in saturated and/or *trans* fatty acids, and choose products low in such fats and oils."
6. The key **carbohydrates** recommendations are to choose "fiber-rich fruits, vegetables, and whole grains often," to choose and prepare "foods and beverages with little added sugars or caloric sweeteners," and to reduce "the incidence of dental caries by practicing good oral hygiene and consuming sugar- and starch-containing foods and beverages less frequently."

7. **Sodium and potassium** guidelines recommend to "consume less than 2,300 mg (approximately 1 tsp of salt) of sodium per day" and to "choose and prepare foods with little salt. At the same time, consume potassium-rich foods, such as fruits and vegetables," aiming at a food potassium intake of 4,700 mg/day.
8. For those who choose to consume them, **alcoholic beverages** should be consumed "sensibly and in moderation—defined as the consumption of up to one drink per day for women and up to two drinks per day for men." Further, "alcoholic beverages should not be consumed by some individuals, including those who cannot restrict their alcohol intake, women of childbearing age who may become pregnant, pregnant and lactating women, children and adolescents, individuals taking medications that can interact with alcohol, and those with specific medical conditions." Finally, "alcoholic beverages should be avoided by individuals engaging in activities that require attention, skill, or coordination, such as driving and operating machinery."
9. The key **food safety** recommendation is "to avoid microbial foodborne illness" by (a) "cleaning hands, food contact surfaces and fruits and vegetables," but not washing meat and poultry, (b) separating "raw, cooked and ready-to-eat foods while shopping, preparing and storing foods," (c) cooking foods "to a safe temperature to kill microorganisms," (d) chilling or refrigerating "perishable food promptly" and defrosting foods properly, (e) avoiding "raw (unpasteurized) milk or any products made from unpasteurized milk, raw or partially cooked eggs or foods containing raw eggs, raw or undercooked meat and poultry, unpasteurized juices and raw sprouts."

The *Dietary Guidelines for Americans, 2005* (1) also offers recommendations for specific population groups (Table 2-2). These recommendations will be discussed in more detail in the chapters that deal with the specific population groups themselves, particularly Chapter 3 (Recommendations for Healthy Elderly Adults) and Chapter 4 (Pregnancy and Lactation).

AMERICAN HEART ASSOCIATION DIETARY GUIDELINES REVISION 2000

The *AHA Dietary Guidelines Revision 2000* (2) recommends four population goals: (i) a healthy eating pattern including foods from all major food groups; (ii) a healthy body weight; (iii) a desirable blood cholesterol and lipoprotein profile; and (iv) a desirable blood pressure. The healthy eating pattern goal is based on recommendations for consuming a variety of fruits, vegetables, and grain products and including low-fat or nonfat dairy products, fish, legumes, poultry, and lean meats in the diet. The healthy body weight goal recommends matching energy intake with energy needs, limiting the consumption of foods with a high caloric density or poor nutritional quality, and maintaining a level of physical activity that is compatible with fitness and balances energy intake. The desirable blood cholesterol and lipoprotein profile goal recommends limiting the intake of foods high in saturated fatty acids and cholesterol, and substituting grains and unsaturated fatty acids derived from vegetables, fish, legumes, and nuts. The desirable blood pressure goal recommends limiting dietary intake of salt and consumption of alcohol while reinforcing the need for maintaining a healthy body weight and consuming the dietary pattern detailed in the other aims.

Since the original publication of the Dietary Guidelines in 2000, the American Heart Association has issued several additional scientific statements (3–8) that relate to, update, and expand on selected issues in the AHA Guidelines. These statements reaffirm the importance of "a dietary pattern that emphasizes fruits, vegetables, breads and cereals, and fish" (3), the health benefits of omega-3 fatty acids and consuming fish at least two times per week (3,4), and associations between moderate alcohol consumption (one to two drinks per day) and a reduced risk of coronary heart disease in populations (5). The more recent statements also emphasize that the highest level of research evidence exists for the blood pressure-lowering effects of diets low in sodium, total fat, and saturated fat and high in potassium when consumed in a DASH diet pattern that emphasizes fruit, vegetable, and low-fat dairy product intake (6) and that medical nutrition approaches aimed at weight management, blood pressure, blood glucose, and blood lipid control are important for the

TABLE 2-2. ***Dietary Guidelines for Americans, 2005:*** **Key Recommendations for Specific Population Groups**

Adequate nutrients within calorie needs	■ *People over age 50*: Consume vitamin B_{12} in its crystalline form (i.e., fortified foods or supplements). ■ *Women of childbearing age who may become pregnant*: Eat foods high in heme-iron or consume iron-rich plant foods or iron-fortified foods with an enhancer of iron absorption, such as vitamin C-rich foods. ■ *Women of childbearing age who may become pregnant and those in the first trimester of pregnancy*: Consume adequate synthetic folic acid daily (from fortified foods or supplements) in addition to food forms of folate from a varied diet. ■ *Older adults, people with dark skin, and people exposed to insufficient ultraviolet band radiation (i.e., sunlight):* Consume extra vitamin D from vitamin-D fortified foods or supplements.
Weight management	■ *Those who need to lose weight*: Aim for a slow, steady weight loss by decreasing calorie intake while maintaining an adequate nutrient intake and increasing physical activity. ■ *Overweight children*: Reduce the rate of body weight gain while allowing growth and development. Consult a health care provider before placing a child on a weight-reduction diet. ■ *Pregnant women*: Ensure appropriate weight gain as specified by a health care provider ■ *Breastfeeding women*: Moderate weight reduction is safe and does not compromise weight gain of the nursing infant. ■ *Overweight adults and overweight children with chronic disease and/or on medication*: Consult a health care provider about weight loss strategies prior to starting a weight-reduction program to ensure appropriate management of other health conditions.
Physical activity	■ *Children and adolescents*: Engage in at least 60 min of physical activity on most, preferably all, days of the week. ■ *Pregnant women*: In the absence of medical or obstetric complications, incorporate 30 min or more of moderate-intensity physical activity on most, if not all, days of the week. Avoid activities with a high risk of falling or abdominal trauma. ■ *Breastfeeding women*: Be aware that neither acute nor regular exercise adversely affects the mother's ability to successfully breastfeed. ■ *Older adults*: Participate in regular physical activity to reduce functional declines associated with aging and to achieve the other benefits of physical activity identified for all adults.
Food groups to encourage	■ *Children and adolescents:* Consume whole-grain products often; at least half the grains should be whole grains. Children 2 to 8 years should consume 2 cups per day of fat-free or low-fat or equivalent milk products. Children 9 years of age and older should consume 3 cups per day of fat-free or low-fat milk or equivalent milk products.
Fats	■ *Children and adolescents:* Keep total fat intake between 30% and 35% of calories for children 2 to 3 years of age and between 25% and 35% of calories for children and adolescents 4 to 18 years of age, with most fats coming from sources of polyunsaturated and monounsaturated fatty acids, such as fish, nuts, and vegetable oils.
Sodium and potassium	■ *Individuals with hypertension, Blacks, and middle-aged and older adults:* Aim to consume less than 1,500 mg of sodium per day, and meet the potassium recommendation (4,700 mg/day) with food.
Food safety	■ *Infants and young children, pregnant women, older adults, and those who are immunocompromised*: Do not eat or drink raw (unpasteurized) milk or any products made from unpasteurized milk, raw or partially cooked eggs or foods containing raw eggs, raw or undercooked meat and poultry, raw or undercooked fish or shellfish, unpasteurized juices, and raw sprouts. ■ *Pregnant women, older adults, and those who are immunocompromised:* Only eat certain deli meats and frankfurters that have been reheated to steaming hot.

primary prevention of cardiovascular disease in individuals with diabetes mellitus (7). On the other hand, current data do not support more than minimal cardiovascular protective effects of soy protein or isoflavone intakes (8).

CONSOLIDATED RECOMMENDATIONS

From the brief summary presented above, the common guiding principles and overall similarity of the recommendations outlined by the two expert committees should be readily apparent. Further, both sets of guidelines emphasize consuming adequate amounts of the known essential nutrients as *whole foods* and incorporating healthy dietary practices into lifestyle patterns to be maintained throughout life. Together, these two sets of dietary recommendations can be consolidated as follows:

Do Not Become Obese

Obesity is the most significant form of malnutrition in the United States today. Data obtained over more than 30 years in the National Health and Nutrition Examination Surveys, consecutive, representative samples of individuals across the United States, have documented disturbing trends in body weight. From 1976 to 1980, 15% of adults aged 20 to 74 years were obese and 47.1% were either overweight or obese (9–11). In 2003 to 2004, overweight adults are now 32.9% of the population and 66.2% of the adult population is either overweight or obese (9–11). In 1995, no state had an obesity prevalence rate of greater than 20% (12). In 2005, only four states had an obesity prevalence rate less than 20%; moreover the prevalence of obesity in 14 states was between 25% and 20% and three states had obesity prevalence rates greater than 30% (12).

Obesity is associated with a wide variety of increased health risks as discussed more fully in Chapter 15. These include an increased risk for morbidity and mortality from coronary heart disease, hypertension, type II noninsulin-dependent diabetes, arthritis, gallstones, and endometrial cancer. In the Framingham Heart Study (and independent of a subject's Framingham Risk Score, race, and family characteristics), for every one unit increase in body mass index (BMI), there was an associated 4% increase in the incidence of coronary heart disease events (13), with a hazard ratio for cardiovascular events in obese individuals of 1.58 [1.07–2.31] (13). Similarly, individuals with a BMI greater than 30 at 18 years of age increase their lifetime risk of developing diabetes by three- to fourfold compared to 18 year olds with a BMI between 18.5 and 24.9 (14).

The first step in devising a dietary plan is to set one's energy intake at a level to maintain a BMI, which is one's weight in kilograms divided by the square of one's height in meters (kg/m^2), within the normal adult range of 18.5 to 25. Remember, however, that all initial estimates of dietary energy intake for an individual person are just that, crude estimates, and must be refined upward or downward based on that person's body weight response to the initial approximation. An individual's estimated energy requirement (EER) in kilocalories per day can be estimated from his or her age, body weight in kilograms, and height in meters according to the following equations (15,16):

Men:

$$EER = 662 - (9.53 \times age) + PA \times [(15.91 \times wt) + (539.6 \times ht)]$$

Women:

$$EER = 354 - (6.91 \times age) + PA \times [(9.36 \times wt) + (726 \times ht)]$$

where PA is the subject's physical activity quotient. The value of PA assigned to the activities of usual daily living is 1.0. PA increases to 1.11 to 1.12 (for women and men, respectively) for the activities of daily life *plus* an additional 30 to 60 minutes of moderate activity daily; 1.25 to 1.27 for at least an *additional* 60 minutes of moderate daily activity; and to 1.45 to 1.48 for the activities of daily life plus an *additional* 180 minutes of moderate activity or at least an *additional* 60 minutes of moderate daily activity plus an *additional* 60 minutes of vigorous activity (15,16). Because most people do not have very active lifestyles, when initially estimating an individual's energy expenditure it is best to estimate the PA quotient on the low side.

Be Physically Active on a Daily Basis

Avoid a sedentary lifestyle. Regular physical activity burns calories. In addition, it is conducive to cardiovascular fitness and reduces the risk for heart disease, hypertension, colon cancer, and type 2 diabetes while maintaining muscle strength and endurance, maintaining bone health and reducing osteoporosis, and promoting psychological well-being (1). In order to reduce the risk of chronic disease, at least 30 minutes of moderate physical activity is recommended on most days of the week (1). This value is *in addition* to the energy expended in an individual's usual activities of daily life. Further, to help maintain energy balance and prevent body weight gain in adult life, approximately 60 minutes of moderate to vigorous physical activity is recommended on most days of the week (1), while at least 60 to 90 minutes of such activity may be necessary to maintain a healthy body weight in obese individuals who have lost excess body weight (1). It is imperative to remember that these physical activity recommendations are made in the context of persons who do not exceed their recommended calorie intakes and maintain adequate hydration. It is also important to remember that, to ensure safety, an older individual should consult his or her physician before beginning moderate or intensive physical activity programs. Table 2-3 shows the approximate number of calories burned by a 154-lb (70-kg) person engaged in 1 hour of various common physical activities.

Enjoy a Wide Variety of Foods

No single food can supply all the known essential nutrients in sufficient amounts. For this reason, it is imperative to consume a wide variety of foods, both within and among the different food groups. The USDA defines the basic food groups as grains; vegetables; fruits; milk, yoghurt, and cheese; and meat, poultry, fish, dry beans, eggs, and nuts. The DASH diet plan includes as food groups grains; vegetables, fruits; low-fat or fat-free dairy products; meat (low-fat), poultry, and fish; and nuts, seeds, and dry beans (17). The Dietary Guidelines state that "Each basic food group is the major contributor of at least one nutrient while making substantial contributions of many other nutrients. Because each food group provides a wide array of nutrients in substantial amounts, it is important to include all food groups in the

TABLE 2-3. Calories Expended for Each Hour of Common Physical Activities

Moderate physical activity	Calories/hr
Hiking	370
Light gardening/yard work	330
Dancing	330
Golf (walking and carrying clubs)	330
Bicycling (<10 mph)	290
Walking (3.5 mph)	280
Weight lifting (general light workout)	220
Stretching	180
Vigorous Physical Activity	
Running/jogging (5 mph)	590
Bicycling (>10 mph)	590
Swimming (slow freestyle laps)	510
Aerobics	480
Walking (4.5 mph)	460
Heavy yard work (chopping wood)	440
Weight lifting (vigorous effort)	440
Basketball (vigorous)	440

From U. S. Department of Health and Human Services. U.S. Department of Agriculture. *Dietary Guidelines for Americans, 2005* 6th ed. Washington, DC: U.S. Government Printing Office, January 2005. http://www.healthierus.gov/dietaryguidelines; http://www.health.gov/dietaryGuidelines. Approximate energy expended, calculated for a person who weighs 70 kg. The values will be higher for those who weigh more and lower for individuals who weigh less.

daily diet" (1). Additionally, variety enhances the enjoyment of eating. Nonetheless, in our society, where an abundance of affordable food is readily available, persons who expend relatively low amounts of energy on a daily basis are at increased risk for becoming obese. To maintain a healthy weight, particular attention must also be paid to portion size and to the energy and nutrient densities of the foods consumed. Energy-dense foods are those that supply calories, but relatively few (if any) essential nutrients. Nutrient-dense foods are those that provide a substantial amount of essential nutrients like vitamins and minerals, but contain relatively few calories. In today's environment, foods that are low in energy but relatively nutrient-dense (e.g., fruits and vegetables) are preferable to energy-dense foods that are relatively nutrient-poor (e.g., fats, oils, and alcohol), both for helping to maintain energy balance and for providing what are known to be health-promoting nutrients.

Consume a Variety of Fruits, Vegetables, and Grain Products Daily

In the context of the statements immediately above, dietary patterns characterized by the consumption of large amounts of fruits, vegetables, and grains (especially whole grains) have been associated with decreased risks for cardiovascular disease, stroke, hypertension, and certain cancers (1,2,18,19) (see also Tables 15-1, 15-3, and 15-4). In addition, because they are rich in nutrients (Table 2-4) but low in caloric density, these foods help one to maintain a healthful weight, and because they are high in fiber, they may promote satiety, enhance bowel function, and modestly lower blood cholesterol levels. For a reference 2,000-cal diet, 4.5 cups (nine servings) of fruits and vegetables per day are recommended. These are generally proportioned as two cups of fruit plus 2.5 cups of vegetables. Obviously, the recommended amounts increase or decrease proportionately, depending on a person's actual calorie intake. Further, because different types of vegetables supply different nutrients (Table 2-4), further recommendations distribute vegetable recommendations as dark green vegetables, legumes, and starch vegetables (3 cups each, weekly), orange vegetables (2 cups weekly), and other vegetables (6.5 cups weekly) (1). Additionally, one should consume "three or more ounce-equivalents of whole-grain products daily and

TABLE 2-4. Selected Nutrients in Fruits and Vegetables

Sources of vitamin A (carotenoids)
- Bright orange vegetables like carrots, sweet potatoes, and pumpkin
- Tomatoes and tomato products, red sweet pepper
- Leafy greens such as spinach, collards, turnip greens, kale, beet and mustard greens, green leaf lettuce, and romaine
- Orange fruits like mango, cantaloupe, apricots, and red or pink grapefruit

Sources of vitamin C
- Citrus fruits and juices, kiwi fruit, strawberries, guava, papaya, and cantaloupe
- Broccoli, peppers, tomatoes, cabbage (especially Chinese cabbage), brussels sprouts, and potatoes
- Leafy greens such as romaine, turnip greens, and spinach

Sources of folate
- Cooked dry beans and peas
- Oranges and orange juice
- Deep green leaves like spinach and mustard greens

Sources of potassium
- Baked white or sweet potatoes, cooked greens (such as spinach), winter (orange) squash
- Bananas, plantains, many dried fruits, oranges and orange juice, cantaloupe, and honeydew melons
- Cooked dry beans
- Soybeans (green and mature)
- Tomato products (sauce, paste, puree)
- Beet greens

From U. S. Department of Health and Human Services. U.S. Department of Agriculture. *Dietary Guidelines for Americans, 2005* 6th ed. Washington, DC: U.S. Government Printing Office, January 2005. http://www.healthierus.gov/dietaryguidelines; http://www.health.gov/dietaryGuidelines.

consume three cups per day of fat-free or low-fat or equivalent milk products" (1). Whole grain products include products *that are specifically labeled as whole grain* wheat, oats, corn, rye and barley, oatmeal, popcorn, brown rice, wild rice, buckwheat, bulgur, millet, quinoa, and sorghum. At least half of one's grain intake should come from whole grain products. Whole grains are excellent sources of dietary fiber, and dietary reference intakes (DRIs) for total fiber have been set at 14 g/1,000 kcal/day (15,16).

When possible, fresh fruits and vegetables should be included in the diet, although frozen and canned fruits and vegetables remain excellent sources of essential nutrients that should be used when fresh products are not available. When vegetables are cooked, a minimal amount of water should be used and the vegetables cooked only until tender to limit the loss of vitamins and nutrients. Legumes are good sources of vegetable protein in addition to fiber. Because most fruits, vegetables, and grains are also low in fat, they are good alternatives to high-fat foods.

Choose a Diet Low in Saturated Fats and Cholesterol

More than 40 years of extensive epidemiologic research has shown that heart disease is increased in populations and persons who consume diets high in saturated fats, *trans*-fats, and, to a lesser extent, cholesterol (2). For this reason, it is prudent to limit one's combined intake of dietary saturated and *trans* fatty acids to less than 10% of total energy intake, and to limit dietary cholesterol intake to less than 300 mg per day (1,2). In the past, these recommendations were part of a general recommendation to reduce the total dietary fat intake. More recently, however, dietary guidelines have recognized that diets rich in mono- and polyunsaturated fats, especially the ω-3 fatty acids, eicosapentenoic acid (EPA) and docosahexaenoic acid (DHA), and, possibly, α-linolenic acid, are beneficial in reducing the risks of adverse cardiovascular events (1–4, 20). Thus, current dietary fat intake recommendations allow a wide range of total dietary fats, from 20% to 35% of energy intake, and focus more specifically on reducing the intakes of the saturated and *trans* fatty acids known to increase the risk of heart disease and increasing the intakes of the polyunsaturated fatty acids known to decrease the risk of heart disease. Nonetheless, it is important to recognize that, for some individuals, reducing dietary fat intake may aid in preventing excessive consumption of dietary energy and, thus, help maintain body weight. The evidence that low-fat diets reduce the risk of developing various cancers is no longer compelling (21–26).

Beef, pork, liver and other organ meats, processed meats and cold cuts, whole milk, nondairy creamers, cheese, ice cream, eggs, butter, margarine, mayonnaise, lard, shortening, salad and cooking oils, deep-fried foods of all types, pastries, doughnuts, cookies, pie crusts, and cakes are the major sources of fat, saturated fat, and cholesterol in the American diet. Further, various prepared foods often contain significant amounts of "hidden" fat. An informed consumer *always* reads the label. A good rule of thumb for reducing cholesterol and total and saturated fat intake is to limit one's daily intake of meat, fish, and poultry to two to three servings (cooked weight of no more than about 5 to 6 oz).

Exercise Moderation in Salt and Sugar Consumption

The relationship between increasing dietary sodium intake and increasing blood pressure is a continuous function with no clear threshold effect. Further, more than 50 clinical trials and meta-analyses support the fact that lower sodium intakes lead to lower blood pressures (27). The most compelling evidence that lowering dietary salt intake is an important factor in maintaining a normal blood pressure and reducing blood pressure in hypertensive individuals is the DASH sodium trial (18,28–30). Based on these data, the *Dietary Guidelines for Americans* recommends limiting sodium intake to less than 2,300 mg per day (approximately 1 teaspoon of table salt) (1). Achieving this goal, however, can be very difficult because the principal sources of salt are processed and prepared foods, over which the consumer has little control other than nonconsumption. The best, proven approach to this problem is to adopt the DASH dietary pattern (17,18,28–30).

The debate about dietary sugar intake is particularly vocal, although the data indicating that dietary sugars are harmful to health are far less compelling than those for salt and are based largely on epidemiologic associations or consumption trends over time (31).

In fact, the only convincing medical consequence of excessive sugar intake is the development of dental caries, and, even here, sugar intake is only one of many contributing factors. No evidence is available to indicate that sugars *per se* cause many of the problems commonly attributed to them, such as hyperactivity, obesity, and diabetes. Additionally, no evidence indicates that "added sugars" produce effects different from those of intrinsic sugars, and absolutely no controlled data have demonstrated long-term beneficial effects of low-sugar diets at any level. Because dietary sugars are often consumed in foods that have a lower density of other nutrients, the principal reasons for recommending moderate sugar consumption are to prevent the overconsumption of unnecessary calories, to allow for consumption of more healthful, nutrient-dense foods by reducing the contribution of sugars to satiety, thus limiting "dilution" of the intake of other essential nutrients in the diet. Nonetheless, these arguments also apply to selective overconsumption of the other macronutrients, especially fat, and are not unique to sugars alone. In controlled feeding studies, diets with a high sugar content do not promote weight gain if energy intake is maintained at the isocaloric level.

Drink Alcoholic Beverages in Moderation, If at All, and Don't Smoke

The evidence for the detrimental effects of smoking on health is overwhelming. Although data now suggest that one and two alcoholic drinks daily for women and men, respectively, may reduce the risk for cardiovascular disease, far more ample evidence indicates that excessive consumption of alcohol has significant detrimental effects on health, including increased risks for hypertension, stroke, liver disease, accidents, violent behavior, and suicide. Additionally, alcohol intake appears to increase the risk of developing some cancers, but not others (32–36). For these reasons, one should consider whether any consumption of alcoholic beverages is prudent. Further, because the risks of alcohol consumption during embryogenesis and fetal development are well established (37), pregnant women and women of childbearing age who may become pregnant should not consume alcohol.

Moderate Your Protein Intake

The estimated average requirement (EAR) for protein in adults of both sexes is 0.66 g/kg/day, with a corresponding recommended dietary allowance (RDA) of 0.8 g/kg/day (15,16). The RDA for protein represents about 10% of dietary energy intake for young adults. There is no evidence to indicate that intakes above the RDA have any benefit, although modest increments, representing about 12% to 15% of total energy intake or 1.0 to 1.2 g/kg/day, are more likely to be consistent with current lifestyle and dietary habits in the United States. These increments should be from plant protein sources rather than from animal proteins. Sources of animal protein are not only more expensive as a rule, but are also generally high in fat calories, saturated fat, and cholesterol. Additionally, prolonged high intakes of animal protein are suspected to contribute to renal failure, reduced bone density, and cancers of the breast and colon, although the evidence is not compelling. However, elimination of all animal sources of protein is not necessarily desirable because these foods are the only source of vitamin B_{12} the best source of readily absorbable iron, and a good source of zinc.

Maintain an Adequate Intake of Calcium

Adequate cellular function, skeletal growth, and proper bone and dental mineralization require the essential nutrient calcium. All but about 1% of total body calcium is found within bones and teeth. Accelerated rates of calcium deposition occur at or near the onset of puberty and continue during the adolescent growth spurt. The net gain of bone calcium during early adolescence is a critical determinant in the prevention of osteoporosis much later in life. After menarche, net bone calcium deposition rates fall, and by the age of about 20, bone calcium accretion is essentially complete. Thus, consumption of adequate dietary calcium intake is especially important for teenagers, particularly girls. An adequate intake (AI) of calcium is 1,300 mg daily for adolescent boys and girls 9 to 18 years of age (16,38). Similarly, maintaining optimal bone mineralization during young adult life is equally important.

For adult men and women between the ages of 19 and 50, the calcium AI is 1,000 g per day (16,38). Pregnancy or lactation does not alter the values for adolescent or adult women (16,38) (see Chapter 4).

The principal dietary sources of calcium are milk and milk products. To maintain the dietary objective of reduced saturated fat intake, the best approach to achieving adequate calcium intake is consumption of low-fat or nonfat milk and milk products in addition to fruit juices and soy products with added calcium. Although calcium is also found in various dark green leafy vegetables, the oxalic acid in some of these vegetables (e.g., spinach) makes the calcium less bioavailable (39). Ensuring adequate calcium and vitamin D intakes are critical for preventing osteoporotic fractures (40); however, there is little evidence that consuming calcium at intake levels above the recommended AI has additional protective effects against such fractures (40,41) although long-term clinical trials using calcium supplements are bedeviled by a low rate of compliance (41,42). The tolerable upper intake level (UL) of calcium is 2.5 g per day for children and adults (16,38).

Do Not Take Unnecessary Dietary Supplements in Excessive Amounts

Except for selected persons in special circumstances, nutritional needs can be met with ordinary foods. Approximately half of adults in the United States take a vitamin or mineral supplement with some regularity. A single daily multivitamin and mineral supplement containing 100% of the RDA is not known to be harmful, but neither is it known to be beneficial for the vast majority of persons already meeting their nutritional needs by consuming a regular diet. By and large, persons who take supplements are those who are more likely to consume an adequate diet. Little evidence is available to indicate that such persons will reap a sizable health "dividend" from this form of nutrition "insurance." At the present time, no convincing direct evidence indicates that the consumption of "pharmacologic" amounts of vitamins, minerals, antioxidants, and other food constituents of unknown or dubious function has any direct, long-term effect of preventing chronic disease in persons who consume a balanced diet containing essential nutrients at the RDA level (43). In fact, the evidence is just the opposite and consuming large amounts of some supplements has been shown to increase mortality in randomized trials (44) (see Chapter 6).

IMPLEMENTATION GUIDANCE

For many years, the U.S. Department of Agriculture used its well-recognized food guide pyramid to provide practical guidance on how individuals might implement the nutritional recommendations in the *Dietary Guidelines for Americans*. In 2005, along with the release of the current Guidelines, the USDA released a revised tool called the MyPyramid food guidance system (45,46) (Figure 2-1). The pyramid was revised to accommodate the new scientific recommendations in the 2005 Guidelines, the new DRI recommendations published by the Institute of Medicine over the immediately preceding years, and new food composition and consumption data that had been published since the last revision of the pyramid. Additionally, the MyPyramid system was designed to improve consumer effectiveness by incorporating motivational and educational tools, including a Web site with interactive functions (45,46).

Specifically, although not intuitively, the color coding of the bands (Figure 2-1) is meant to remind the consumer that consumption of foods from all the different basic food groups is necessary for health maintenance. The different widths of the bands are meant to indicate the proportional differences in the amounts of foods that should be consumed from each food group. The progressive narrowing of the bands from the bottom to the top of the pyramid are meant to signify that more nutrient-dense foods should be consumed in each group. The person climbing the pyramid's steps symbolizes the principle that physical activity should be an essential part of everyday life. The slogan "steps to a healthier you" is meant to reinforce this principle as well as to indicate that an individual can improve his or her diet and lifestyle in steps or stages over a period of time (45,46). The most useful advantage of the MyPyramid food guidance system is the personalization provided at the

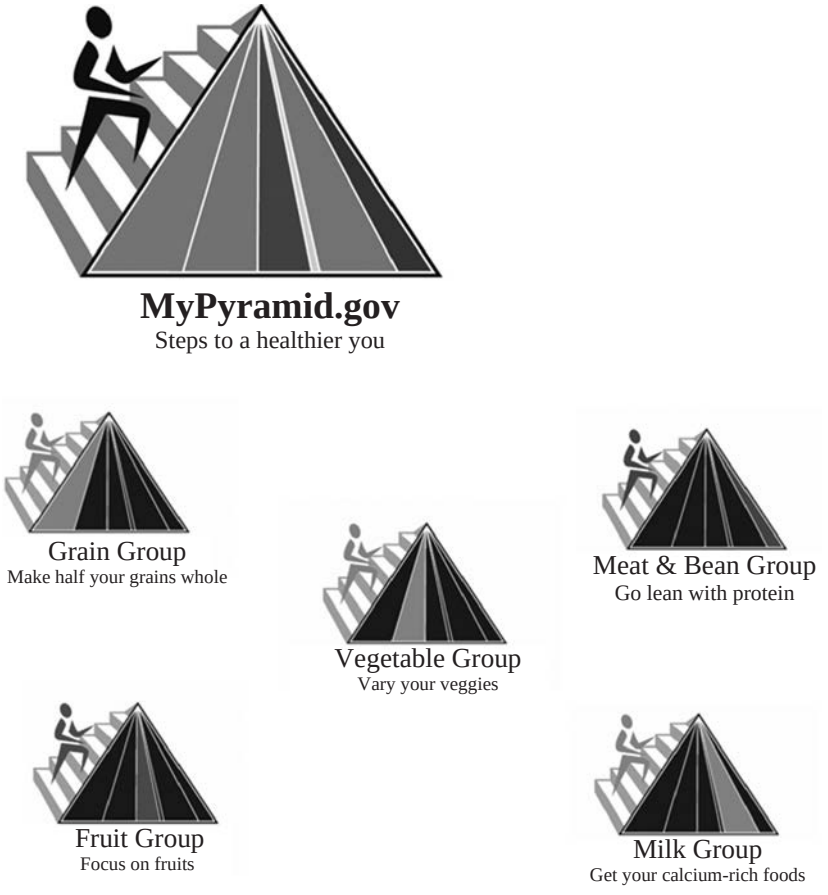


FIGURE 2-1. U.S. Department of Agriculture MyPyramid.

MyPyramid.gov website (45). Detailed information for both consumers and professionals can be found at this site. By using the function "Inside MyPyramid," individuals can obtain detailed information about the foods in each of the basic food groups. Additionally, and most importantly, an individual can obtain a personalized "MyPyramid Plan" by entering his or her age, gender, weight, height, and activity level. In addition, the personalized plan can be one designed for the individual's current weight, or one calculated to move the person gradually to a healthier weight (45). Further, by using the available utility called "MyPyramid Tracker," an individual can analyze his or her food intake, energy expenditure, and physical activity and obtain individualized recommendations. This feature includes access to the >8,000 food item database that is used in the national food consumption surveys, allowing calculation of specific nutrient intakes for the person in question. Using this function, a person can compare his or her intakes with Dietary Guidelines recommendations for basic food group, nutrient, and energy consumption and follow one's progress in meeting these guidelines over time.

It is important to realize that alternative approaches to dietary guidance exist as well. Based on extensive data from many large epidemiological studies conducted worldwide that relate dietary intake patterns to health outcomes, Walter Willett and Meir Stampfer at

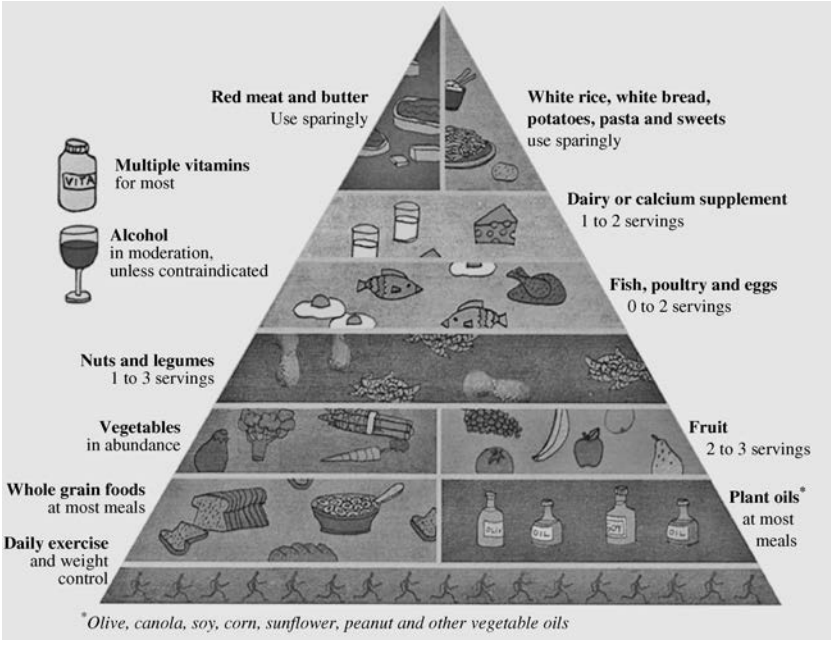


FIGURE 2-2. Alternative diet pyramid. (From Willet WC, Stampfer MJ. Rebuilding the food pyramid. *Scientific American Reports* 2006 (Dec.); 12–21.)

the Harvard School of Public Health have devised an alternative pyramidal guidance system designed to promote a healthy lifestyle (47) (Figure 2-2). This system differs significantly from the MyPyramid system by explicitly distinguishing between healthy and unhealthy kinds of fats, by minimizing intakes of red meat and refined carbohydrates, by placing less focus on the intake of dairy products, and by emphasizing the consumption of whole grains, mono- and polyunsaturated vegetable oils, fruits, and vegetables. Additionally, daily physical activity forms the base of the entire pyramid, emphasizing its importance in weight maintenance and health promotion (47) (Figure 2-2).

SUGGESTIONS FOR IMPLEMENTATION

The following are various practical suggestions for achieving the dietary guidelines outlined earlier.

1. **Cook at home as frequently as possible.** At home, you can best control the composition of your diet. Restaurant food, particularly "fast food," tends to be high in saturated fat, cholesterol, and salt. If you eat out, ask the chef to prepare food the way you want it. After all, that's his or her job, and you're paying the bill.
2. **Start shopping in the supermarket produce department.** Continue around the perimeter of the store, where fresh foods, unprocessed foods, fish, poultry, and dairy products are generally located. Avoid processed foods, and be careful not to consume too many foods that can contribute more calories to your diet than nutrients.
3. **Always read the label.** ***REPEAT: Always Read the Label.*** With the present vast array of food technologies and the plethora of foods prepared accordingly and obtainable in today's supermarket, it is impossible to know the actual composition of a processed food without reading the label. Virtually all processed foods must carry the food label

described in Appendix C. The information on the label provides a good guide to the calories in a product, in addition to the content of fat, saturated and *trans* fat, protein, carbohydrate and total sugars, sodium, calcium, iron, and vitamins A and C. Reading the label will help you identify hidden sources of dietary fat.

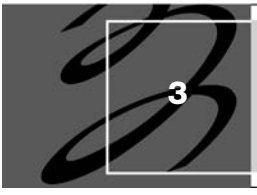
4. **Understand the difference between grams of fat and percentage of calories from fat.** The dietary guidelines discussed earlier include moderating total fat intake between 20% and 35% of total calorie intake. While 8 oz of plain yogurt made from whole milk contains 8 g of fat and 150 calories, nearly 50% of the calories in the yogurt come from fat because 8 g of fat provides 72 cal.
5. **Steam, broil, bake, or microwave foods** to avoid increasing the fat content. Use nonstick cookware and very little oil when sautéing. Stir-frying is an additional acceptable alternative because proper stir-frying techniques require intense heat but almost no fat. However, stir-fried foods obtained in many oriental restaurants are often not low in fat because excessive oil is used in the frying process.
6. Slowly **wean yourself from adding salt** while cooking or eating. Proper seasoning with herbs and spices helps reduce the need for salt. The taste for salt is largely acquired, and once you adapt to the taste of unsalted food, you will find salted food "too salty." Adopt a diet high in fresh fruits and vegetables. This will not only reduce your salt intake, it will increase your intake of potassium, an additional beneficial factor in lowering blood pressure.
7. **Maintain calcium intake** by consuming low-fat or nonfat dairy products. Although dairy products are the best source of dietary calcium, full-fat dairy products are also the second largest source of saturated fats after meats, the leading source. However, a very large array of reduced-fat or nonfat dairy products of all descriptions is now available in supermarkets, in addition to a variety of calcium-fortified juices and other products. These facilitate attaining the adult AI for calcium without jeopardizing the goals for fat reduction.
8. **Avoid fads and "magic bullets."** Excellent nutritional health can be achieved by following the sensible dietary guidelines discussed previously. No fad diet has ever been shown to provide better nutrition, and many have been shown to provide less than adequate nutrition. Similarly, no individual plant, animal, biochemical, or chemical "magic bullet" has ever been shown to achieve effects beyond those provided by a nutritionally adequate diet alone.

References

1. U. S. Department of Health and Human Services. U.S. Department of Agriculture. *Dietary Guidelines for Americans, 2005* 6th ed. Washington, DC: U.S. Government Printing Office, January 2005. http://www.healthierus.gov/dietaryguidelines; http://www.health.gov/dietaryGuidelines.
2. Krauss RM, Eckel RH, Howard B, et al. AHA Scientific Statement: AHA dietary guidelines: Revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation*. 2000;102:2284.
3. Kris-Etherton P, Eckel RH, Howard BV, et al. AHA Science Advisory: Lyon diet heart study: Benefits of a Mediterranean-style, national cholesterol education program/American Heart Association step I dietary pattern on cardiovascular disease. *Circulation*. 2001;103:1823–1825.
4. Kris-Etherton PM, Harris WS, Appel LJ, et al. Editorial: Omega-3 fatty acids and cardiovascular disease: New recommendations from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2003;23:151–152.
5. Goldberg IJ, Mosca L, Piano MR, et al. AHA Science Advisory: Wine and your heart: A science advisory for healthcare professionals from the Nutrition Committee, Council on Epidemiology and Prevention, and Council on Cardiovascular Nursing of the American Heart Association. *Circulation*. 2001;103:472–475.
6. Goldstein LB, Adams R, Alberts MJ, et al. AHA/ASA Guideline: Primary prevention of ischemic stroke: A guideline from the American Heart Association/American Stroke Association Stroke Council: Cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Stroke*. 2006;37:1583–1633.
7. Buse JB, Ginsberg HN, Bakris GL, et al. AHA/ADA Scientific Statement: Primary prevention of cardiovascular diseases in people with diabetes mellitus: A scientific statement from the American Heart Association and the American Diabetes Association. *Circulation*. 2007;115:114–126.
8. Sacks FM, Lichtenstein A, Van Horn L, et al. Editorial: Soy protein, isoflavones, and cardiovascular health: A summary of a statement for professionals from the American Heart Association Nutrition Committee. *Arterioscler Thromb Vasc Biol*. 2006;26:1689–1692.

9. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA*. 2002;288:1723–1727.
10. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA*. 2006;295:1549–1555.
11. Department of Health and Human Services. National Center for Health Statistics. Prevalence of overweight and obesity among adults: United States, 2003–2004. http://www.cdc.gov/nchs/products/pubs/pubd/hestats/overweight/overwght_adult_03.htm.
12. Department of Health and Human Services. National Center for Health Statistics. U.S. Obesity Trends 1985–2005. http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/
13. Mora S, Yanek LR, Moy TF, et al. Coronary heart disease: Interaction of body mass index and Framingham Risk Score in predicting incident coronary disease in families. *Circulation*. 2005;111:1871–1876.
14. Narayan KMV, Boyle JP, Thompson TJ, et al. Effect of BMI on lifetime risk for diabetes in the U.S. *Diabetes Care*. 2007;30:1562–1566.
15. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academies Press, 2005.
16. Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press, 2006.
17. Lin P-H, Aickin M, Champagne C, et al. Perspectives in practice. Food group sources of nutrients in the dietary patterns of the DASH-sodium trial. *J Am Diet Assoc*. 2003;103:488–496.
18. Appel LJ, Brands MW, Daniels SR, et al. AHA Scientific Statement: Dietary approaches to prevent and treat hypertension: A scientific statement from the American Heart Association. *Hypertension*. 2006;47:296–308.
19. Heber D. Vegetables, fruits and phytoestrogens in the prevention of diseases. *J Postgrad Med*. 2004; 50:145–149.
20. Wang C, Harris WS, Chung M, et al. n-3 fatty acids from fish or fish-oil supplements, but not α-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: A systematic review. *Am J Clin Nutr*. 2006;84:5–17.
21. Mazhar D, Waxman J. Dietary fat and breast cancer. *Q J Med*. 2006;99:469–473.
22. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: The women's health initiative randomized controlled dietary modification trial. *JAMA*. 2006;295:629–642.
23. Chlebowski RT, Blackburn GL, Thomson CA, et al. Dietary fat reduction and breast cancer outcome: Interim efficacy results from the women's intervention nutrition study. *J Natl Cancer Inst*. 2006;98:1767–1776.
24. Smith-Warner SA, Stampfer MJ. Fat intake and breast cancer revisited. *J Natl Cancer Inst*. 2007;99:418–419.
25. Genkinger JM, Hunter DJ, Spiegelman D, et al. A pooled analysis of 12 cohort studies of dietary fat, cholesterol and egg intake and ovarian cancer. *Cancer Causes Control*. 2006;17:273–285.
26. Smith-Warner SA, Ritz J, Hunter DJ, et al. Dietary fat and risk of lung cancer in a pooled analysis of prospective studies. *Cancer Epidemiol Biomarkers Prev*. 2002;11:987–992.
27. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate*. Washington, DC: National Academies Press, 2004.
28. Sacks FM, Svetkey LP, Vollmer WM, et al., for the DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet: DASH-sodium collaborative research group. *N Engl J Med*. 2001;344:3–10.
29. Vollmer WM, Sacks FM, Ard J, et al., for the DASH-Sodium Trial Collaborative Research Group. Effects of diet and sodium intake on blood pressure: Subgroup analysis of the DASH-sodium trial. *Ann Intern Med*. 2001;135:1019–1028.
30. Bray GA, Vollmer WM, Sacks FM, et al., for the DASH-Collaborative Research Group. A further subgroup analysis of the effects of the DASH diet and three dietary sodium levels on blood pressure: Results of the DASH-Sodium Trial. *Am J Cardiol*. 2004;94:222–227.
31. Drewnowski A. The real combination of added sugars and fats to obesity. *Epidemiol Rev*. 2007 [Epub ahead of print].
32. Smith-Warner SA, Spiegelman D, Shiaw-Shyuan Y, et al. Alcohol and breast cancer in women: A pooled analysis of cohort studies. *JAMA*. 1998;279:535–540.
33. Freudenheim JL, Ritz J, Smith-Warner SA, et al. Alcohol consumption and risk of lung cancer: A pooled analysis of cohort studies. *Am J Clin Nutr*. 2005;82:657–667.
34. Cho E, Smith-Warner SA, Ritz J, et al. Alcohol intake and colorectal cancer: A pooled analysis of 8 cohort studies. *Ann Intern Med*. 2004;140:603–613.
35. Genkinger JM, Hunter DJ, Anderson KE, et al. Alcohol intake and ovarian cancer risk: A pooled analysis of 10 cohort studies. *Br J Cancer*. 2006;94:757–762.
36. Lee JE, Hunter DJ, Spiegelman D, et al. Alcohol intake and renal cell cancer in a pooled analysis of 12 prospective studies. *J Natl Cancer Inst*. 2007;99:801–810.
37. Riley EP, McGee CL. Fetal alcohol spectrum disorders: an overview with emphasis on changes in brain and behavior. *Exp Biol Med*. 2005;230:357–365.
38. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride*. Washington, DC: National Academies Press, 1997.

39. Morris J, Nakata PA, McConn M, et al. Increased calcium bioavailability in mice fed genetically engineered plants lacking calcium oxalate. *Plant Mol Biol.* 2007;64:613–618.
40. Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: A prospective study among postmenopausal women. *Am J Clin Nutr.* 2003;77:504–511.
41. Prince RL, Devine A, Dhaliwal SS, et al. Effects of calcium supplementation on clinical fracture and bone structure: Results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Arch Intern Med.* 2006;166:869–875.
42. Prince RL, Devine A, Dhaliwal SS, et al. Does daily calcium supplementation reduce the risk of clinical fractures in elderly women? *Nature Nat Clin Pract Rheumatol.* 2007;3:18–19.
43. Bleys J, Miller ER III, Pastor-Barriuso R, Appel LJ, et al. Vitamin-mineral supplementation and the progression of atherosclerosis: A meta-analysis of randomized controlled trials. *Am J Clin Nutr.* 2006;84:880–887.
44. Bjelakovic G, Nikolova D, Gluud LL, et al. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: Systemic review and meta-analysis. *JAMA.* 2007;297:842–857.
45. U.S. Department of Agriculture. http://www.mypyramid.gov/
46. Haven J, Britten P. MyPyramid—The complete guide. *Nutr Today.* 2006;41:253–259.
47. Willet WC, Stampfer MJ. Rebuilding the food pyramid. *Sci Am Rep.* 2006 (Dec.); 12–21.



3 RECOMMENDATIONS FOR HEALTHY ELDERLY ADULTS

INTRODUCTION

Definitions

Aging is a continuous function, and one does not suddenly pass from young to elderly at any specific time. Furthermore, chronologic age alone is not a particularly precise indicator of biologic or functional age because of differences in genotypes, individual characteristics, such as physical ability and mental health, and environmental circumstances, all of which vary widely among people as they age. No uniform legal criteria exist. At age 60, a person can participate in the benefits of the Older Americans Act, but the same person does not receive Medicare or full Social Security benefits until age 65. Society has its own arbitrary definition. Age 60 defines an old-age pensioner in the United Kingdom. Many banks, theaters, shops, and service organizations in the United States offer discounts or special services to senior citizens, but the eligibility criteria for the designation "senior citizen" vary widely. At age 50, a person can join the largest information, advocacy, and service group for older adults in the United States, the AARP (formerly the American Association of Retired Persons). Only recently, the U.S. Census Bureau recognized the demographic heterogeneity of the elderly by classifying them into three groups: ages 65 through 74, 75 through 84, and 85 or older.

Population Trends

In the year 2000, the median age of the United States population reached 35.3 years, the highest in the nation's history. At the time, 12.4% of the population was 65 years of age or older and 1.5% of the population was 85 years of age or older (1). Given that the U.S. population in 2007 has grown to nearly 302 million people, more than 37 million Americans are aged 65 or older and 4.5 million are 85 years of age or older (1). In the year 2000, in fact, there were already nearly 1.5 million individuals over the age of 90 and about 50,000 centenarians living in the United States. By the year 2050, demographers project that nearly 80 million people in the United Stataes will be 65 years of age or older.

Even more importantly, the elderly population is getting older. In 1980, the "oldest old" (those aged 85 years or more) numbered 2.2 million; today, there are about twice as many in the nation. In 2010, the number is expected to increase to 6 million and in 2050 will rise to approximately 18 million, when the last "baby boomers" reach the age of 85. Similar trends occur in aging populations worldwide, although the elderly population is growing proportionately faster in the developing world compared with the growth rate observed in developed countries.

Life Expectancy

During the twentieth century, the average life expectancy of an American increased dramatically. In 1900, average life expectancy was approximately 50 years, and only 0.03% of people survived to the age of 100. In 2003, life expectancy was 74.8 years for men and 80.1 years for women (2). A person aged 65 today can expect to live an additional 18.4 years and a centenarian can expect to survive for another 2.6 years (2). During the first half of the 20th century, the principal contributor to the gain in life span reflected the improved survival of infants and children because of immunization, treatment of infectious diseases, and public health sanitary measures, including safe food and water supplies. In 1990, only 87.6% of infants survived the first year while today this figure is 99.3% (2). In the latter half of the 20th century, the principal gains in survivorship occurred mostly in the elderly population. Today's average 65-year-old man lives more than 3 years longer and the average 65-year-old woman today lives more than 6 years longer than corresponding adults who reached age 65 in 1990.

Nonetheless, there remain significant disparities in life expectancy. On average, women live more than 5 years longer than men (2) and life expectancy remains significantly different among black and white individuals of either gender (2,3). On average, white women have the highest life expectancy, 80.5 years, and black women live 76.1 years. The life expectancy of white men is 75.3 years, but black men live only to 69.0 years, on average. The reasons for these disparities are discussed elsewhere (2,3). Population distribution by age and sex are shown in Figure 3-1.

Dietary Intakes

The National Health and Nutrition Examination Surveys (NHANES) have collected successive, cross-sectional data on the health and nutritional status of representative adults from across the nation for nearly four decades. In persons over the age of 60, dietary energy intake declines with increasing age and the median energy intakes for both men and women are below the estimated energy requirements (EERs) for sedentary adults (4). On average, elderly subjects consume about 33% of their dietary energy as fat, with about 10% coming from saturated fats (4,5). Median cholesterol intake is less than 200 mg per day (4,5). About 16% of dietary energy comes from the intake of protein (4), a percentage equivalent to approximately 60 to 70 grams of dietary protein. This amount would satisfy the protein RDA for men and women above the age of 51 (6).

Average calcium intake, however, is about half the adequate intake (AI) level; important medical issues relating to adequate calcium intake are discussed later. Vitamin E intake is about 60% of the estimated average requirement (EAR) level, but it is difficult to accurately assesses dietary vitamin E intakes, and the average intake of potassium is about 50% of the RDA for potassium (4,7,8). However, median intakes of thiamin, riboflavin, niacin, pyridoxine, vitamin B_{12}, vitamin A, vitamin C, iron, selenium, copper, and phosphorus are above their respective EAR levels (4,7,8). Median intakes of folic acid, magnesium, and zinc were approximately equivalent to the EAR for each, and sodium intakes well exceeded recommended tolerable upper intake levels (UL) (4,7,8). These current NHANES data are consistent with various other surveys of dietary energy and calcium intake in elderly adults and with earlier data reported from the NHANES study itself from 1988 to 1994 when deficient calcium intakes were observed in about 70% to 75% of elderly men and 87% of elderly women, and inadequate zinc intakes were observed in 35% to 45% of elderly subjects (9).

Vitamin D levels tend to be low in elderly adults who do not consume vitamin D-fortified dairy products. Vitamin E intakes were low, but this was likely the result of

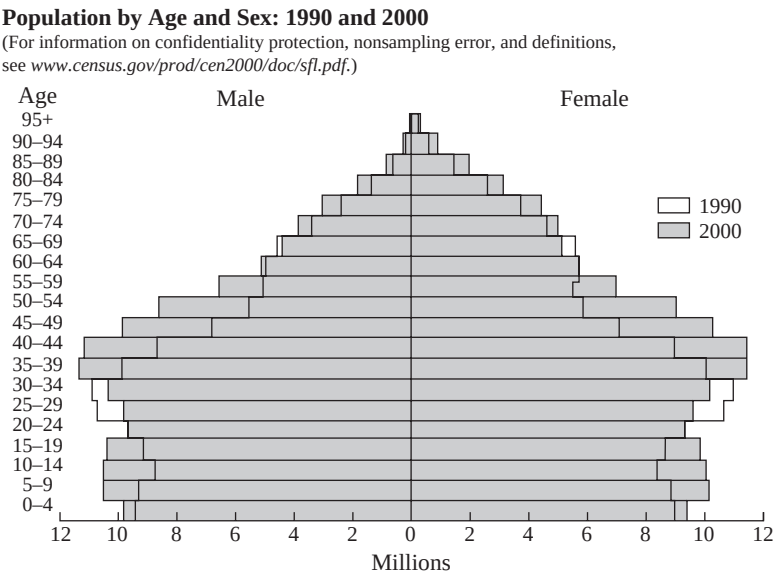


FIGURE 3-1. Distribution of U.S. population by age and sex in 1990 and 2000.
Source: U.S. Census Bureau Census 2000 Summary File 1:1990 Census of Population, *Central Population Charecteristics.* United States (1990 CP 1.1).

underreporting because of the inability to estimate the amounts and types of fats and oils used in food preparation and due to incomplete data on vitamin E content of food sources in available databases. Because of the currently increased use of polyunsaturated oils, which contain vitamin E, the intake of this vitamin is almost certainly more than sufficient in most persons. Further, according to the NHANES data, the dietary intakes of protein, iron, niacin, thiamine, riboflavin, and vitamin C in elderly adults were within acceptable ranges. Information from assorted other studies on dietary intakes of folate and vitamin B_{12} support the fact that a significant minority of elderly adults does not consume these vitamins in adequate amounts or do not absorb them adequately. The latter is particularly relevant in the case of vitamin B_{12} because absorption of the vitamin is well documented to be impaired in elderly individuals secondary to atrophic gastritis. Nonetheless, one of the considerations in interpreting the adequacy of nutrient intake levels based on the RDAs is the fact that healthy adults may be consuming less than the RDAs because these are set at the upper end of the normal distribution curve to ensure adequacy in nearly all persons. A convenient, conventional population index of potential nutrient inadequacies is the fraction of the population consuming less than two-thirds of the RDA. Recommended dietary allowances are not intended to be used to estimate inadequacy of nutrient intakes in specific individuals. However, an individual who is generally consuming more than the RDA is very unlikely to have an inadequate intake of a specific nutrient. The best estimate for assessing the adequacy of nutrient intakes in an individual is to compare the average observed nutrient intakes of an individual with the respective EAR for those nutrients, when EAR values for the nutrient(s) are known. Nonetheless, the amount of a nutrient necessarily adequate for an individual elderly adult is not known accurately or precisely without specific biochemical testing. As a practical, general clinical guideline, however, elderly persons are more likely to be nutritionally deficient as they advance in age, if they are poor, if they suffer from significant chronic medical problems (particularly gastrointestinal or neurological disorders), or if they are hospitalized or institutionalized.

PATHOBIOLOGY OF AGING

Theories of Aging

Although the specific causes of some progeroid syndromes have been identified (10–12), there are no known specific causes for the common forms of aging. A variety of currently debated theories are discussed in detail elsewhere (13) and include the following (Table 3-1): (a) evolutionary theories that view aging as the result of the diminishing advantage of natural selection that is the consequence of survival beyond the age of reproductive fitness (14); (b) genetic molecular theories that postulate that aging results from effects at the gene level that cause molecular damage to DNA, alter gene expression, reduce the accuracy and fidelity of translation, and related effects (15–17); (c) cellular theories that relate the generation of aging to the consequences of repeated damage to cellular components and metabolic processes, oxidative damage to the proteins or the mitochondrial electron transfer system or to mitochondrial DNA (18), the intracellular accumulation of altered proteins resulting from oxidative damage, glycosylation or other posttranslational modifications, or

TABLE 3-1. Theories of Aging

Biological level/theory	Description
Evolutionary	
Mutation accumulation[a]	Mutations that affect health at older ages are not selected against.
Disposal soma[a]	Somatic cells are maintained only to ensure continued reproductive success; after reproduction, soma becomes disposable.
Antagonistic pleiotropy[a]	Genes beneficial at younger age become deleterious at older ages.
Molecular	
Gene regulation[a]	Aging is caused by changes in the expression of genes regulating both development and aging.
Codon restriction	Fidelity/accuracy of mRNA translation is impaired due to inability to decode codons in mRNA.
Error catastrophe	Decline in fidelity of gene expression with aging results in increased fraction of abnormal proteins.
Somatic mutation	Molecular damage accumulates, primarily to DNA/genetic material.
Dysdifferentiation	Gradual accumulation of random molecular damage impairs regulation of gene expression.
Cellular	
Cellular senescence-telomere theory	Phenotypes of aging are caused by an increase in frequency of senescent cells. Senescence may result from telomere loss (replicative senescence) or cell stress (cellular senescence).
Free radicals [a]	Oxidative metabolism produces highly reactive free radicals that subsequently damage lipids, protein, and DNA.
Wear-and-tear	Accumulation of normal injury.
Apoptosis	Programmed cell death from genetic events or genome crisis.
System	
Neuroendocrine[a]	Alterations in neuroendocrine control of homeostasis result in aging-related physiological changes.
Immunologic[a]	Decline of immune function with aging results in decreased incidence of infectious diseases but increased incidence of autoimmunity.
Rate of living	Assumes a fixed amount of metabolic potential for every living organism (live fast, die young).

[a] From Weinert BT, Timiras PS. Physiology of aging. Invited reviews: Theories of aging. *J Appl Physiol.* 2003;95:1706–1716. With permission.

to accelerated apoptosis and cell senescence (19,20); and (d) system theories that consider aging to be the consequence of slow, but inexorable failure of fine regulatory control within major biological systems such as the neuroendocrine or immunological systems (13). One of the most consistent and compelling observations, valid across a wide range of species from *Caenorhabditis elegans* to primates, is that animals whose energy intakes are modestly restricted live longer than those consuming a full complement of calories (21). There are suggestive data that these observations may apply to man as well, but we do not know with any confidence that calorie restriction will extend human life span (22).

PATHOPHYSIOLOGIC CONSEQENCES OF AGING

Body Composition

Lean body mass declines approximately 6% per decade after age 30. To a significant extent, this decrement is a consequence of diminished physical activity rather than of the aging process itself. Muscle, a principal component of lean mass, is altered both structurally and functionally as one ages (23), largely on the basis of reduced mitochondrial energy production through ATP. These changes result in frailty and disability. One additional consequence of the decline in lean body mass is a corresponding increase in fat mass. Many elderly persons are overweight or frankly obese. Others who fit within normal weight-for-height ranges are relatively obese—that is, for the same BMI as young adults, elderly adults have a disproportionate increase in adipose tissue. Nonetheless, data across a wide variety of studies support the observation that a BMI in the overweight range is not associated with increased mortality in elderly individuals and BMIs in the obese range are associated with only a slight increase in mortality (24).

Protein and Energy Metabolism

Rates of whole body protein turnover (synthesis and breakdown) decline slightly with age. When corrected for the age-related changes in lean body mass, however, protein turnover rates are relatively constant throughout adult life. No consistent body of evidence indicates that protein needs are altered by aging. Even though the rates of protein synthesis and breakdown are slowed, body net nitrogen balance is achieved at the same levels of dietary protein intake in aging persons. For these reasons, the dietary reference intake (DRI) values for protein are not altered in elderly adults (6). However, there are some limited data in adults that suggest that the RDA for protein in elderly individuals should be increased slightly (25,26). Energy is expended principally by the metabolically active lean tissues. Because lean body mass declines with age, energy expenditure declines correspondingly. Thus, to maintain energy balance, an elderly person must consume fewer calories. This is the most uniform and consistent nutritional consequence of aging. DRI equations for estimating the energy requirements of elderly individuals are provided below.

Organ System Function

During aging, a generalized decline in organ function involves the gastrointestinal system, but not primarily its absorptive or nutrient assimilation properties. Aging is associated with diminished smell and taste, particularly the loss of sweet and salty tastes. A reduction in salivary flow, loss of teeth, and disturbances of swallowing and esophageal dysfunction may be noted. Many persons experience various forms of discomfort associated with eating, including heartburn, gas, and constipation. Approximately 10% to 30% of persons over age 60 have atrophic gastritis, and its prevalence reaches about 40% over age 80. Although originally thought to be a consequence of aging, atrophic gastritis is principally the consequence of infection with *Helicobacter pylori*. Reductions in gastric acid, pepsin, and intrinsic factor lead to slower emptying of mixed meals and diminished absorption of iron, folate, and vitamin B_{12}. Bacterial overgrowth in the proximal small bowel is sometimes an accompanying feature. Pancreatic secretion is usually normal, but some people have a reduced hepatic function that is secondary to reduced blood flow, not to altered hepatocyte function. Nonetheless, except for the vitamins and iron mentioned above,

absorption of macronutrients, vitamins, and minerals is generally normal. Aging is also associated with declining cardiac, pulmonary, and renal function and with diminished secretion of growth hormone, which some believe contributes to the decline in lean body and muscle mass (sarcopenia) that accompanies aging, although growth hormone replacement does not convincingly rectify the problem. Furthermore, a decrease in cell-mediated immunity is manifested by decreased numbers of circulating T cells and defective cell-mediated immune responses, which may contribute to the morbidity associated with aging. Humoral immunity is generally less severely affected, but the incidence of autoimmune disorders is increased. Atherosclerosis, arthritis, osteoporosis, diabetes, assorted cancers, and diminished sight and hearing are all commonly present. To varying degrees, these conditions can limit mobility and access to food, affect mood, and diminish appetite.

NUTRITIONAL ISSUES IN ELDERLY PERSONS

Food Access and Selection

Economics. A reduced income generally accompanies aging. This reduction often entails alterations in dietary habits, including the elimination of relatively high-priced items such as meat. Food insecurity is a significant issue in maintenance of nutritional health in elderly adults whose incomes are limited (27,28).

Mobility. Because of physical infirmities, various illnesses, and, especially, loss of a means of transportation, the mobility of elderly adults is often limited. Such limitation can directly or indirectly restrict access to food purchase. It is particularly important for a medical caregiver to know whether elderly individuals under their care have the ability to travel to places where they can purchase food.

Psychosocial and Neurologic Problems. Depression, mental deterioration, and other psychosocial and neurologic problems, may lead to loss of the desire to shop, a diminished appetite, forgetfulness about meals, or frank inability to eat. A medical caregiver must carefully assess an elderly patient's mental state and evaluate the practical consequences of functional inadequacies.

Bone Health: Calcium, Phosphorus, Vitamin D, and Vitamin K

Osteopenia secondary to osteoporosis and osteomalacia is a significant problem in the elderly, particularly elderly women (29,30,31). The resultant increased incidence of fractures is responsible for a very high level of physical and psychosocial disabilities in addition to substantial financial costs. Obligatory calcium losses increase, but calcium intake and absorption decline with age. Reduced absorption may be a consequence of decreased vitamin D function, in turn caused by the combined effects of reduced dietary intake, decreased exposure to sunlight and capacity of the aged skin to synthesize vitamin D (32), reduced intestinal absorption of the vitamin, and reduced hepatic and renal ability to hydroxylate vitamin D to its active form (33,34). The average calcium intake in women over age 51 is only about 50% of the AI level (4,7,9). The calcium intake of men over age 51 is somewhat better, but the mean is still only about 60% of the AI, which has been set at 1,200 mg for persons over 51 years of age (35) because of growing evidence that increasing calcium intake in the elderly is a factor in maintaining bone density when accompanied by an adequate intake of vitamin D (31,35,36), including several recent meta-analyses of randomized controlled trials (37–41). Correspondingly, the AI level for vitamin D has been set at 10 μg cholecalciferol daily (400 IU vitamin D) for adults aged 51 through 70 years and 15 μg per day (600 IU vitamin D) for adults older than age 70 (35), although many believe that these levels are not sufficient to ensure optimal vitamin D status in aged individuals (32–34,37–39,41). Nonetheless, while one major study, the Women's Health Initiative clinical trial (42), was able to show improved hip bone density in women receiving calcium and vitamin D supplements, it was unable to demonstrate a reduced risk of hip fracture. When data analysis was restricted to those women known to be compliant, the risk of hip fracture was decreased. Importantly, however, study subjects had suffered an

unintended, increased risk of kidney stones (42). The Women's Health Initiative was also unable to confirm a suggested protective effect of vitamin D in reducing colorectal cancer (43) although a subsequent quantitative meta-analysis suggested that a daily intake of 1,000 to 2,000 IU per day of vitamin D can reduce the incidence of such cancers (44).

Phosphorus intake is generally higher than calcium intake, and most diets provide ample phosphorus. Data from various NHANES surveys show that the elderly generally meet the current EAR levels of phosphorus of 580 mg per day or the RDA of 700 mg per day (35).

In addition to its function in blood coagulation, Vitamin K also functions as a cofactor for the vitamin K-dependent carboxylase that catalyzes the posttranslational formation of γ-carboxyated bone proteins such as osteocalcin (45). The AI levels for vitamin K have been set at 120 μg per day for men and 90 μg per day for women (46,47). A recent meta-analysis of randomized, controlled trials of vitamin K supplementation lasting longer than 6 months showed that such supplementation significantly reduced hip and vertebral fractures (48). These, and other data (49), may provide support for recommending an increase in the DRI levels for vitamin K in the elderly (49).

Antioxidants

The theory that highly reactive free radicals, generated during normal oxidative metabolic processes, contribute to the tissue deterioration of aging is a highly popular one. The free radicals damage tissue through membrane lipid peroxidation, oxidation of proteins and carbohydrates, and abnormal DNA cross-linking. Considerable experimental evidence indicates that these events occur at the cellular level during normal metabolism, Therefore, to prevent or ameliorate the consequences of aging, many people consume increased quantities of antioxidants: vitamins E and C, β-carotene, selenium (a cofactor for glutathione peroxidase), and cofactors of the superoxide dismutase system, including copper, zinc, and manganese (50,51,52). However, repeated randomized, controlled trials have failed to confirm the benefit of antioxidant supplements (52) in preventing atherosclerosis (53) and most cancers (54–57), or in improving bone mineral density (58), cognitive function (59), or mood (60), and the expert panel that reviewed antioxidant nutrients for the Institute of Medicine's Dietary Reference Intake report (61) concluded that there was no convincing evidence to support recommendations for antioxidant supplementation in humans (61). In fact, a recent extensive meta-analysis of antioxidant primary and secondary prevention trials reported that β-carotene, vitamin A, and vitamin E supplement users had an *increased*, rather than a decreased, risk of mortality (62). Vitamin C and selenium users were not at an increased risk of death (62). Nonetheless, high intakes of antioxidants either as dietary constituents or as supplements appear to be beneficial for preventing age-related macular degeneration, but not cataracts (63,64), although the Food and Drug Administration concluded that there was not sufficient evidence to assert that leutein and zeaxanthin were effective in reducing either macular degeneration or cataracts (65). Further, while there are indications that antioxidants may be beneficial in reducing prostate cancer, stomach cancer, and skin squamous cell carcinoma (57), additional data are required for confirmation and confidence. (See also Chapter 15 for discussion of the antioxidant hypothesis.)

The levels of vitamin C in plasma and leukocyte levels decline with age, apparently as a function of intake, as absorption, metabolism, and excretion do not change consistently with age. Data on saturation of the vitamin C body pool have led to the recommendation of an EAR for vitamin C of 60 mg per day in women and 75 mg per day in men. Corresponding RDAs are 75 mg per day in women and 90 mg per day in men (47,61).

As discussed, vitamin E intakes are repeatedly reported as low in dietary surveys. Vitamin E deficiency is not a clinical problem in the United States. The dietary survey results are the combined effect of inadequate accounting for all the vitamin E present in foods and some debate over whether the DRI recommendations for vitamin E are too high (66). The EAR for vitamin E in the elderly is 12 mg per day of α-tocopherol and the RDA is set at 15 mg per day of α-tocopherol (47,61).

Selenium is an essential cofactor for the antioxidant enzyme glutathione peroxidase, and dietary selenium requirements are based on intake levels that maximize plasma glutathione peroxidase levels (61). No evidence has been found that selenium requirements or biochemical markers of selenium status are affected by age (61). Selenium intake varies enormously

among populations according to the selenium content of the soils. Although various surveys have reported low selenium intakes in elderly adults, NHANES III, which evaluated more than 6,000 persons over the age of 51, showed a mean selenium intake of 134 μg in men between the ages of 51 and 70, and 112 μg in men over the age of 70. Corresponding values for women were 94 μg and 83 μg. The fifth percentile intake levels in all groups were at or above the current RDA of 55 μg per day for men and women over the age of 50 years (61). There is also no reason to suspect selenium deficiency on the basis of dietary intake information, food composition data, or available metabolic indices. Selenium deficiency is a problem only in areas of the world where food is grown in soil with an extremely low selenium content and in patients undergoing long-term parenteral nutrition with selenium-deficient solutions. As discussed above, there is no compelling reason to consume excess dietary selenium to improve cardiovascular function or prevent cancer. Because selenium is stored in the body, excessive consumption can result in toxicity, and a UL of 400 μg has been established (61).

Fiber

Dietary fibers are the nondigestible, nonabsorbable carbohydrates and lignin present in food plants, principally fruits, vegetables, legumes, and grains (6). Increasing the intake of dietary fiber is an important adjunct in the treatment of constipation in the elderly, although abdominal discomfort, flatulence, and potentially decreased absorption of iron and zinc may be the unwanted side effects of excess consumption. The mechanism by which dietary fiber improves gastrointestinal mobility is unknown, but presumably is related to its bulking effects. A high intake of dietary fiber is also associated with a modest reduction in serum LDL cholesterol and may reduce circulating triglyceride concentrations and attenuate the blood glucose response to meals (6). Epidemiological studies have demonstrated that high fiber intakes are associated with a reduced risk of diabetes, coronary heart disease, and colon cancer, but data on the protective effects of dietary fiber intakes on the risks of developing breast, endometrial, ovarian, and prostate cancers are not compelling (6). Because fiber is an essential component of fruits, vegetables, and whole grains, the cancer protective effects of fiber cannot definitely be attributed to fiber alone. Nonetheless, improving the intake of foods high in dietary fiber is a healthful nutritional option for elderly adults because these foods contain important vitamins and minerals. The AI level of 14 g per 1,000 kcal per day for dietary fiber in adults was set primarily on the intake level in epidemiological studies that was associated with a protective effect against coronary heart disease (6).

Folic Acid, Vitamin B_{12}, and Pyridoxine

Vitamin B_{12} levels are often low in elderly adults (67,68). Aging, *per se*, does not alter vitamin B_{12} absorption. However, B_{12} malabsorption is more frequent in elderly adults because of an increased prevalence of pernicious anemia and atrophic gastritis. The absorption of vitamin B_{12} is altered in atrophic gastritis not because of any abnormal intrinsic factor, but because dissociation of the vitamin from food proteins is limited by inadequate acid digestion (69,70). Additionally, because of bacterial overgrowth in the proximal small intestine secondary to atrophic gastritis, some vitamin B_{12} that reaches the small bowel is metabolized by bacteria rather than absorbed. Vitamin B_{12} is found only in animal products, and some elderly adults have low levels of B_{12} because of their decreased consumption of meat, fish, poultry, and dairy products. Often, this is for economic reasons, although the prevalence of B_{12} deficiency is not increased in the low-income elderly. Elderly vegetarians are particularly at risk for vitamin B_{12} deficiency.

The current RDA for vitamin B_{12} is 2.4 μg per day for elderly men and women (47,71), and nearly all elderly Americans consumed this level in NHANES III. However, because atrophic gastritis is present in about 10% to 30% of elderly adults (72), the vitamin B_{12} present in food may not be absorbed adequately in many elderly people. Thus, elderly individuals are advised to meet their vitamin B_{12} requirements by consumption of food products fortified with vitamin B_{12} or by taking a dietary supplement containing vitamin B_{12} (68,71,72). This is one of the very few circumstances in human nutrition in which supplements are recommended in preference to foods to satisfy nutrient requirements. Nonetheless, even though vitamin B_{12} inadequacy is known to impair cognition and other neurological functions, and to increase the circulating level of homocysteine, a known risk factor for

cardiovascular disease and osteoporotic fractures, recent studies provide no support for the fact that lowering homocysteine levels with vitamin B_{12}, or with vitamin supplement mixes that include vitamin B_{12}, can improve cardiovascular, bone, or neurological risks (73–78).

Folate is widely distributed in foods, although the amounts and bioavailability of folate in various foods are the subject of some debate because of analytical issues. However, synthetic folic acid, the form found in supplements and fortified food products, is nearly twice as bioavailable (>85%) as naturally occurring food folate (~50%). National dietary survey data show that average folate intakes in elderly individuals are within the range of the EAR, but red blood cell folate levels, the best clinical index of folate status, show diminished folate status in a small fraction of elderly adults. The prevalence of low folate nutriture is higher in persons with low incomes, whose intake of foods high in folate is reduced. Although folate absorption is limited by the atrophic gastritis often found in elderly adults, a compensatory increase in folate production occurs in bacterial overgrowth in the proximal small bowel. Folate is required to convert homocysteine to methionine, and folate intakes below 400 μg per day are associated with elevated homocysteine levels, an independent risk factor for coronary artery and cerebrovascular disease (71). For this reason, the RDAs for folate have recently been revised upward to 400 μg of dietary folate equivalents in elderly men and women (47,71). Dietary folate equivalents take into account the fact that synthetic folic acid is more bioavailable than dietary food folates, particularly when taken without food. Thus, one dietary folate equivalent equals 1 μg of food folate, 0.6 μg of folic acid from fortified foods or from a folic acid supplement taken with food, or 0.5 μg of a folic acid supplement taken on an empty stomach (47,71). Because grain products are now fortified with folic acid and because many elderly adults consume other folic acid fortified products as well as take dietary supplements containing folic acid, there is concern that some elderly adults who take supplements are at greater risk for exceeding the tolerable UL of folate (1 mg per day) than they are at risk for folate inadequacy. This is particularly important, because many individuals are consuming dietary folate supplements to reduce plasma homocysteine levels; however, a recent meta-analysis of randomized control trials could not show the benefit of folic acid supplementation on the risk of cardiovascular disease (79), although a recent small trial has demonstrated improved cognitive performance with folic acid supplementation (80).

Pyridoxine (vitamin B_6) intakes appear to vary widely, although incomplete vitamin B_6 food composition data limit our ability to quantify them with any precision. Although the data are very limited, vitamin B_6 needs appear to increase with age (71), and estimated average intakes for individuals over the age of 50 are 1.4 mg per day for men and 1.3 mg per day for women. The corresponding RDAs are 1.7 mg per day for men and 1.5 mg per day for women (71). Although various earlier nutrition surveys and biochemical assessments of vitamin B_6 status suggest that vitamin B_6 intake may be inadequate in a significant fraction of elderly men and women, the most recent national survey data show that median pyridoxine intakes in men exceed, and median pyridoxine intake in women approximate, the EAR (8), and clinical evidence of vitamin B_6 deficiency is rare.

Thiamin, Riboflavin, and Niacin

Thiamin status, measured by the erythrocyte transketolase assay, has been highly variable and reported to be low in small to significant fractions of elderly adults. In NHANES III, only about 10% of elderly Americans consumed less than the RDA of thiamin. The most significant clinical cause of thiamin deficiency in aging adults is alcohol consumption coupled with decreased dietary intake. The current EAR for thiamin is 0.9 mg per day in women and 1.0 mg per day in men, with corresponding RDAs of 1.1 and 1.2 mg per day (47,71).

Riboflavin absorption and metabolism are unaffected by aging, and riboflavin status appears to be normal in most aging adults. In NHANES III, only about 10% of American men and women consumed less than the RDA for riboflavin set at 1.1 mg per day and 1.3 mg per day, respectively (47,71). The corresponding EAR for riboflavin is 0.9 mg per day in women and 1.0 mg per day in men (47,71). Milk and other dairy products (except butter) are the best and most convenient dietary sources of riboflavin for elderly adults.

Niacin requirements do not change with age. In NHANES III, only about 10% of elderly Americans consumed less than the RDA of niacin, which has been set at 14 mg per

day for elderly women and 16 mg per day for elderly men (47,71). Corresponding EARs are 11 mg per day and 12 mg per day, respectively (47,71).

Vitamin A

The vitamin A requirement does not increase with age and there is evidence that elderly individuals retain vitamin A in liver and fat stores longer than younger people. Vitamin A intakes also appear to increase with age. Thus, vitamin A status appears adequate in the majority of elderly men and women, although about one-third of Americans older than 70 questioned in NHANES III reported that they consume less than two-thirds of the current RDA for vitamin A. This apparent contradiction is explained by the fact that the RDA may be excessive for elderly adults, since vitamin A absorption appears to be increased and plasma clearance of vitamin A decreased in elderly persons. The EARs for vitamin A are 500 μg retinol activity equivalents (RAE) daily for women and 625 μg RAE per day for men, with corresponding RDAs of 700 μg RAE and 900 μg RAE daily for women and men, respectively.

Except in special circumstances, vitamin A supplementation is to be avoided because it has known serious toxicity. Further, there is now a body of evidence suggesting that excess vitamin A intake increases the risk of osteoporotic fractures (81–85), although not all the data support this association (81,85–87).

Magnesium, Iron, Zinc, Iodine, and Other Minerals

Magnesium intake in about 50% of elderly adults is generally below two-thirds of the current RDA levels (35). Because magnesium occurs in many foods and in drinking water (albeit at highly variable concentrations), and because clinical magnesium deficiency is rare, the EAR (265 mg per day for women; 350 mg per day for men) and the RDA (320 mg per day for women; 420 mg per day for men) may be set at very generous levels, particularly in light of the fact that the RDAs were based on the results of magnesium balance studies in a limited number of elderly men and the results of a single study in young adult women extrapolated to elderly women (35). Recently, pooled data from 27 controlled balance studies have provided experimental support for the lowering of the DRI values for magnesium (88). In elderly persons, however, one must be aware that digoxin, diuretics, and impaired renal tubular function may enhance magnesium loss. Laxatives also can augment intestinal magnesium loss, but magnesium-containing laxatives and antacids are common sources of excessive magnesium intake in the elderly. Although there has been some suggestion that increasing magnesium intake may have a cardiovascular protective effect, this effect was not observed in the Women's Health Study (89).

Iron absorption does not diminish with age, and iron status understandably improves in women following the cessation of menses. Most anemia in the elderly is the result of iron deficiency, chronic inflammation, or chronic renal disease (90), but anemia due to a deficient dietary intake of iron is not the most prevalent cause of iron deficiency anemia. When iron deficiency occurs in the elderly, one must first eliminate possible causes of chronic occult blood loss and the reduction of nonheme iron absorption associated with atrophic gastritis, which account for most cases of iron deficiency, before searching for other reasons related to inadequate dietary iron intake. NHANES surveys show that iron intake averages about 13 to 14 mg per day in elderly men and about 9 to 10 mg per day in elderly women. The EAR for iron is 5 mg per day in postmenopausal women and 6 mg per day in men (46,47). The corresponding RDA values are 8 mg per day in both elderly men and women (46,47).

Zinc absorption declines with age, but endogenous zinc losses also decline, so zinc balance is preserved. Various dietary intake surveys show that many elderly adults generally consume less than two-thirds the current RDA levels for zinc, set at 11 mg per day for men and 8 mg per day for women (46,47). Nonetheless, normal plasma zinc levels are generally maintained, and only 3% of elderly adults in NHANES II had plasma zinc levels in a deficient range. Little clinical evidence of zinc deficiency has been found in elderly adults, although some have questioned whether a lowered zinc status may contribute to the altered immune competence of the elderly, because zinc is important to maintaining immune function. Given this consideration, it appears prudent to aim for the current zinc RDA intake levels, although there is little cause for concern as zinc intakes are above the EAR levels of 6.8 mg per day for women and 9.4 mg per day for men (46,47).

Iodine has only a single essential function, which is thyroid hormonogenesis. Iodine levels in the United States have declined slightly during the last decade. However, since the introduction of iodized salt in 1924, the use of iodate dough oxidizers in bread making, and recent patterns of increased seafood consumption, there has been little evidence of clinical iodine deficiency. The EARs for iodine in elderly individuals are not different from those in young adults—95 μg per day for both men and women (46,47). The current RDA for iodine is set at 150 μg per day for both sexes (46,47). One gram of iodized salt provides 76 μg of iodine.

The DRI values for other micronutrient minerals are the same in young and elderly adults. The RDA for copper is 900 μg per day and for molybdenum 45 μg per day (46,47). The AI level set for manganese is 2.3 mg per day in men and 1.8 mg per day in women (46,47).

Drugs

Elderly adults use almost 25% of the over-the-counter drugs sold in the United States, and the vast majority of elderly adults take at least one prescription drug daily. Many adults take multiple medications daily. Some common drugs known to affect nutritional status are listed in Table 3-2. Conversely, nutrients affect drug absorption, as shown in Table 3-3. Thus, both physicians and the elderly adults under their care are responsible for assessing potential nutrient–drug interactions. The physician must be alert to potentially detrimental nutritional effects of the prescribed therapeutic regimen. Likewise, the patient must pay close attention to the package insert and physician's instructions regarding the timing of drug ingestion relative to the consumption of food and drink (see Table 1-22 for the effect of vitamins and minerals on drug action, and Table 1-23 for the effect of drugs on food intake).

PRACTICAL NUTRITIONAL ADVICE FOR ELDERLY ADULTS

The principal biologic factor underlying the altered nutrient needs of the elderly adult is the decline in energy expenditure secondary to a reduction of lean body mass. Because of this decline, less macronutrient intake is needed to satisfy energy needs; concomitantly, the intake of various vitamin and mineral constituents of the diet is diminished. Additional physical infirmities, dentures, neuropsychological disorders, social conditions, and economic constraints may aggravate further the inability to consume diets adequate in quantity or quality. In this context, then, elderly individuals should consume foods that are nutrient-dense, that is, those that have a high ratio of nutrients to energy.

Although it is clear that significant biologic, physical, and psychosocial differences exist between very old (>85 years of age) and moderately old (between 70 and 85 years of age) persons, no specific dietary standards for the very old, who often have special needs because of physical disabilities or mental infirmity, have been generally agreed on. However, if elderly adults remain physically and mentally capable of following the dietary guidelines outlined in Chapter 2 for young adults, with the relatively minor adjustments discussed below, it is unlikely that they will become malnourished. Finally, regular physical exercise and a balanced diet do more to promote and preserve health in elderly adults than all other so-called health supplements, "nutritional" or otherwise. The desire and ability of elderly adults to prepare and consume a wide variety of foods are often enhanced by simple companionship during grocery shopping and meals.

Resting energy expenditure declines as a function of age and lean body mass after age 50. Regular exercise, particularly resistance exercise, can help preserve strength and lean mass. Reduced physical activity further contributes to the loss of lean mass and decline in energy expenditure seen in the elderly. Based on available energy expenditure data, the DRI committee developed equations for daily EERs. These are

Men:

$$EER = 662 - (9.53 \times \text{age [y]}) + PA \times [(15.91 \times \text{wt [kg]}) + (539.6 \times \text{ht [m]})]$$

Women:

$$EER = 354 + (6.91 \times \text{age [y]}) + PA \times [(9.36 \times \text{wt [kg]}) + (726 \times \text{ht [m]})]$$

TABLE 3-2. Effects of Drugs on Nutrients

Drug	Effect
Anti-infective agents	
Amikacin, gentamicin, sisomicin, tobramycin	Hypokalemia, hypomagnesemia, and hypocalcemia; increased urinary potassium and magnesium loss
Aminosalicylic acid	Decreased vitamin B_{12} and fat absorption
Amphotericin B	Increased urinary excretion of potassium and decreased serum potassium and magnesium levels
Capreomycin	Hypokalemia, hypomagnesemia, and hypocalcemia
Cycloserine	Decreased serum folate
Isoniazid	Pyridoxine deficiency
Neomycin	Decreased absorption of carotene, iron, vitamin B_{12}, and cholesterol
Rifampin	Decreased serum 25-hydroxycholecalciferol level
Sulfasalazine	Folate deficiency
Tetracycline	Decreased absorption of Ca, Mg, Fe, Zn
Anticoagulants	
Warfarin	Decreased vitamin K-dependent coagulation factors
Cardiovascular drugs	
Colestipol	Decreased absorption of fat-soluble vitamins and folic acid
Hydralazine	Pyridoxine deficiency
Sodium nitroprusside	Decreased total serum vitamin B_{12}
Thiazides, ethacrynic acid	Increased urinary loss of Na, K, Mg, Zn, P
Triamterene, spironolactone	Increased urinary loss of K, Ca, Mg, Zn
CNS drugs	
Alcohol	Increased urinary loss of Mg, Zn, Ca
Aspirin	Decreased serum folate
Monoamine oxidase inhibitors	
Isocarboxazid	Decreased leukocyte and platelet ascorbic acid levels
Pargyline	Increased iron loss
Phenelzine	Increased sensitivity to tyramine-containing foods; possible development of hypertensive crisis
Tranylcypromine	Pyridoxine deficiency
Phenobarbital	Decreased serum vitamin K_1
Phenytoin	Decreased serum folate, calcium, 25-hydroxycholecalciferol levels
Electrolyte drugs	
Potassium chloride, slow-release	Decreased vitamin B_{12} absorption
Gastrointestinal drugs	
Aluminum hydroxide	Decreased absorption of iron, phosphate, vitamin B_{12}
Cholestyramine	Decreased absorption of vitamins A, D, E, K, and B_{12} and folate along with decreased absorption of inorganic phosphate and fat
H_2-receptor antagonists, proton pump inhibitors	Decreased absorption of protein-bound vitamin B_{12}
Laxatives	Increased fecal loss of Na, K, Ca, Mg
Mineral oil	Decreased absorption of vitamins A, D, E, and K
Hormones	
Glucocorticoids	Increased urinary loss of K, Ca; increased Na absorption
Oral contraceptives	Decreased serum folate, pyridoxine deficiency, riboflavin deficiency
Other agents	
Colchicine	Decreased absorption of vitamin B_{12}, sodium, potassium, fat, nitrogen
Penicillamine	Pyridoxine deficiency

From Weinsier RL, Morgan SL. *Fundamentals of Clinical Nutrition.* St. Louis: Mosby, 1993:186, with permission.

TABLE 3-3. Effects of Nutrients on Drugs

Food can change the absorption characteristics of certain drugs. The mechanisms for the effect include physicochemical interactions with food in the intestinal lumen, changes in gastric emptying, competition between drug and food components for absorption, and altered first-pass hepatic kinetics. These effects can decrease the efficacy of the drug or increase the absorption of the drug, so that a greater response to the drug or a side effect results. There can be large differences from one formulation to another, and no drug class effects can be assumed. The reader should check carefully with the literature and the manufacturer's information concerning individual formulations, especially when the therapeutic window is narrow. Listed below are some of the drugs commonly used that can be affected by food and instructions on how to minimize the effects of food on the drug.

Decreased absorption (avoid taking these drugs with food; take at least 1 hour before or 2 hours after a meal)

Ampicillin	Erythromycin stearate	Levodopa/carbidopa	Quinidine
Atenolol	Ferrous salts	Lisinopril	Sotalol
Calcium carbonate	Folic acid	Methotrexate	Sulfamethoxazole
Captopril	Furosemide	Omeprazole	Tetracycline
Cephalexin	Iron	Penicillin G	Trimethoprim
Cloxacillin	Isoniazid	Penicillin V	Zinc sulfate
Digitalis	Isosorbide	Phenytoin	
Disopyramide	Lansoprazole	Propantheline	

Increased absorption (food will alter the amount of the drug absorbed; therefore, the drug should be taken at the same time(s) each day relative to meals)

Buspirone	Gemfibrozil	Methoxsalen	Propranolol
Carbamazepine	Griseofulvin	Metoprolol	Spironolactone
Chlorothizide	Labetalol	Nifedipine	Sulfadiazine
Diazepam	Lithium	Nitrofurantoin	Trazodone
Dicumarol	Lovastatin	Phenytoin	

Delayed absorption (food will delay the absorption of these drugs but not the overall amount absorbed; these drugs should be taken at least 1 hour before or 2 hours after a meal)

Acetaminophen	Hydrochlorothiazide	Pentobarbital	Suprofen
Aspirin	Hydrocortisone	Pentoxifylline	Tocainide
Cimetidine	Indomethacin	Sulfisoxazole	
Doxycycline	Ketoprofen		

From Weinsier RL, Morgan SL. *Fundamentals of Clinical Nutrition.* St. Louis: Mosby, 1993:188, with permission; and Utermohlen V. In: Shils ME, Olson JA, Shike M, et al., eds., *Modern Nutrition in Health and Disease,* 9th ed. Baltimore: Williams & Wilkins, 1998:1621.

where PA is the subject's physical activity quotient. The values of PA range from 1.0 for the activities of usual daily living to 1.11 to 1.12 for women and men, respectively, for the activities of daily life plus an additional 30 to 60 minutes of moderate activity daily; to 1.25 to 1.27 for at least an additional 60 minutes of moderate daily activity; to 1.45 to 1.48 for the activities of daily life plus an additional 180 minutes of moderate activity or at least an additional 60 minutes of moderate daily activity plus an additional 60 minutes of vigorous activity (6,47). Needless to say, unless there is otherwise clear evidence for a very active lifestyle, it is most prudent to initially estimate the PA quotient in elderly subjects as 1.00 or 1.11 to 1.12. These equations were recently tested in individuals above the age of 70 and proved to be accurate, although the DRI equations tended to underestimate energy expended in physical activity (91). However, as with all calorie intake recommendations at any age, the value initially estimated for an individual person must be tailored to the value that maintains body weight within a desirable range. Above the age of 80, and for persons who are physically inactive, either as a result of advanced age or physical incapacity, dietary energy intakes must be reduced correspondingly. Although there is no systematic evidence that dietary protein needs are increased in elderly adults, dietary protein intake is closely linked to dietary energy intake. Therefore, elderly adults with low energy intakes are also at risk for inadequate protein intakes, and medical caregivers should be alert to this possibility.

While there is no consensus that dietary nutrient intakes need to be drastically altered in otherwise healthy elderly adults, based on the risks discussed above, the *Dietary Guidelines for Americans* (Table 2-2) recommends that adults over the age of 50 consume B_{12} in its crystalline form (i.e., fortified foods or supplements) and consume extra vitamin D from vitamin D-fortified foods or supplements (Table 3-4). Fortified cereals are a good source of vitamin B_{12}, but it is important to read the label and confirm that the particular commercial cereal product is fortified with vitamin B_{12}. Vitamin D-fortified milk and orange juice are good sources of vitamin D. Nonetheless, many health care providers commonly recommend that elderly adults consider taking a multivitamin or mineral supplement that contains vitamin B_{12} (12 to 25 μg), vitamin D (400 IU), and up to 100% of the RDAs for the other essential nutrients. Because over-the-counter multivitamin and mineral preparations do not generally contain sufficient calcium to meet the requirements for calcium or enough vitamin D to provide this vitamin at the intake levels recommended by some authorities (up to 25 μg or 1,000 IU), other health care providers also often recommend

TABLE 3-4. Recommended Nutrient Intakes for Persons 51 Years of Age and Older

	Recommended dietary allowances[a]	
	Men	**Women**
Energy (kcal)	2,300	1,900
Protein (g)	63	50
Vitamin A (μg RAE)[b]		700
Vitamin C (mg)	90	75
Vitamin E (mg)[c]	15	15
Vitamin K (μg)	120	90
Thiamin (mg)	1.2	1.1
Riboflavin (mg)	1.3	1.1
Niacin (mg)[d]	16	14
Vitamin B_6 (mg)	1.7	1.5
Folate (μg)	400	400
Vitamin B_{12} (μg)[e]	2.4	2.4
Iron (mg)	10	10
Zinc (mg)	15	12
Phosphorus (mg)	700	700
Magnesium (mg)	420	320
Selenium (μg)	55	55
Iodine (μg)	150	150
Adequate intakes[f]		
Calcium (mg)	1,200	1,200
Vitamin D (μg)[g]	10	10

[a] From National Research Council, Food and Nutrition Board. *Recommended Dietary Allowances,* 10th ed. Washington, DC: National Academies Press, 1989.
[b] Retinol activity equivalents: 1 RAE = 1 μg all-*trans*-retinol or 6 μg β-carotene = 24 μg α-carotene and β-cryptoxanthin.
[c] As α-tocopherol, including *RRR*-α-tocopherol, the natural food form, and the 2*R*-stereoisomeric forms that occur in fortified foods and supplements, but not the 2*S*-stereoisomers that are also found in fortified foods and supplements.
[d] As niacin equivalents: 1 NE = 1 mg niacin or 60 mg dietary tryptophan.
[e] Because elderly individuals may malabsorb food-bound vitamin B_{12}, it is advisable for the elderly to meet the requirement by consuming foods fortified with vitamin B_{12} or with a supplement containing vitamin B_{12}.
[f] From Ramírez CL, Cadiñanos J, Varela I, et al. Human progeroid syndromes, aging and cancer: New genetic and epigenetic insights into old questions. *Cell Mol Life Sci.* 2007;64:155–170; Kirkwood T. Ageing: Too fast by mistake. *Nature.* 2006;444:1015–1017; Weinert BT, Timiras PS. Physiology of aging. Invited reviews: Theories of aging. *J Appl Physiol.* 2003;95:1706–1716; Kirkwood TBL. Evolution of ageing. *Mech Ageing Dev.* 2002;123:737–745.
[g] As cholecalciferol: 1 μg cholecalciferol = 40 IU of vitamin D. Above the age of 70 years, the daily recommended intake for vitamin D increases to 15 μg/day.

an additional supplement containing 400 to 800 mg of calcium and 200 to 600 U of vitamin D (92). Thus, an elderly individual might reach a daily intake of 25 μg (1,000 IU) of vitamin D by consuming three cups of vitamin-D fortified milk (7.5 μg), 1 cup of vitamin D-fortified orange juice (2.5 μg), and 15 μg of vitamin D as a supplement.

RESOURCES

Because of the ever-growing elderly population, a wide variety of public and private societal resources have become available. A selected small number of these are listed in Table 3-5.

TABLE 3-5. Selected Sources of Reliable Information for Elderly Adults

Administration on Aging
One Massachusetts Ave.
Suites 4100 and 5100
Washington, DC 20201
Tel. 202-619-0724
www.aoa.gov

Alzheimer's Association
225 North Michigan Ave.
Floor 17
Chicago, IL 60601-7633
Tel. 800-272-3900
www.alz.org

AARP
601 E St., NW
Washington, DC 20049
Tel. 888-687-2277
www.aarp.org

American Cancer Society
1599 Clifton Road, NE
Atlanta, GA 30329
Tel. 800-227-2345
www.cancer.org

American Diabetes Association
1701 North Beauregard St.
Alexandria, VA 22311
Tel. 800-342-2383
www.diabetes.org

American Federation for Aging Research
55 West 39th St., 16th Floor
New York, NY 10018
Tel. 888-582-2327
www.afar.org

American Geriatrics Society
Empire State Building
350 Fifth Ave., Suite 801
New York, NY 10118
Tel. 212-308-1414
www.americangeriatrics.org

American Heart Association
National Center
7272 Greenville Ave.
Dallas, TX 75231
Tel. 800-242-8721
www.americanheart.org

American Society for Nutrition
9650 Rockville Pike
Bethesda, MD 20814
Tel. 301-634-7050
www.nutrition.org

Department of Agriculture
1400 Independence Ave., SW
Washington, DC 20250
Tel. 202-720-2791
www.usda.gov

Gerontology Research Center, National Institute on Aging
5600 Nathan Shock Dr.
Baltimore, MD 21224-6825
Tel. 410-558-8110
www.grc.nia.nih.gov

National Resource Center for Health Promotion and Aging
c/o National Council on Aging
1901 L. Street, NW, 4th Floor
Washington, DC 20036
Tel. 202-479-1200
www.athealth.com/Consumer/rcenter/resource_data.cfm?TopicCF=Aging

National Institute on Aging
National Institutes of Health
Bldg. 31, Room 5C27
31 Center Drive, MSC 2292
Bethesda, MD 20892
Tel. 301-496-1752
www.nih.gov/nia

Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University
711 Washington St.
Boston, MA 02111-1524
Tel. 617-556-3000
www.hnrc.tufts.edu

References

1. U. S. Census Bureau. Census 2000. http://www.census.gov/main/www/cen2000.html
2. U.S. Department of Health and Human Services. National Center for Health Statistics. Centers for Disease Control and Prevention. United States Life Tables, 2003. *Natl Vital Stat Rep*. 2006;54.
3. Harper S, Lynch J, Burris S, et al. Trends in the black-white life expectancy gap in the United States, 1983–2003. *JAMA*. 2007;297:1224–1232.
4. Wright JD, Wang C-Y, Kennedy-Stephenson J, et al. U.S. Department of Health and Human Services. National Center for Health Statistics. Centers for Disease Control and Prevention. Dietary intake of ten key nutrients for public health, United States: 1999–2000. *Adv Data Vital Health Stat*. 2003; 334:1–4.
5. Ervin RB, Wright JD, Wang C-Y, et al. U.S. Department of Health and Human Services. National Center for Health Statistics. Centers for Disease Control and Prevention. Dietary intake of fats and fatty acids for the United States Population: 1999–2000. *Adv Data Vital Health Stat*. 2004;348:1–6.
6. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academies Press, 2005.
7. Ervin RB, Wang C-Y, Wright J. U.S. Department of Health and Human Services. National Center for Health Statistics. Centers for Disease Control and Prevention. Dietary intake of selected minerals for the United States population: 1999–2000. *Adv Data Vital Health Stat*. 2004;341:1–5.
8. Ervin RB, Wright JD, Wang C-Y. U.S. Department of Health and Human Services. National Center for Health Statistics. Centers for Disease Control and Prevention. Dietary intake of selected vitamins for the United States population: 1999–2000. *Adv Data Vital Health Stat*. 2004;339:1–4.
9. Ervin RB, Kennedy-Stephenson J. Mineral intakes of elderly adult supplement and non-supplement users in the Third National Health and Nutrition Examination Survey. *J Nutr*. 2002;132:3422–3427.
10. Navarro CL, Cau P, Lévy N. Molecular bases of progeroid syndromes. *Hum Mol Genet*. 2006;15: R151–R161.
11. Ramírez CL, Cadiñanos J, Varela I, et al. Human progeroid syndromes, aging and cancer: New genetic and epigenetic insights into old questions. *Cell Mol Life Sci*. 2007;64:155–170.
12. Kirkwood T. Ageing: Too fast by mistake. *Nature*. 2006;444:1015–1017.
13. Weinert BT, Timiras PS. Physiology of aging. Invited reviews: Theories of aging. *J Appl Physiol*. 2003;95: 1706–1716.
14. Kirkwood TBL. Evolution of ageing. *Mech Ageing Dev*. 2002;123:737–745.
15. Hekimi S, Guarente L. Genetics and the specificity of the aging process. *Science*. 2003;299:1351–1354.
16. Hamet P, Tremblay J. Genes of aging. *Metabolism*. 2003;52:5–9.
17. Kim SK. Common aging pathways in worms, flies, mice and humans. *J Exp Biol*. 2007;210:1607–1612.
18. Alexeyev MF, LeDoux SP, Wilson GL. Mitochondrial DNA and aging. *Clin Sci*. 2004;107:355–364.
19. Friguet B, Bulteau A-L, Chondrogianni N, et al. Protein degradation by the proteosome and its implications in aging. *Ann N Y Acad Sci*. 2000;908:143–154.
20. Higami Y, Shimokawa I. Apoptosis in the aging process. *Cell Tissue Res*. 2000;301:125–132.
21. Wolf G. Calorie restriction increases life span: A molecular mechanism. *Nutr Rev*. 2006;64:89–92.
22. Fontana L, Klein S. Aging, adiposity, and calorie restriction. *JAMA*. 2007;297:986–994.
23. Nair KS. Aging muscle. *Am J Clin Nutr*. 2005;81:953–963.
24. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. *Obesity Rev*. 2007;8: 41–59.
25. Evans WJ. Protein nutrition, exercise and aging. *J Am Coll Nutr*. 2004;23:601S–609S.
26. Chernoff R. Protein and older adults. *J Am Coll Nutr*. 2004;23:627S–630S.
27. Wellman NS, Weddle DO, Kranz S, et al. *J Am Dietary Assoc*. 1997;97:S120–S122.
28. Rose D. Economic determinants and dietary consequences of food insecurity in the United States. *J Nutr*. 1999;129:517S–520S.
29. Siris ES, Brenneman SK, Barrett-Connor E, et al. The effect of age and bone mineral density on the absolute, excess, and relative risk of fracture in postmenopausal women aged 50–99: Results from the National Osteoporosis Risk Assessment (NORA). *Osteoporos Int*. 2006;17:565–574.
30. Khosla S, Melton LJ. Osteopenia. *N Engl J Med*. 2007;356:2293–2300.
31. Heaney RP. Bone health. *Am J Clin Nutr*. 2007;85:300S–303S.
32. Heaney RP. Barriers to optimizing vitamin D_3 intake for the elderly. *J Nutr*. 2006;136:1123–1125.
33. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clinic Proc*. 2006;81:353–373.
34. Holick MF. The role of vitamin D for bone health and fracture prevention. *Current Osteoporosis Rep*. 2006;4:96–102.
35. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride*. Washington, DC: National Academies Press, 1997.
36. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285:785–795.
37. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation. A mega-analysis of randomized controlled trials. *JAMA*. 2005;293:2257–2264.

38. Boonen S, Lips P, Bouillon R, et al. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: Evidence from a comparative metaanalysis of randomized controlled trials. *J Clin Endocr Metab*. 2007;92:1415–1423.
39. Shea B, Wells G, Cranney A, et al. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocr Rev.* 2002;23:552–559.
40. Papadimitropoulos E, Wells G, Shea B, et al. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. *Endocr Rev.* 2002;23:560–569.
41. Bischoff-Ferrari HA. How to select the doses of vitamin D in the management of osteoporosis. *Osteoporosis Int*. 2007;18:401–407.
42. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354:669–683.
43. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med*. 2006;354:684–696.
44. Gorham ED, Garland CF, Garland FC, et al. Optimal vitamin D status for colorectal cancer prevention: A quantitative meta analysis. *Am J Prevent Med*. 2007;32:210–216.
45. Berkner KL. The vitamin K-dependent carboxylase. *Annu Rev Nutr*. 2005;25:127–149.
46. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Energy for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc*. Washington, DC: National Academies Press, 2001.
47. Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press, 2006.
48. Cockayne S, Adamson J, Lanham-New S, et al. Vitamin K and the prevention of fractures. Systematic review and meta-analysis of randomized controlled trials. *Arch Int Med*. 2006;166:1256–1261.
49. Booth SL. Vitamin K status in the elderly. *Curr Opin Clin Nutr Metab Care*. 2007;10:20–23.
50. Ervin RB, Wright JD, Reed-Gillette D. U.S. Department of Health and Human Services. National Center for Health Statistics. Centers for Disease Control and Prevention. Prevalence of leading types of dietary supplements used in the Third National Health and Nutrition Examination Survey, 1988–94. *Adv Data Vital Health Stat*. 2004;349:1–7.
51. Buettner C, Phillips RS, Davis RB, et al. Use of dietary supplements among United States adults with coronary artery disease and atherosclerotic risks. *Am J Cardiol.* 2007;99:661–666.
52. Verhagen H, Buijsse B, Jansen E, et al. The state of antioxidant affairs. *Nutr Today*. 2006;41:244–250.
53. Bleys J, Miller ER, Pastor-Barriuso R, et al. Vitamin-mineral supplementation and the progression of atherosclerosis: A meta-analysis of randomized controlled trials. *Am J Clin Nutr.* 2006;84:880–887.
54. Wright ME, Virtamo J, Hartman AM, et al. Effects of α-tocopherol and β-carotene supplementation on upper aerodigestive tract cancers in a large, randomized controlled trial. *Cancer*. 2007;109:891–898.
55. Bjelakovic G, Nagorni A, Nikolova D, et al. Meta-analysis: Antioxidant supplements for primary and secondary prevention of colorectal adenoma. *Aliment Pharmacol Ther*. 2006;24:281–291.
56. Reid ME, Duffield-Lillico AJ, Sunga A, et al. Selenium supplementation and colorectal adenomas: An analysis of the nutritional prevention of cancer trial. *Int J Cancer*. 2006;118:1777–1781.
57. Taylor PR, Greenwald P. Nutritional interventions in cancer prevention. *J Clin Oncol*. 2005;23: 333–345.
58. Wolf RL, Cauley JA, Pettinger M, et al. Lack of a relation between vitamin and mineral antioxidants and bone mineral density: Results from the Women's Health Initiative. *Am J Clin Nutr.* 2005;82:581–588.
59. Kang JH, Cook N, Manson J, et al. A randomized trial of vitamin E supplementation and cognitive function in women. *Arch Int Med*. 2006;166:2462–2468.
60. Rayman M, Thompson A, Warren-Perry M, et al. Impact of selenium on mood and quality of life: A randomized, controlled trial. *Biol Psychiatry*. 2006;59:147–154.
61. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: National Academies Press, 2000.
62. Bjelakovic G, Nikolova D, Gluud LL, et al. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention. Systematic review and meta-analysis. *JAMA*. 2007;297:842–857.
63. Seddon JM. Multivitamin-multimineral supplements and eye disease: Age-related macular degeneration and cataract. *Am J Clin Nutr.* 2007;85:304S–307S.
64. van Leeuwen R, Boekhoorn S, Vingerling JR, et al. Dietary intake of antioxidants and risk of age-related macular degeneration. *JAMA*. 2005;294:3101–3107.
65. Trumbo PR, Ellwood KC. Lutein and zeaxanthin intakes and risk of age-related macular degeneration and cataracts: An evaluation using the Food and Drug Administration's evidence-based review system for health claims. *Am J Clin Nutr.* 2006;84:971–974.
66. Horwitt MK. Critique of the requirement for vitamin E. *Am J Clin Nutr.* 2001;73:1003–1005.
67. Loikas S, Koskinen P, Irjala K, et al. Vitamin B12 deficiency in the aged: A population-based study. *Age Ageing*. 2007;36:177–183.
68. Park S, Johnson MA. What is an adequate dose of oral vitamin B_{12} in older people with poor vitamin B_{12} status? *Nutr Rev*. 2006;64:373–378.

69. Carmel R. *In vitro* studies of gastric juice in patients with food-cobalamin malabsorption. *Dig Dis Sci.* 1994; 39:2516–2522.
70. Hurwitz A, Brady DA, Schaal ES, et al. Gastric acidity in older adults. *JAMA.* 1997;278:659–662.
71. Institute of Medicine, National Academy of Sciences. Folate. In: *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin and Choline.* Washington, DC: National Academies Press, 2006.
72. Bailey LB. Folate and vitamin B_{12} recommended intakes and status in the United States. *Nutr Rev.* 2004; 62:S14–S20.
73. Ray JG, Kearon C, Yi Q, et al. Homocysteine-lowering therapy and risk for venous thromboembolism: A randomized trial. *Ann Int Med.* 2007;146:761–767.
74. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med.* 2006;354:1567–1577.
75. McMahon JA, Skeaff CM, Williams SM, et al. Lowering homocysteine with B vitamins has no effect on blood pressure in older adults. *J Nutr.* 2007;137:1183–1187.
76. Green TJ, McMahon JA, Skeaff CM, et al. Lowering homocysteine with B vitamins has no effect on biomarkers of bone turnover in older persons: A 2-y randomized controlled trial. *Am J Clin Nutr.* 2007;85: 460–464.
77. McMahon JA, Green TJ, Skeaff CM, et al. A controlled trial of homocysteine lowering and cognitive performance. *N Engl J Med.* 2006;354:2764–2772.
78. Kang JH, Irizarry MC, Grodstein F. Prospective study of plasma folate, vitamin B_{12}, and cognitive function and decline. *Epidemiology.* 2006;17:650–657.
79. Bazzano LA, Reynolds K, Holder KN, et al. Effect of folic acid supplementation on risk of cardiovascular diseases: A meta-analysis of randomized controlled trials. *JAMA.* 2006;296:2720–2726.
80. Durga J, van Boxtel MPJ, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: A randomised, double blind, controlled trial. *Lancet.* 2007;369: 208–216.
81. Barker ME, Blumsohn A. Is vitamin A consumption a risk factor for osteoporotic fracture? *Proc Nutr Soc.* 2003;62:845–850.
82. Feskanich D, Singh V, Willett WC, et al. Vitamin A intake and hip fractures among postmenopausal women. *JAMA.* 2002;287:47–54.
83. Michaëlsson K, Lithell H, Vessby B, et al. Serum retinol levels and the risk of fracture. *N Engl J Med.* 2003;348:287–294.
84. Melhus H, Michaëlsson K, Kindmark A, et al. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Ann Int Med.* 1998;129:770–778.
85. de Souza Genaro P, Araújo Martini L. Vitamin A supplementation and risk of skeletal fracture. *Nutr Rev.* 2004;62:65–72.
86. Rejnmark L, Vestergaard P, Charles P, et al. No effect of vitamin A intake on bone mineral density and fracture risk in perimenopausal women. *Osteoporos Int.* 2004;15:872–880.
87. Lim LS, Harnack LJ, Lazovich D, et al. Vitamin A intake and the risk of hip fracture in postmenopausal women: The Iowa Women's Health Study. *Osteoporos Int.* 2004;15:552–559.
88. Hunt CD, Johnson LK. Magnesium requirements: New estimations for men and women by cross-sectional statistical analyses of metabolic magnesium balance data. *Am J Clin Nutr.* 2006;84:843–852.
89. Song Y, Manson JE, Cook NR, et al. Dietary magnesium intake and risk of cardiovascular disease among women. *Am J Cardiol.* 2005;96:1135–1141.
90. Eisenstaedt R, Pennix BWJH, Woodman RC. Anemia in the elderly: Current understanding and emerging concepts. *Blood Rev.* 2006;20:213–226.
91. Blanc S, Schoeller DA, Bauer D, et al. Energy requirements in the eighth decade of life. *Am J Clin Nutr.* 2004;79:303–310.
92. Johnson MA. Nutrition and aging – practical advice for healthy eating. *JAMA.* 2004;59:262–269.

4 PREGNANCY AND LACTATION

NUTRITION DURING PREGNANCY

Studies in humans and animals indicate that nutrition during pregnancy influences not only the normal development of the fetus and immediate health of the newborn infant, but there are now also compelling data that nutrition during pregnancy influences the subsequent morbidity and mortality of the offspring when they are grown adults (1–10). We have long appreciated that low maternal weight before pregnancy, inadequate weight gain during pregnancy, and inadequate intake of protein and calories by the expectant mother are all associated with the delivery of low-birth-weight infants. Similarly, we have known for some time that low birth weight, in turn, is associated with increased perinatal mortality, impaired neurologic development, and a retarded postnatal growth pattern. More recently, however, compelling evidence has continued to accrue that infants born small, as a consequence of nutritional or other negative influences on fetal growth, are at increased risk for the development of hypertension, coronary artery disease, diabetes, and possibly other conditions during adult life (1–10). Current recommendations for nutrition during pregnancy stress the importance of a proper pattern of weight gain and an adequate intake of calories, protein, vitamins, and minerals to allow for optimal fetal development and the preservation of maternal health. These recommendations also stress evaluation of the mother, either before conception or early in pregnancy, for the presence of nutritional risk factors that might jeopardize the outcome of the pregnancy.

Energy and Protein Requirements

Resting metabolic rate increases about 5% during the first trimester of pregnancy, 10% during the second trimester, and 25% during the third trimester (11). Nonetheless, because the mother's activity declines on the order of 2% to 6% from her pre-pregnancy levels, a pregnant woman's total daily energy expenditure increases minimally during the first trimester of pregnancy, only 1% to 3% on average, rises modestly by about 5% to 6% during the second trimester, and continues to increase during the third trimester, averaging about 10% to 20% above that of the mother's pre-pregnancy total daily energy expenditure (11,12). It is also important to recognize that changes in energy expenditure increase significantly under circumstances of excessive gestational weight gain. Thus, inappropriately increased maternal energy intake leads to augmented deposition of calories in maternal fat stores, and increases the risk of poor maternal and fetal outcomes (11–13).

Thus, based on total daily energy expenditure data, and accounting for changes in maternal physical activity, dietary energy deposited in fetal tissue accretion, and dietary energy deposited in maternal organs supporting the fetus and in maternal fat stores, there is no recommended increase in the mother's estimated energy requirement (EER) during the first trimester of pregnancy, an increase in EER of about ~350 kcal per day during the second trimester, and an increase of approximately ~450 kcal per day during the last trimester (14).

The estimated average requirement (EAR) for dietary protein in adult, nonpregnant women is 0.66 g/kg/day, with a recommended dietary allowance (RDA) of 0.80 g/kg/day (14). Pregnancy requires no change in maternal EAR or RDA for dietary protein during the first trimester of pregnancy. During the second and third trimesters, protein intake allowances increase modestly to an EAR of 0.88 g/kg/day (an increase of approximately 20 g of protein daily) and an RDA of 1.1 g/kg/day (an increase of about 25 g per day). The calculated additional intakes of dietary protein are those required to support the

TABLE 4-1. Tissue and Nutrient Deposition during Pregnancy

	Week of gestation			
	10	**20**	**30**	**40**
Products of conception				
Fetus (g)	5	300	1500	3400
Placenta (g)	20	170	430	650
Amniotic fluid (g)	30	250	750	800
Maternal tissue gain				
Uterus (g)	140	320	600	970
Mammary gland (g)	45	480	360	405
Plasma volume (mL)	50	800	1200	1500
Nutrient accretion in mother + fetus				
Fat deposition (g)	328	2064	3594	3825
Protein deposition (g)	36	165	498	925
Iron accretion (g)				565
Calcium accretion (g)				30
Zinc accretion (mg)				100

From King JC. Physiology of pregnancy and nutrient metabolism. *Am J Clin Nutr*. 2000;71:1218S–1225S. With permission.

deposition of protein in new maternal and fetal tissues (15) (Table 4-1) and account for the efficiency of converting consumed dietary protein to the tissue protein deposited. Based on the limited data available (14), these values average about 20 g of protein per day over the last two trimesters of pregnancy, being somewhat less in the second trimester and somewhat more during the third (14). This level of increased protein intake is achieved easily on the standard middle class Western diet. However, women from lower socioeconomic groups or women who, by preference, consume a diet low (or absent) in animal protein or dairy products may require dietary counseling to meet this level of increased protein intake and assure an adequate intake of high quality proteins.

Maternal Weight Gain

Severe restriction of weight gain during pregnancy (total weight gain of 16 to 18 lb) was recommended widely until several decades ago in an attempt to prevent preeclampsia and eclampsia. Maternal obesity and insulin resistance strongly predispose a pregnant woman to preeclampsia (16–19); however, the pathogenesis of this disorder remains an enigma (20–22) and the precise role of maternal body weight or body composition in the pathophysiology of preeclampsia is unclear. Nonetheless, maternal pregravid obesity and excessive maternal weight gain during pregnancy convey significant risks to both mother and fetus (23–25). Given the dramatic trend in the rise of obesity prevalence worldwide, the issue of optimal weight gain during pregnancy has become increasingly important.

Likewise, restricted weight gain may affect pregnancy adversely, resulting in an infant with a low or very low birth weight, and the consequences of low birth weight may be more encompassing than previously thought, as discussed earlier (1–10). Limited weight gain during pregnancy, especially when the mother's weight is low before pregnancy, increases the risk for fetal growth retardation. The risk for mortality is markedly increased in infants with a low birth weight, especially in those with a very low birth weight. Similarly, in low-birth-weight infants who survive, many studies over the last several decades documented an inverse relationship between birth weight and degree of neonatal morbidity and between birth weight and adverse neurologic outcomes.

Despite the observed increased prevalence of maternal obesity during the last two decades and despite contemporaneous recognition of the adverse consequences of low birth

TABLE 4-2. Pregnancy Weight Gain Recommendations

Body mass index category	Recommended weight gain in kilograms (pounds)
Low (<19.8)	12.5–18.0 (28–40)
Normal (19.8–26.0)	11.5–6.0 (25–35)
High (>26.0–29.0)	7.0–11.5 (15–25)
Obese (>29.0)	≥6.0 (15)

Adapted with permission from the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Nutrition During Pregnancy*. Washington, DC: National Academies Press, 1990.

weight in adult life, the last comprehensive expert committee recommendations for appropriate weight gain during pregnancy were those published by the Institute of Medicine in 1990 as a report titled *Nutrition during Pregnancy* (13). These differed in several important ways from prior recommendations by recognizing that healthy, normal infants are delivered to mothers whose gestational weight gains vary by as much as 30 lb. The report also recognized that weight accretion during pregnancy is affected by the mother's pre-pregnancy BMI. Thus, mothers with a low BMI before pregnancy can gain more weight during pregnancy than mothers whose BMI is high before pregnancy. Based on this information, the *Nutrition During Pregnancy* report recommends a set of target ranges of weight gain according to the mother's pre-pregnancy BMI (13) (Table 4-2). Nonetheless, there have been virtually no subsequent studies that have directly tested the validity of these recommendations in today's "obesegenic" environment. Recently, Jain et al. (26) compared pregnancy outcome risks against the Institute of Medicine maternal weight gain guidelines in a sample of 7,661 women, of whom 18% were obese and 13% were overweight. The data showed that pregnancy outcomes of women who gained 25 to 34 lb during pregnancy were indistinguishable from those of women who gained 16 to 24 lb, thus supporting the recommendations published by the Institute of Medicine, while women whose weight gain during pregnancy exceeded 35 lb had dramatically increased rates of macrosomia and cesarean delivery (26). Further, however, when weight gain during pregnancy was controlled for, women who were overweight and obese had significantly higher rates of fetal macrosomia and cesarean section (26).

REQUIREMENTS FOR SPECIFIC NUTRIENTS DURING PREGNANCY

The requirements for specific nutrients in pregnancy have been reviewed extensively by others (27, 28) based on the Institute of Medicine *Dietary Reference Intakes* (29).

Iron

Iron requirements are dramatically increased during pregnancy. Hematologic changes during pregnancy profoundly affect iron homeostasis. The maternal red cell volume increases 20% to 30%, so that the delivery of an extra 500 mg of iron to the maternal marrow is required for erythropoiesis (30). This is in addition to the basal losses of iron, averaging about 250 mg, the 320 mg, or so, of iron that is transferred to the fetus and placenta. Thus, the additional iron required during pregnancy is about 1,100 mg. Of this increment, approximately 150 to 250 mg of blood iron is trapped in the placenta or lost during delivery, but the mother recovers about 250 to 300 mg when her blood volume diminishes after delivery (31). Thus, the total net iron "debt" during pregnancy is about 750 or 850 mg (1,100 minus 250–350). Of this amount, almost all of the extra iron is required during the second and third trimesters of gestation, amounting to approximately 20 mg per day (31). Based on these considerations, the estimated average requirement (EAR) for iron during

pregnancy is 22 mg per day and the recommended dietary allowance (RDA) for iron during pregnancy is 27 mg per day (31). These amounts are on the order of 14 mg per day and 9 mg per day greater than the respective EAR and RDA for nonpregnant women (31).

Only about 10% of dietary iron is absorbed before pregnancy or during the first trimester. Efficiency of absorption increases to about 20% in iron deficiency and may increase up to 15% to 20% during the third trimester. The typical American diet provides only about 1 to 2 mg of absorbed iron each day. Thus, even a diet carefully selected for foods rich in iron may not satisfy the increased iron requirements of the last half of pregnancy and an attempt to provide the total iron RDA with dietary iron is likely to result in excessive calorie intake. For this reason, most women will require an iron supplement to meet the RDA (28,29). The standard recommendation of the Centers for Disease Control and Prevention (CDC) is a daily supplement of 30 mg of elemental iron (generally in the form of simple iron salts such as ferrous gluconate, ferrous sulfate, or ferrous fumarate) beginning at the first prenatal visit (32). This amount is recommended for women whose hemoglobin and iron stores are normal before pregnancy. Pregnant women with confirmed anemia should be carefully evaluated medically for the cause of the anemia and, if due to iron deficiency, should be treated with 60 to 120 mg of supplemental elemental iron daily until the hemoglobin concentration becomes normal, at which time the supplementation can be reduced to 30 mg per day. Commonly used prenatal vitamin and mineral supplements contain 45 to 60 mg of elemental iron per tablet; a 320-mg ferrous sulfate tablet contains 64 mg of elemental iron.

It is important to recognize that oral iron supplements can cause *gastrointestinal side effects,* including heartburn, nausea, constipation or diarrhea, abdominal cramps, and change in stool color. The unpleasant gastrointestinal side effects of iron can be minimized by taking the iron supplement after a meal rather than on an empty stomach. Unfortunately, iron ingested with or after a meal is not absorbed as well as iron taken during fasting. Because nausea is a problem for many women early in pregnancy and this problem may be exacerbated by iron supplements, and because iron requirements do not increase significantly until the second trimester of pregnancy, it is reasonable to defer iron supplementation until the second trimester in women who have nausea that is worsened by iron supplements. The constipation that is commonly associated with oral iron supplementation can be treated with conventional laxatives and stool softeners, but patients taking iron supplements should be warned that their stools may turn black.

Pregnant women with small children should be warned to keep iron supplements out of reach. Ingestion of maternal prenatal iron supplements is a common cause of significant *iron intoxication in children.* Antacids impair the absorption of iron, and the two should not be taken together. This is of some importance because gastroesophageal reflux with heartburn develops frequently in late pregnancy.

Pica, the craving for unnatural foods, develops occasionally in pregnant women and is often associated with iron-deficiency anemia (33,34). However, most individuals with iron deficiency do not exhibit pica, and although various explanations have been offered for the occurrence of pica, none are either fully satisfactory conceptually or proven by experimentation (33). From a clinical practice perspective, however, pregnant women with iron-deficiency anemia should be asked about pica, and those with pica should be tested for iron-deficiency anemia.

Folic Acid

The role of folic acid in human reproduction has been extensively reviewed (35). Folic acid is the most commonly deficient vitamin during pregnancy. Folate is required for the synthesis of the thymidylate moiety and, thus, for DNA synthesis. Folate, then, is required in increasing amounts during gestation to satisfy the needs of cell division in order to accommodate new growth of maternal and fetal tissues. A principal reason for the markedly increased folate requirement in pregnancy is increased maternal erythropoiesis, since maternal erythrocyte volume increases 20% to 30% during the last two trimesters.

The primary maternal manifestation of severe folate deficiency is megaloblastic anemia. Severe folate deficiency is not commonly seen as a complication of pregnancy in the United States. If, however, depletion of folate stores estimated from red blood cell folate concentrations

or from elevation of plasma homocysteine levels is employed to uncover folate insufficiency, the incidence of inadequate folate status during pregnancy is much higher (35).

Folic acid antagonists, such as aminopterin and methotrexate, have long been recognized as human teratogens (36). Additionally, commonly prescribed drugs such as phenobarbital, phenytoin, primidone, carbamazepine, trimethoprim, and triamterene that either inhibit dihydrofolate reductase or interfere with folic acid metabolism by other mechanisms more than double the relative risk for fetal cardiovascular defects, urinary tract defects, or oral clefts when taken during the second or third month after the mother's last menstrual period, but appear to have no deleterious effects on fetal development when taken in the second or third trimesters (37). The use of folic acid supplements during pregnancy diminished the effects of dihydrofolate reductase inhibitors, but not the teratogenic effects of antiepileptic drugs (37).

As discussed extensively elsewhere (35,38), various studies have reported higher incidences of spontaneous abortion, stillbirth, abruptio placentae, preeclampsia, premature rupture of the membranes, preterm delivery, orofacial clefts, Down syndrome, congenital heart defects, impaired fetal growth, and limb defects in association with diminished maternal red cell folate levels. However, each of these consequences remains unproven either because the data are conflicting among studies or because, among other potential confounders, it is difficult in such surveys to isolate the specific effects of low folate status from other manifestations of poor nutrition and low socioeconomic status.

Neural Tube Defects

Convincing data from many sources have proven the adverse effects of low maternal folate status during the periconceptional period and within the first month of pregnancy on the closure of the neural tube with the devastating consequence of an increased incidence of neural tube defects (anencephaly and spina bifida) among the offspring (35). Further, and most importantly, overwhelming evidence is now available to indicate that the incidence of neural tube defects in the offspring of women who take folic acid supplements of at least 400 μg per day before and during the first 4 weeks of pregnancy is approximately 25% to 50% that of women who do not (35,39–41). Nonetheless, despite more than a decade of intensive research on the mechanism(s) for folate's beneficial effects, the precise reason or reasons for this effect remain elusive (35,42,43), although women who are homozygous for a genetic variant of the methylene tetrahydrofolate reductase (MTHFR) gene have a 60% increased risk of bearing a child with a neural tube defect and those heterozygous for the variant have a 10% increased risk (42).

The effect of supplemental folic acid is lost after the first month of gestation because embryonic neural tube closure is complete by then. Only about 5% of neural tube defects are recurrences. Approximately half the women of childbearing age who become pregnant do not plan to do so. In addition, by the time most women realize that they are pregnant, they are halfway through the first 4 weeks of gestation. For these reasons, in September of 1992, the CDC issued the recommendation that *all women of childbearing age* take supplemental folic acid (40). Further, to help ensure adequate levels of folate in women of childbearing age, cereal grain products in the United States are now fortified with 140 μg of folic acid per 100 g of grain (44), a value calculated to provide individuals with approximately 100 μg of additional folic acid intake daily. This practice was adopted by several other countries including Canada, Chile, and Costa Rica, but no European country has yet adopted folic acid fortification of grain products. As a consequence of the U.S. fortification policy, population blood folate levels have increased and there has been a 19% to 50% decline in the incidence of neural tube defects (35,45). Because average decline in the incidence of neural tube defects has been somewhat less than that found in research studies using higher doses of folic acid taken as supplements and because women of childbearing age and pregnant women may not be able to meet dietary folate requirements from food sources alone (45,46), some experts have advocated for increasing the level of folic acid fortification of grains (47); others have advocated for the addition of vitamin B_{12} along with folic acid (48), because there are some data that indicate that low B_{12} status in pregnancy contributes to the incidence of neural tube defects and because the additional inclusion of B_{12} will eliminate the worry of masking pernicious anemia if higher amounts of folic acid

are consumed. These positions must be balanced cautiously against the newly described epigenetic effects of high dietary intakes of folic acid and B_{12} during pregnancy in animals (49).

Folate Requirements

For adult women of childbearing age who are not pregnant, definition of the folate requirement is based largely on controlled metabolic studies, although epidemiological data were used as supportive information. Based on this information, the EAR is defined as 320 μg dietary folate equivalents (DFE) daily, and the RDA is set at 400 μg DFE per day (50–53). Based on similar controlled metabolic study data, approximately 200 μg of *additional* folate is required daily to maintain folate status in pregnant women (50,52), so that the RDA for folate in pregnant women is set at 600 μg of folate equivalents per day (50–53) (Table 4-3). It is important to realize that this recommendation is made on the basis of different studies from those that led to the CDC recommendation of folic acid supplementation to prevent neural tube defects (40) (see below). The latter recommendation was based both on the minimum tested dose of folic acid supplementation that was effective in preventing neural tube defects in controlled clinical studies and on the relevant public health consideration that the neural tube is substantially formed before most women know that they are pregnant and seek professional advice.

A "healthful" diet in individuals who do not take dietary supplements contains approximately 700 μg of food folates, of which about half is bioavailable. Thus, while this diet approaches the estimated average requirement for folate in women of childbearing age, a slightly substandard diet that is more typical of the current American diet would be deficient in folate. In fact, there is good evidence that dietary folate intakes in women do not meet the DRIs (45,46). Thus, in women of childbearing age, increased attention should be paid to improving dietary sources of this vitamin. Good dietary sources of folate include dark green leafy vegetables, green and lima beans, orange juice, fortified cereals, yeast, mushrooms, liver, and kidneys. Root vegetables, eggs, and most dairy products are poor sources of folate. Remember, too, that dietary folate is markedly influenced by food storage and methods of food preparation. Folate is destroyed by boiling and other food-processing methods, including canning.

TABLE 4-3. Recommended Dietary Allowances for Nonpregnant, Pregnant, and Lactating Women

	Nonpregnant women	Pregnancy	Lactation
Vitamin A (μg)	800	800	800
Vitamin D (μg)[a]	5	5	5
Vitamin E (mg)	15	15	19
Vitamin C (mg)	75	85	120
Thiamin (mg)	1.1	1.2	1.4
Riboflavin (mg)	1.1	1.4	1.6
Vitamin B_6 (mg)	1.3	1.9	2.0
Niacin (mg NE)	14	18	17
Folate (μg DFE)	400	600	500
Vitamin B_{12} (μg)	2.4	2.6	2.8
Calcium (mg)[a]	1000	1000	1000
Phosphorus (mg)	700	700	700
Magnesium (mg)	320	350	310
Iron (mg)	15	30	15
Zinc (mg)	12	11	12
Iodine (μg)	150	175	200
Selenium (μg)	55	60	70

[a] Values are adequate dietary intakes for vitamin D and calcium. RDA have not been set for these nutrients. Data from Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press, 2006.

Normal body stores of folate are in the range of 12 to 18 mg. A pregnant woman consuming a folate-deficient diet could deplete her normal folate stores in a few weeks to a few months, depending on the level of her prior stores and the degree of dietary deficiency. Women consuming a diet chronically deficient in folate (including alcoholics and many from lower socioeconomic groups) have small folate stores that would be depleted even more rapidly. Furthermore, the effects of oral contraceptives on folate metabolism are not completely defined and there are some data indicating that red cell levels of folate are diminished in long-time users of oral contraceptives, drugs that have variously been described to interfere with folate absorption and accelerate folate degradation in the liver. Whatever the mechanism, it appears that folate stores may be reduced in women who have used oral contraceptives, and that folate deficiency is more likely to develop in these women during pregnancy.

Folate Supplementation

As discussed earlier, because of accumulating data showing that folic acid supplementation in the periconceptional period profoundly decreased the incidence of neural tube defects, the U.S. Public Health Service through the CDC issued the following recommendation in September 1992:

> All women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purposes of reducing their risk of having a pregnancy affected with spina bifida and other neural tube defects. Because the effects of high intakes are not well-known but include complicating the diagnosis of B_{12} deficiency, care should be taken to keep total folate consumption under 1 mg per day, except under the supervision of a physician. Women who have a prior NTD-affected pregnancy are at high risk of having a subsequent affected pregnancy. When these women are planning to become pregnant, they should consult their physician for advice (40).

It is important to realize that the current RDA of 400 μg of DFEs for nonpregnant women does not strictly conform to the CDC recommendation because, in clinical studies of the prevention of neural tube defects, folic acid was taken as a *supplement* to the usual diet containing food folates. Therefore, the CDC recommendation, as written, is supplementation in the form of folic acid. An important consequence is that the recommended intake of folic acid/folates as DFEs in women capable of becoming pregnant exceeds the RDA. Thus, the Institute of Medicine recommends that "women capable of becoming pregnant consume 400 μg of folate daily from supplements, fortified foods, or both in *addition* to consuming food folate from a varied diet. At this time, the evidence for a protective effect from folate supplements is much stronger than that for food folate" (50). It is further assumed that "women will continue consuming 400 μg from supplements or fortified foods until their pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period—the critical time for formation of the neural tube" (29). Finally, it is important to counsel women who have previously delivered a child with a neural tube defect that *considerably higher doses of folic acid (generally in the range of 4–5 mg per day) taken as supplements are required to prevent a recurrence of a NTD in subsequent pregnancies.*

Calcium, Phosphorus, Zinc, and Vitamin D

The added calcium requirement of pregnancy is about 25 to 30 g—the amount of calcium in the fetus at term. Almost all the fetal calcium is added during the last trimester, when the fetus takes up an average of 300 mg per day. In the first half of pregnancy, fetal calcium accretion is only about 50 mg per day.

Unlike maternal iron stores, which are relatively small, maternal calcium stores are large. Almost all the maternal stores are in the skeleton, some of which can be mobilized easily if needed. The 30-g calcium requirement of a single pregnancy represents only about 2.5% of the total maternal stores. Further increased maternal absorption of dietary calcium easily fulfills the small additional need, and no evidence has been found that maternal bone mineral density changes during pregnancy in relation to calcium intake. Therefore, the recommended adequate intake (AI) of calcium during pregnancy remains unchanged from the corresponding recommendation for nonpregnant women, 1,000 mg per day in women above the age of 19 and 1,300 mg per day for adolescents aged 18 or less (29,54) (Table 4-3). For similar reasons,

the RDA for phosphorus remains unchanged by pregnancy at 700 mg per day in women over the age of 19 and 1,250 mg per day in adolescent girls aged 18 or below (29,54).

An adequate dietary calcium intake is easily achieved by women who consume dairy products (1 qt of milk contains 1,200 mg of calcium), and dietary calcium sources from regular or fortified food products are plentiful (55). Even women who avoid dairy products because of lactose intolerance can achieve an adequate dietary calcium intake. Those who are relatively lactose-deficient may substitute hard cheese for milk. For example, 2 oz of Swiss cheese has twice as much calcium as 8 oz of milk but only one-eleventh as much lactose. Further, a much wider array of calcium fortified food products, such as orange juice, are now widely available. Rare cases of osteomalacia have been reported in multiparous women in underdeveloped countries, who have very low levels of dietary calcium. This has not been a problem in the United States. The calcium intakes recommended for pregnancy are sometimes not achieved with dietary sources alone in some groups having special or selective food preferences and in some African-American, Hispanic, and Native American populations. These groups should be encouraged to increase their intake of calcium from acceptable food sources or, less preferably, be given a calcium supplement.

When calcium supplementation is needed, calcium carbonate, citrate, gluconate, or lactate can be given (55) to provide significant extra calcium intake daily and make up the difference between the recommended AI of calcium and the amount of calcium consumed as food in the diet. For example, a 500-mg tablet of calcium carbonate contains 200 mg of elemental calcium. Although there are some data indicating that calcium carbonate may be less bioavailable than calcium salts having an organic anion such as citrate, gluconate, or lactate (56), calcium bioavailability from calcium carbonate was identical to its bioavailability from calcium citrate in a carefully controlled study by Heaney et al. (57). Given its low price, a cost/benefit analysis clearly favors the use of calcium carbonate. The Institute of Medicine has set the tolerable upper intake limit (UL) for calcium during pregnancy at 2,500 mg per day, a value no different from that advised for nonpregnant women (54). When supplements are necessary to treat deficiency, the degree of replacement can be followed by measuring the 24-hour urinary excretion of calcium.

As is the case with calcium, the additional zinc required to satisfy the needs of pregnancy is only a small fraction of maternal body zinc stores (54) and primarily occurs in the last trimester pregnancy, with about half of the extra zinc deposited in the fetus. Thus, it is likely that pregnant women can continue to satisfy their zinc requirements from dietary sources if they are consuming an adequate zinc intake at the RDA level (8 mg per day) prior to becoming pregnant. Nonetheless, to account for the additional daily zinc requirement of about 2.5 mg per day during the last trimester of pregnancy, the Institute of Medicine has set the RDA for zinc intake in pregnancy at 11 mg per day.

Vitamin D regulates calcium and phosphorus metabolism after conversion of the parent compound, cholecalciferol, to its active hormonal form, 1,25-dihydroxycholecalciferol. It increases calcium and phosphorus absorption from the small intestine and potentiates bone resorption induced by parathyroid hormone. Maternal vitamin D is transported across the placenta to the fetus. In the United States, frank vitamin D deficiency is rare and routine vitamin D supplementation during pregnancy is not currently recommended. The AI recommendation for vitamin D in pregnant women is 5 μg of cholecalciferol (200 IU of vitamin D), the same as the AI defined for nonpregnant women (13).

However, it is important to recognize several important issues about vitamin D nutrition. First, vitamin D does not occur naturally in almost all foods eaten by humans, except for that in certain oily fish and their livers, cod liver oil, and a small amount in egg yolks. Vitamin D obtained from dietary food sources is almost exclusively due to fortification. In the United States, for example, milk is fortified with 400 IU vitamin D per quart, and margarine, some cereals, yoghurts, and orange juice are also fortified. Secondly, relatively short exposures of skin to sunlight allow the synthesis of all the vitamin D required by man, although more exposure is required in dark skinned individuals and in those living in northern latitudes. On the other hand, increasingly restrictive outdoor environmental practices, the wearing of protective clothing, and the widespread use of sunscreen lotions has reduced the amount of vitamin D that individuals now obtain via skin synthesis. Third, a wide variety of studies measuring blood levels of 25-hydroxycholecalciferol (25-OHD), an index of vitamin D status, have now shown that up to one-third of the population has

levels of 25-OHD that indicate a marginal vitamin D status (58,59). These data have led some to question the adequacy of the Institute of Medicine's current AI recommendations for vitamin D in pregnancy and lactation (60).

Evidence suggests that maternal vitamin D deficiency can result in fetal vitamin D deficiency, manifested by neonatal hypocalcemia. Vitamin D deficiency is usually the result of a very low dietary intake combined with minimal exposure to sunlight. Daily supplementation with 5 μg of vitamin D should be considered for complete vegetarians and for persons who avoid sunlight or vitamin D-fortified milk. Excessive maternal intake of vitamin D may result in severe infantile hypercalcemia. The precise amount of ingested vitamin D and the duration of exposure to the dose that is necessary to induce hypervitaminosis D is not known with any degree of certainty. For this reason, the tolerable UL for vitamin D intake during pregnancy has been cautiously set at 50 μg (2,000 IU) (54).

Requirements for Selected Other Nutrients

The EAR for magnesium in nonpregnant adult women is about 255 to 265 mg per day with a corresponding RDA for magnesium set in the range of 310 to 320 mg per day (54). The data available to set DRIs for magnesium in pregnancy are very limited. The EAR for magnesium is calculated to increase by an additional 35 mg per day based on estimates of magnesium accretion in maternal and fetal lean body mass, corrected for bioavailability. Thus the magnesium EAR in pregnancy is calculated as 290 to 300 mg per day and the pregnancy RDA for magnesium is increased to 50 to 360 mg per day for pregnant women, although no direct experimental data are available to support the increased need (54).

The adult woman's RDA for vitamin C is 75 mg per day (29,61). During pregnancy, this value is increased to 85 mg per day on the basis of declining maternal plasma vitamin C levels and the necessary transfer of vitamin C to the fetus (61). However, no direct experimental data support the need for additional vitamin C during pregnancy. Because vitamin C is actively transported from the maternal to the fetal circulation, because there are no proven benefits of vitamin C intake above the RDA intake levels, and because of uncertainty of potential harm to the fetus of pharmacological exposures to vitamin C, a tolerable UL for vitamin C intake in pregnancy has been set at 1,800 to 2,000 mg (61).

With very limited experimental data, and from calculations based largely on changes in maternal metabolism during pregnancy and estimates of fetal nutrient accretion, the RDAs for thiamin, riboflavin, niacin, vitamin A, vitamin B_6, vitamin B_{12}, and selenium have been modestly increased for pregnant women, as have the RDAs for copper, iodine, and molybdenum and the AI recommendations for chromium and manganese (29) (Table 4-3). The RDAs for vitamin E and biotin remain unchanged for women who are pregnant.

Assessment of Nutritional Status during Pregnancy

A pregnant woman should be assessed for nutritional risk factors that would jeopardize the outcome of her pregnancy. A history of previous pregnancies should be obtained, with attention to complications, duration of pregnancy, birth weight and length, and development of the child after delivery. A history of eclampsia, abortion, low-birth-weight infant, hyperemesis, or anemia during past pregnancies has implications for the outcome of the present pregnancy. A nutritional assessment also should include the patient's weight, a brief diet history (including alcohol intake and smoking), and a history of the use of medications that might affect nutrient absorption (e.g., folic acid antagonists, anticonvulsants, thyroid medications, vitamins).

NUTRITIONAL RISK FACTORS AT THE ONSET OF PREGNANCY

Adolescence

An adolescent who becomes pregnant within 3 years of menarche is at special risk for a poor outcome of pregnancy. The nutritional demands of pregnancy are added to the needs of a mother who may still be still growing. The demands for calories, protein, and calcium are all increased and the corresponding RDAs during pregnancy are higher than those for adult women. Further, adolescents are more likely than adults to have inadequate diets, and so

special attention must be paid to the diet of pregnant adolescents. Pregnant adolescents are also more likely to come from low socioeconomic groups, among which poor nutrition is common.

Three or More Pregnancies within 2 Years

Multiple pregnancies at close intervals deplete stored nutrients, including iron and folate. Iron deficiency is an especially significant problem in this group.

Poor Reproductive Performance

A past history of low-birth-weight infants, abortions, or perinatal loss may reflect nutritional deficiency. The factor most highly correlated with the delivery of a low-birth-weight infant is the past history of a low-birth-weight infant.

Economic Deprivation

The diets of patients with low incomes are more likely to be deficient in iron, folate, protein, and B vitamins.

Food Restriction and Fadism

Women who are on unusual diets, diets designed to significantly achieve a healthy body weight, or diets that are deficient in specific nutrients are at risk for adverse outcomes during pregnancy.

Women who are underweight at the beginning of pregnancy (body mass index [BMI] <18.5) are at risk for having low-birth-weight babies. Underweight mothers also may be at increased risk for toxemia. If a woman who is underweight before pregnancy does not gain enough weight during pregnancy, the risks are increased further. Obviously, the optimal time for dealing with the underweight woman is before pregnancy. An underweight woman who is considering pregnancy should be encouraged to gain weight first. When an underweight woman does become pregnant, she should be encouraged to gain more weight than is recommended for the woman who enters pregnancy at a normal weight. Protein–calorie supplements may be necessary to correct previous nutritional deficits and provide for the needs of pregnancy. Very low calorie, restrictive diets during the periconceptional period may limit the ability to become pregnant and may diminish the success of *in vitro* fertilization efforts in mothers undergoing such procedures. Further, mothers on aggressive weight-loss programs during pregnancy, especially severely carbohydrate-restricted diets that result in ketosis, are at risk for a poor outcome. The reasons to avoid severe calorie restriction during pregnancy are compelling. When caloric intake is severely restricted, inadequate intakes of calcium, iron, folate, B vitamins, and protein result. If ingested protein is to be used in the synthesis of maternal and fetal proteins, total energy intake must also be adequate. If caloric intake is inadequate, ingested proteins are catabolized for energy needs. Furthermore, severe restriction of total caloric intake, especially when carbohydrate intake is also restricted, results in ketosis. Studies of diabetic women indicate that ketosis is poorly tolerated by the fetus. Ketosis may be associated with a reduction in uterine blood flow. Ketone bodies are concentrated in the amniotic fluid and taken up by the fetus. The mental development of the offspring of mothers who have had ketonuria during pregnancy, as a consequence of either diabetes or starvation, may be compromised. Whether this is a direct effect of fetal ketosis or the effect of an associated metabolic problem is not clear.

Strict vegans may be deficient in vitamin B_{12} and riboflavin in addition to iron. These problems are readily preventable by careful dietary choices.

The ingestion of vitamins in excessive quantities (megavitamin therapy) may have harmful effects on the fetus. "Rebound" scurvy has been reported in the infants of mothers who have taken massive doses of vitamin C (>5 g per day). The fetus becomes metabolically dependent on high levels of vitamin C that are provided by the mother *in utero* but not by the infant's diet after birth. Studies in rats have shown unequivocally that high doses of vitamin A are teratogenic, 13-*cis*-retinoic acid has been demonstrated to be teratogenic in humans (62), and several epidemiological studies support possible teratogenicity due to high intakes of preformed vitamin A (31). Pregnant women are advised not to take more than 800 μg of retinol equivalents per day.

Smoking, Drug Addiction, and Alcoholism

Maternal smoking during pregnancy reduces birth weight (63) and increases the risk of a woman having a low-birth-weight baby from 7.5% to 12.2% (64). In addition, smoking may increase a woman's chance of having placenta previa and placental abruption (65), and there is some evidence that infants born to smoking mothers are at increased risk for sudden infant death syndrome (65). The CDC estimates that "smoking during pregnancy is the single most preventable cause of illness and death among mothers and infants" (66). The full contraindications to smoking are both more comprehensive and independent of those occurring in pregnancy, but pregnancy surely adds one more immediately compelling reason for adult women who smoke to stop doing so.

Heavy maternal drinking is associated with prenatal growth retardation. Heavy alcohol consumption is associated with a diet deficient in B vitamins, folate, and protein. Maternal alcoholism is associated with fetal toxicity in addition to nutritional deficiencies. Animal studies show that alcohol is a teratogen. Fetal abnormalities associated with heavy maternal alcohol ingestion in humans (fetal alcohol syndrome) include microcephaly, cleft palate, and micrognathia. Alcohol intakes on the order of two drinks per day have been shown to significantly reduce infant Mental Developmental Index scores at 12 to 13 months of age (67). The effects of limited or occasional alcohol intake are undefined and it is not known whether a minimum alcohol intake exists below which risk is not increased. For this reason, the National Institute of Alcohol Abuse and Alcoholism advises against drinking during pregnancy. Likewise, the *Dietary Guidelines for Americans, 2005* advises that alcoholic beverages should not be consumed by pregnant women and women of childbearing age who may become pregnant.

Chronic Systemic Disease

Pregnant diabetic women must be diligent to avoid both hypoglycemia and hyperglycemia with ketosis. Diabetes in pregnancy is associated with resistance to insulin and an increased insulin requirement. On the other hand, fetal glucose utilization may cause maternal fasting hypoglycemia. Diseases associated with malabsorption may cause problems during pregnancy. Primary diseases of the small intestine, such as Crohn disease, may result in malabsorption of many nutrients or malabsorption of selected nutrients, such as vitamin B_{12} or iron. Chronic pancreatic disease is associated with malabsorption of fats and, to a lesser extent, fat-soluble vitamins. Usually, malabsorption can be managed either by treating the underlying disease or by appropriate nutritional supplementation.

NUTRITIONAL RISK FACTORS THAT DEVELOP DURING PREGNANCY

Anemia

Beginning at 3 months' gestation, the maternal blood volume increases markedly. The increase in blood volume precedes the increase in red cell mass, which begins at 6 months, and the increase in blood volume is proportionally greater than the increase in red cell mass. This dilutional anemia is characterized by decreased "normal" values for hemoglobin and hematocrit. The decrease begins at 3 to 5 months of gestation. Hemoglobin and hematocrit continue to fall until 5 to 8 months. They begin to rise at term and are normal by 6 weeks after delivery. In many pregnant women, a nutritional anemia develops along with the normal dilutional anemia. In the vast majority of cases, nutritional anemia is a consequence of inadequate iron intake. The hemoglobin levels of up to 40% of women who are not given supplemental iron drop below 11 g per dL. With iron supplementation, a hemoglobin level this low is uncommon. Nutritional megaloblastic anemia secondary to folate deficiency also occurs, but much less often.

Inadequate Weight Gain

The normal pattern of weight gain is a total of about 6 lb during the first trimester, followed by a relatively steady gain of almost a pound per week during the second and third

trimesters (3). Inadequate weight gain (<2 lb per month during the second and third trimesters) is associated with low birth weight, intrauterine growth retardation, and fetal jeopardy. Failure of fetal growth frequently correlates with inadequate weight gain. Negative discrepancy in gestational age versus uterine size or biparietal diameter of the fetal head as measured by sonography is a sign of intrauterine growth retardation. Women with inadequate weight gain or actual weight loss should be evaluated. A careful diet history should be taken to determine if protein and calorie intake are adequate, and supplements should be given if needed.

Excessive Weight Gain

Rapid weight accumulation (>1.5 to 2 lb per week) is usually a sign of fluid retention. Fluid retention is associated with toxemia, although it does not cause toxemia. Not everyone who retains fluid becomes toxemic, and fluid retention in the absence of hypertension or proteinuria is not an indication for salt restriction or diuretic therapy. Women who retain fluid should be observed for other signs of toxemia. Edema in the lower extremities is commonly seen in the later stages of pregnancy; it is caused by the accumulation of interstitial fluid secondary to obstruction of the pelvic veins. The edema can be treated by elevating the legs and wearing support hose. Excessive weight gain during pregnancy may be caused by fat deposition rather than fluid retention. The consequences of excessive weight gain in pregnancy have been discussed earlier and these should be assessed and managed according to accepted obstetrical practices.

GASTROINTESTINAL PROBLEMS IN PREGNANCY

Nausea and Vomiting

Nausea and vomiting are common in early pregnancy. Eating foods high in carbohydrates, such as crackers, bread, or dry cereal, before rising in the morning may help. Drinking liquids between meals should be encouraged. Fatty foods and caffeine should be avoided.

Constipation

Constipation is common in pregnancy and is caused by pressure of the enlarging uterus, hormonal changes, and iron supplements. Constipation can be treated with increased exercise, increased fluid intake, and either increased dietary fiber or the use of a supplemental psyllium or polycarbophil preparation.

Heartburn

Reflux esophagitis is common in pregnancy secondary to increased abdominal pressure caused by the enlarging uterus. Hormonal changes may loosen the lower esophageal sphincter. The initial approach is very similar to that used in nonpregnant patients with reflux esophagitis.

- Elevate the head of the bed four inches with bed blocks.
- Avoid eating within the 2 to 3 hours before retiring.
- Avoid alcohol, especially before retiring.
- Eat frequent small meals.
- Take antacids as needed. Be alert to their effects on iron absorption.

NUTRITION DURING LACTATION

Human milk is the optimal food for human infants (68). It contains a plethora of unique dietary components and host resistance factors that cannot be provided by conventional commercial formulas (69,70). Every authoritative source recommends that infants be exclusively breast-fed for the first 4 to 6 months of life and, preferably, continued for the first year of life in combination with appropriate complementary foods. Most women in

the United States are capable of breast-feeding their infants adequately, and the nutritional needs during lactation were extensively reviewed by a panel of the National Academy of Sciences in 1993 (71).

Maternal nutritional status is not related to milk volume in the United States and other industrialized countries. Average milk volumes of 750 to 800 mL per day are comparable among thin, normal-weight, and obese women despite large differences in dietary intakes. Regular exercise also does not appear to affect milk volume. The nutritional quality of human milk is not usually affected adversely by modest deficiencies in maternal nutrition. In fact, a mother often loses weight gradually during the normal period of lactation. Even milk from malnourished women may provide an infant with adequate calories, proteins, vitamins, and minerals, although not necessarily in the amounts provided by adequately nourished mothers. The levels of many nutrients in milk are maintained at the expense of maternal stores, and maternal dietary intake does not dramatically alter the macronutrient contents of milk, although the type and amount of specific fatty acids (omega-3 fatty acids, for example) are strongly influenced by the nature of the maternal diet. Milk calcium, phosphorus, sodium, potassium, and magnesium contents are not altered by the maternal diet, although the levels of iodine and selenium in milk tend to parallel maternal intake. The concentrations of vitamins in human milk depend on the mother's stores and her current intake. However, within usual dietary intake levels, these differences are not generally practically important for the infant. The levels of pyridoxine and vitamins A, D, and B_{12} in milk are the most likely to decline as a result of sustained maternal malnutrition. Conversely, increasing maternal nutrient intakes above the RDA level usually does not result in correspondingly high nutrient levels in milk, with the exception of iodine, selenium, vitamin D, and pyridoxine. Thus, excessive maternal calorie intake is not only of no benefit to the infant, but consequent development of obesity can be an adverse effect in the mother. Further, there is substantial evidence that obesity itself impairs lactation performance (72).

NUTRIENT REQUIREMENTS DURING LACTATION

Nutritional requirements in lactation are largely set on the amount of calories and nutrients removed from maternal stores due to their net loss in human milk produced in the amount of about 750 mL per day plus the metabolic costs to the mother of producing the milk. In the first 4 to 5 months of life, the average, exclusively breast-fed infant gains about the same weight that the average fetus accrues during 9 months of term gestation. It is easy to appreciate, then, that the requirements for most nutrients consumed by a lactating mother exceed those for the pregnant woman. Thus, on average during the first 6 months postpartum, the total dietary energy requirements of a lactating woman are increased by about 500 to 600 kcal per day (14,29,73), but a lactating woman mobilizes about 150 to 175 kcal per day as energy stored in her body fat stores during pregnancy (14,73). Thus, the net EER of lactating women averages an additional 350 to 400 kcal per day above their nonpregnant, nonlactating energy requirement (i.e., the approximate difference between +500 and 600 kcal per day and −150 and 175 kcal).

Similarly, during lactation the RDAs for many nutrients, including vitamin A, vitamin E, thiamin, riboflavin, zinc, iodine, and selenium are increased above those necessary during pregnancy (Table 4-3), as is the RDA for protein, which is set at 1.3 g/kg/day, largely on the basis of the amount of nitrogen lost in milk (14,29).

The lactating woman mobilizes calcium and phosphorus from her skeleton to supply milk with these minerals. There is no evidence that increasing dietary calcium or phosphorus intakes prevents this process (54). For this reason, the RDA for dietary calcium and phosphorus during lactation are identical to those of both pregnant and nonpregnant, nonlactating women (54) (Table 4-3). Likewise, iron requirements of the lactating mother are not significantly increased compared to the nonlactating woman (Table 4-3) because the amount of iron secreted into milk is less than that normally lost during menstruation. It is common obstetric practice, however, to prescribe an iron supplement.

During lactation, the RDA for folate is based principally on the extra amount of folate necessary to supply milk folate (50). Thus, the lactation daily RDA for folate (500 μg DFE)

remains above that of the nonlactating woman (400 μg DFE), but is less than that of the pregnant woman (600 μg DFE) because the folate demands for new tissue synthesis are significantly greater during pregnancy (50) (Table 4-3).

SPECIAL CONSIDERATIONS

Lactating women should be educated to obtain adequate nutrition from a well-balanced diet rather than through the use of nutritional supplements. Further, almost all women can breast-feed their infants successfully. Thus, a mother who is having problems with lactation should seek the professional help of individuals who have extensive experience helping women with these problems. Lactation counseling is widely and freely available throughout the nation, from public (state and local government) and private sources. Trained lactation consultants will have the initials CLC (Certified Lactation Consultant) or IBCLC (International Board Certified Lactation Consultant) after their name. A directory of certified lactation consultants can be found at the Web site of the International Lactation Consultant Association (www.ilca.org), and extensive help with breast-feeding issues can be obtained from La Leche League International (www.llli.org).

Women with specialized dietary habits, such as strict vegans, should receive competent nutritional advice from trained professionals to ensure the adequate nutritional health of their infants and themselves during lactation. There is absolutely no reason to discourage breast-feeding in women with unique dietary patterns. Rather, appropriate educational advice should be provided to ensure the mother consumes adequate amounts of essential nutrients from acceptable foods. If necessary, dietary supplements can provide limiting nutrients.

As is the case for any human being, substance abuse and the use of illicit drugs should be actively discouraged in pregnant and lactating women as well. Perhaps it is more appropriate to say especially discouraged or absolutely contraindicated for the health and normal development of the fetus and infant. Addicted persons should be actively encouraged to enter appropriate treatment programs. Lactating women should not smoke. Besides the known long-term health risks, smoking reduces milk volume. Modest consumption of coffee and alcohol, less than one to two cups and one to two drinks daily, respectively, is not known to affect lactation or the health of the infant adversely.

Women with HIV/AIDS should not breast-feed their infants when safe alternatives are available. Approximately 50% of HIV infections are transmitted to the infant at the end of pregnancy and approximately 50% are transmitted after birth in breast-fed populations (74). In 2005, an estimated 280,000 to 360,000 infants were infected through breast-feeding (75). The rate of HIV transmission from mother to infant is approximately nine transmissions per 100 child-years of breast-feeding, resulting in a cumulative probability of HIV transmission to infants breast-fed for 18 months on the order of 9% (76), with a rate that may be as high as 15% if breast-feeding is prolonged to 2 years of age (74). Surprisingly, however, data indicate that infants who received formula or other foods after 14 weeks of age were approximately twice as likely to become infected as those who were exclusively breast-fed (75). Over the course of the study, infants who were exclusively breast-fed were 11 times less likely to become infected with HIV than those infants who had received foods along with breast milk (75). These data have significant implications for global public health guidelines concerning infant feeding practices in environments where safe alternatives to breast-feeding and antiretroviral agents are not available.

References

1. Barker DJ, Winter PD, Osmond C, et al. Weight in infancy and death from ischemic heart disease. *Lancet*. 1989;2:577–580.
2. Barker DJP. The origins of the developmental origins theory. *J Int Med*. 2007;261:412–417.
3. Barker DJP. Adult consequences of fetal growth restriction. *Clin Obstet Gynecol*. 2006;49:270–283.
4. Leon DA, Johansson M, Rasmussen F. Gestational age and growth rate of fetal mass are inversely associated with systolic blood pressure in young adults. An epidemiology study of 165,136 Swedish men aged 18 years. *Am J Epidemiol*. 2000;152:597–604.

5. Lawlor DA, Hübinette A, Tynelius P, et al. Associations of gestational age and intrauterine growth with systolic blood pressure in a family-based study of 386,485 men in 331,089 families. *Circulation*. 2007;115: 562–568.
6. Gamborg M, Byberg L, Rasmussen F, et al. Birth weight and systolic blood pressure in adolescence and adulthood: meta-regression analysis of sex- and age-specific results from 20 Nordic studies. *Am J Epidemiol*. 2007Apr 23; [Epub ahead of print]
7. Lithell HO, McKeigue PM, Berglund L, et al. Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50–60 years. *Br Med J*. 1996;312:406–410.
8. Lawlor DA, Davey Smith G, Clark H, et al. The associations of birthweight, gestational age and childhood BMI with type 2 diabetes: findings from the Aberdeen Children of the 1950s cohort. *Diabetalogia*. 2006; 49:2614–2617.
9. Hovi P, Andersson S, Eriksson JG, et al. Glucose regulation in young adults with very low birth weight. *N Engl J Med*. 2007;356:2053–2063.
10. Huxley R, Owen CG, Whincup PH, et al. Is birth weight a risk factor for ischemic heart disease in later life? *Am J Clin Nutr*. 2007;85:1244–1250.
11. Butte NF. Energy requirements during pregnancy and consequences of deviations from requirement on fetal outcome. In: Vevey S, Karger AG, eds. *Nestlé Nutrition Workshop Series Pediatric Program*. Basel: Nestec, 2005;49–71.
12. Butte NF, Wong WW, Treuth MS, et al. Energy requirements during pregnancy based on total energy expenditure and energy deposition. *Am J Clin Nutr*. 2004;79:1078–1087.
13. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Nutrition During Pregnancy*. Washington, DC: National Academies Press, 1990.
14. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academies Press, 2005.
15. King JC. Physiology of pregnancy and nutrient metabolism. *Am J Clin Nutr*. 2000;71:1218S–1225S.
16. O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: A systematic overview. *Epidemiology*. 2003;14:368–374.
17. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *Br Med J*. 2005;330(7491):549–550.
18. Wolf M, Sandler L, Muñoz K, et al. First trimester insulin resistance and subsequent preeclampsia: A prospective study. *J Clin Endocrinol Metab*. 2002;87:1563–1568.
19. Festschrift B, Barden A. Pre-eclampsia: Contribution of maternal constitutional factors and the consequences for cardiovascular health. *Clin Exp Pharmacol Physiol*. 2006;33:826–830.
20. Noris M, Perico N, Remuzzi G. Mechanisms of disease: pre-eclampsia. *Nature*. 2005;1:98–114.
21. Widmer M, Villar J, Benigni A, et al. Mapping the theories of preeclampsia and the role of angiogenic factors. *Obstet Gynecol*. 2007;109:168–180.
22. Spinnato JA. New therapies in the prevention of preeclampsia. *Curr Opin Obstetr Gynecol*. 2006;18: 601–604.
23. Yu CKH, Teoh TG, Robinson S. Obesity in pregnancy. *Br J Obstet Gynaecol*. 2006;113:1117–1125.
24. Krishnamoorthy U, Schram CMH, Hill SR. Maternal obesity in pregnancy: is it time for meaningful research to inform preventive and management strategies? *Br J Obstet Gynaecol*. 2006;113: 1134–1140.
25. Catalano PM. Management of obesity in pregnancy. *Obstet Gynecol*. 2007;109:419–433.
26. Jain NJ, Denk CE, Kruse LK, et al. Maternal obesity: can pregnancy weight gain modify risk of selected adverse pregnancy outcomes? *Am J Perinatol*. 2007;24:291–298.
27. Turner RE. Nutrition during pregnancy. In: Shils ME, Shike M, Ross AC, et al., eds. *Modern Nutrition in Health and Disease*, 10th ed. Philadelphia: Lippincott Williams & Wilkins, 2006;771–782.
28. Allen LH. Pregnancy and lactation. In: Bowman BA, Russell RM, eds. *Present Knowledge in Nutrition*, 9th ed. Washington, DC: International Life Sciences Institute, 2006;529–543.
29. Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press, 2006.
30. Food and Agriculture Organization of the United Nations/World Health Organization. *Requirements of Vitamin A, Iron, Folate and Vitamin B_{12}*. FAO Food and Nutrition Series No. 23. Rome: Food and Agriculture Organization of the United Nations, 1988;33–50.
31. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Energy for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc*. Washington, DC: National Academies Press, 2001.
32. Centers for Disease Control and Prevention. CDC Recommendations to prevent and control iron deficiency in the United States. *Morbid Mortal Weekly Rep*. 1998;47:1–29.
33. Erhard Danforth D. Pica and nutrition. *Ann Rev Nutr*. 1982;2:303–322.
34. Horner RD, Lackey CJ, Kolasa K, et al. Pica practices of pregnant women. *J Am Diet Assoc*. 1991;91:34–38.
35. Tamura T, Picciano M. Folate and human reproduction. *Am J Clin Nutr*. 2006;83:993–1016.
36. Kalter H. Folic acid and human malformations: a summary and evaluation. *Reprod Toxicol*. 2000;14: 463–476.

37. Hernández-Díaz S, Werler MM, Walker AM, et al. Folic acid antagonist during pregnancy and the risk of birth defects. *N Engl J Med*. 2000;343:1608–1614.
38. Bailey LB, Berry RJ. Folic acid supplementation and the occurrence of congenital heart defects, orofacial clefts, multiple births, and miscarriage. *Am J Clin Nutr*. 2005;81:1213S–1217S.
39. Medical Research Council Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet*. 1991;338:131–137.
40. Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *Morbid Mortal Weekly Rep*. 1991;41:1.
41. Pitkin RM. Folate and neural tube defects. *Am J Clin Nutr*. 2007;82:285S–288S.
42. Blom HJ, Shaw GM, den Heijer M, et al. Neural tube defects and folate: case far from closed. *Nature Rev*. 2006;7:724–731.
43. Kibar Z, Capra V, Gros P. Toward understanding the genetic basis of neural tube defects. *Clin Genet*. 2007;71:295–310.
44. Food standards: amendment of the standards of identity for enriched grain products to require addition of folic acid. Final rule. (Codified at 21 CFR parts 136, 137, and 139.) *Fed Regist*. 1996;61:8781.
45. Yang QH, Carter HK, Mulinare J, et al. Race-ethnicity differences in folic acid intake in women of childbearing age in the United States after folic acid fortification: findings from the National Health and Nutrition Examination Survey, 2001–2002. *Am J Clin Nutr*. 2007;85:1409–1416.
46. Sherwood KL, Houghton LA, Tarasuk, et al. One-third of pregnant and lactating women may not be meeting their folate requirements from diet alone based on mandated levels of folic acid fortification. *J Nutr*. 2006;136:2820–2826.
47. Oakley GP. When will we eliminate folic acid-preventable spina bifida? *Epidemiology*. 2007;18:367–368.
48. Ray JG, Wyatt PR, Thompson MD, et al. Vitamin B_{12} and the risk of neural tube defects in a folic-acid-fortified population. *Epidemiology*. 2007;18:362–366.
49. Waterland RA, Michels KB. Epigenetic epidemiology of developmental origins hypothesis. *Annu Rev Nutr*. 2007;27:363–388.
50. Institute of Medicine, National Academy of Sciences. Folate. In: *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin and Choline*. Washington, DC: National Academies Press, 2006.
51. Suitor CW, Bailey LB. Dietary folate equivalents: interpretation and application. *J Am Diet Assoc*. 2000; 100:88–94.
52. Bailey LB. New standard for dietary folate intake in pregnant women. *Am J Clin Nutr*. 2000;71: 1304S–1307S.
53. Bailey LB. Folate and vitamin B_{12} recommended intakes and status in the United States. *Nutr Rev*. 2004; 62:S14–S20.
54. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride*. Washington, DC: National Academies Press, 1997.
55. Fishbein L. Multiple sources of dietary calcium – some aspects of its essentiality. *Regul Toxicol Pharmacol*. 2003;39:61–80.
56. Sakhaee K, Bhuket T, Adams-Huet B, et al. Meta-analysis of calcium bioavailabilty: a comparison of calcium citrate with calcium carbonate. *Am J Ther* 1999;8:73–74.
57. Heaney RP, Dowell MS, Bierman J, et al. Absorbability and cost effectiveness in calcium supplementation. *J Am Coll Nutr*. 2001;20:239–246.
58. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: Implications for establishing new effective dietary intake recommendations for vitamin D. *J Nutr*. 2005;135:317–322.
59. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc*. 2006;81:353–373.
60. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr*. 2004;79:717–726.
61. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: National Academies Press, 2000.
62. Lammer EJ, Chen DT, Hoar RM, et al. Retinoic acid embryopathy. *N Engl J Med*. 1985;313:837–841.
63. Lindbohm ML, Sallmen M, Taskinen H. Effects of exposure to environmental tobacco smoke on reproductive health. *Scand J Work, Environ Health*. 2002;28:84S–96S.
64. Martin JA, Hamilton BE, Sutton PD, et al. Births: Final data for 2002. *National Vital Stat Rep*. 2003; 52:1–113.
65. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General – 2004*. Atlanta: Centers for Disease Control and Prevention, Office on Smoking and Health, 2004.
66. Centers for Disease Control and Prevention. Maternal and Infant Health: Smoking During Pregnancy. http://www.cdc.gov/reproductivehealth/MaternalInfantHealth/related/SmokingPregnancy.htm
67. Testa M, Quigley BM, Das Eiden R. The effects of prenatal alcohol exposure on infant mental development: A meta-analytical review. *Alcohol Alcohol*. 2003;38:295–304.
68. American Academy of Pediatrics Committee on Nutrition. Breastfeeding. In: Kleinman RE, ed. *Pediatric Nutrition Handbook*, 5th ed. Chicago: American Academy of Pediatrics, 2004;55–85.

69. Lawrence RM, Pane CA. Human breast milk: current concepts of immunology and infectious diseases. *Curr Probl Pediatr Adolesc Health Car.* 2007;37:7–36.
70. Picciano MF, McDonald SS. Lactation. In: Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, eds. *Modern Nutrition in Health and Disease*, 10th ed. Philadelphia: Lippincott Williams & Wilkins, 2006; 784–796.
71. Committee on Nutritional Status During Pregnancy and Lactation, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Nutrition During Lactation*. Washington, DC: National Academies Press, 1993.
72. Rasmussen KM. Association of maternal obesity before conception with poor lactation performance. *Annu Rev Nutr*. 2007;27:103–121.
73. Butte NF, King JC. Energy requirements during pregnancy and lactation. *Public Health Nutr*. 2005;8: 1010–1027.
74. Kourtis AP, Lee FK, Abrams EJ, et al. Mother-to-child transmission of HIV-1: timing and implications for prevention. *Lancet Infect Dis*. 2006;6:726–732.
75. Coovadia HM, Rollins NC, Bland RM, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet*. 2007;369:1107–1116.
76. The Breastfeeding and HIV International Transmission Study Group. Late postnatal transmission of HIV-1 in breast-fed children: An individual data meta-analysis. *J Infect Dis*. 2004;189:2154–2166.

Individual Nutrient Components

II

PROTEIN AND CALORIES: REQUIREMENTS, INTAKE, AND ASSESSMENT

5

ESTIMATION OF NORMAL DAILY REQUIREMENTS

The physician is often faced with patients who are losing weight, are undergoing surgery, or have a disease that increases their usual energy needs. To ensure the proper caloric intake, a reasonable estimate of energy needs must be made. Most of these estimates rely on the carefully measured and standardized determination of the basal metabolic rate and of energy utilization during exercise. The general principles behind the estimation of energy requirements have been reviewed in detail (1,2).

Energy Equation

It is impossible to predict daily energy use precisely because of the complex factors involved. The methods used to determine energy needs experimentally are flawed, including diet recall and metabolic rates. Current recommendations do not allow for diversity in body composition, dietary intake, or level of activity. Nonetheless, if the principles involved in deriving the recommendations are understood, one can use the various methods to estimate energy needs. Energy requirements in humans are defined by the following formula:

$$TEE = BMR\ (60\% - 75\%) - EEA\ (15\% - 30\%) + TEF\ (\sim 10\%)$$

where *TEE* = total energy expenditure
BMR = basal metabolic rate, or BEE = basal energy expenditure
EEA = energy expenditure of activity
TEF = thermal effect of food

Basal metabolic rate is a measure of the amount of energy expended to maintain a living state at rest and 12 to 18 hours after a meal; synonyms for this measurement are *basal energy requirement* (BER), *basal energy expenditure* (BEE), *resting metabolic rate* (RMR), and *resting energy expenditure* (REE), though REE is not usually measured under basal conditions. REE is the sum of BEE, nonshivering thermogenesis, and stress hypermetabolism.

In practice, BMR and REE differ by less than 10%. The BMR or RMR is proportional to the fat-free mass but is influenced by age, sex, body composition, and genetics. It decreases about 2% to 3% per decade and is greater in men than in women of equal weight. In the current Dietary Reference Intake (DRI) volume covering energy (2), the BEE and TEE are assessed from a doubly labeled water (DLW) database, because this provided more reliable data than the older methods that relied either on factorial approaches or on food intake data. By following the decay in labeled body water ($^3H_2{}^{18}O$) for 1 to 2 weeks, one can calculate the rate of carbon dioxide production and estimate total daily energy needs in free-living individuals.

Energy expenditure of activity, or thermal effect of activity (TEA), is a measure of the energy expended by the body to support a variety of physical activities. This is the most variable item in the energy equation, ranging from about 100 kcal per day in sedentary persons to about 3,000 kcal per day in moderately active persons. The EEA decreases with age and loss of fat-free mass and is greater in men than in women of equal weight. In the derivation of DRI energy estimates (2), the EEA is replaced by a physical activity level (PAL). The PAL is defined as the ratio of TEE to BEE. Thus, the impact of PAL on TEE depends on body size and age, as these are factors that affect the BEE. The data for PAL have been derived from the DLW database for BEE, and from the multiples of an individual's resting oxygen uptake (metabolic equivalents [METs]) for a variety of activities (see Section III, Energy Requirements). A range of PALs has allowed individuals to be classified as sedentary, low active, active, or very active. Because walking is the most significant activity in the lives of most people, this is taken as the reference activity.

The PAL can be envisioned by equating the various PAL levels with an estimated walking distance for individuals of various builds, assuming that all of their activity would be performed by walking.

TEF is an estimate of the number of calories produced as heat during the ingestion and metabolism of food, also called the *specific dynamic action of food* (SDA). The obligatory components of the TEF represent the energy needed for absorption and transport of nutrients plus synthesis and storage. Protein increases heat production by 12%, carbohydrate by 6%, and fat by 2%. A mixed diet yields a 6% increase in heat, but 10% is the usual figure used. The lower the TEE, the greater the relative importance of the calorigenic effect in determining total energy requirements. The calorigenic effect of food seems to be related closely to the energy required for adenosine triphosphate (ATP) formation and occurs even after food is administered intravenously. The TEF decreases with age and insulin resistance. Excess energy above the TEF is modulated by the sympathetic nervous system.

In hypermetabolic or infected, febrile patients, the specific dynamic action of food is lower than normal because heat production is already increased. Thus, the figure used to calculate additional energy requirements for these patients should be 5% rather than 10%. When nutrients are provided continuously, as for hospitalized patients, energy is not needed for storing and recovering nutrients, and the TEF can be ignored for purposes of estimating energy needs.

The estimated energy requirement (EER) derived in the DRI (2) comprises a number based on BEE obtained from the DLW database, plus the PAL coefficient, with age, height, and weight factored in.

DRI equations for estimating EER include TEE, PAL, and a factor for energy deposition for ages up to 18, but only TEE and PAL for older ages. Energy is reported in kilocalories (kcal) for DRIs , but the World Health Organization (WHO) has adopted kilojoules, the mechanical equivalent of heat, as their unit of energy: 4.184 kj = 1 kcal, or 1 kj = 0.239 kcal.

For ages 0 to 36 months:

0–3 months	(89 × weight [kg] − 100) + 175 kcal
4–6 months	(89 × weight [kg] − 100) + 56 kcal
7–12 months	(89 × weight [kg] − 100) + 22 kcal
13–36 months	(89 × weight [kg] − 100) + 20 kcal

For ages 3 to 8 years:

Boys 135.3 − (30.8 × age [y] + PA × (10.0 × weight [kg] + 903 × height [m]) + 20 kcal
Girls 135.3 − (30.8 × age [y] + PA × (10.0 × weight [kg] + 934 × height [m]) + 20 kcal

TABLE 5-1. Physical Activity Level (PAL) Categories and Walking Equivalence

PAL category	PAL range	PAL	Light (44 kg)	Medium (70 kg)	Heavy (120 kg)
			[Mean Walking Equivalence (miles/day at 3–4 mph)]		
Sedentary	1.0–1.39	1.25	~0	~0	~0
Low active	1.4–1.59	1.5	2.9	2.2	1.5
Active	1.6–1.89	1.75	9.9	7.3	5.3
Very active	1.9–2.49	2.2	22.5	16.7	12.3

Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids.* Food and Nutrition Board, Institute of Medicine, Washington, DC: The National Academies Press, 2005, p. 161.

PA is based on PAL status and = 1.0 for sedentary, 1.13 (M) or 1.16 (F) for low active, 1.31 (F) or 1.26 (M) for active, and 1.56 (F) or 1.42 (M) for very active.

For ages 9 to 18:

Boys $88.5 - (61.99 \times \text{age [y]}) + \text{PA} \times (26.7 \times \text{weight [kg]} + 903 \times \text{height [m]} + 25$ kcal
Girls $135.3 - (30.8 \times \text{age [y]}) + \text{PA} \times (10.0 \times \text{weight [kg]} + 934 \times \text{height [m]}) + 25$ kcal

PA is based on PAL status as noted for ages 3 to 8.

For ages 19 and older:

Men $662 - (9.53 \times \text{age [y]}) + \text{PA} \times (15.91 \times \text{weight [kg]} + 539.6 \times \text{height [m]})$
Women $354 - (6.91 \times \text{age [y]}) + \text{PA} \times (9.36 \times \text{weight [kg]} + 726 \times \text{height [m]})$

PA is based on PAL status (Table 5-1) and = 1.0 for sedentary, 1.11 (M) or 1.12 (F) for low active, 1.25 (M) or 1.27 (F) for active, and 1.48 (M) or 1.45 (F) for very active. An online spreadsheet is available to calculate EER based on PAL (http://www.cdc.gov/pcd/issues/2006/OCT/06_0034.htm).

Choice of Method

Although the DRI estimates of EER are considered the most accurate that can be made using current technology, more easily derived numbers are used for clinical purposes. The physician can be confused by the large number of empirically derived methods for estimating the three components of the daily energy requirement. More than 190 methods have been reported to predict energy expenditures (3). The following sections outline a number of the available methods. It is important to use a single method of calculation for each of the three components and to understand the limitations of that method. It is not necessary to learn multiple methods for calculating the BMR or any of the other components because the methods all provide only an estimate and not a precise calculation.

CALCULATION OF BASAL METABOLIC RATE

Energy consumption is assessed by measuring oxygen consumption under carefully controlled conditions. Oxygen uptake is related to carbon dioxide output plus heat. It is translated into calories by assuming the amount of expired carbon dioxide that would yield a nonprotein respiratory quotient of 0.82—that is, a caloric value for oxygen of 4.825 kcal (20.19 kJ) per L. Most of the energy estimates are derived from older measures of BMR. Although measurements of basal metabolism over 1 hour were used to calculate a 24-hour requirement, a more meaningful determination of metabolic rate would reflect the rate at which energy is consumed in a normal life situation while the body is at rest and ingesting

food under neutral climatic conditions. This measurement of resting metabolism would include the specific dynamic action of food.

Although the equipment for measuring BMR is not complicated, the actual measurement is time-consuming, and considerable variability is involved unless the conditions maintained during measurement are carefully standardized. It has become accepted practice that estimates of BMR are derived from carefully collated data from normal subjects obtained under controlled conditions. Additional energy requirements attributed to the thermal effect of food, growth (in children), and illness are estimated independently and added to the calories required for the BMR.

Methods for Calculating BMR

The BMR can be estimated in a variety of ways by using calculations based on (a) body size (height and weight), (b) weight alone, (c) body size and age, (d) weight and sex, and (e) weight, height, age, and sex. Not surprisingly, the BMR values based on different individual parameters are not identical for each method in the same person. In regard to clinical usefulness, all these methods are satisfactory. The first group of methods presented requires the use of tables to estimate the BMR. Shorter methods not requiring tables are reasonably accurate for estimating the BMR over the entire range of existing body sizes and are currently in widespread use.

The cells of the body require oxygen for their integrity; the greater the number of cells, the greater the oxygen consumption. Adipose cells are relatively inert from a metabolic point of view; they constitute about 20% of the body mass but account for only 2% to 4% of the BMR. Thus, in overweight persons, whose adipose cells are increased in number and size, the correlation between weight alone and oxygen consumption is not linear, and oxygen consumption per pound of extra weight is not equivalent to that per pound of lean body weight. Instead of the old, portable BMR apparatus, DLW ($^3H_2{}^{18}O$) is used. Body surface area is a more reasonable determinant of lean body mass—that is, metabolically active tissues. Muscle makes up 35% to 40% of body weight but contributes only 20% to the BMR. The brain and liver require high levels of energy but change less with body size than does muscle mass. The increase in BMR per kilogram of body weight or per square meter of surface area depends primarily on the relative proportions of skeletal muscle and adipose tissue and their metabolic activity (different for various states of conditioning). Thus, oxygen consumption increases at the same rate in any person for every unit of increase in body surface area. As body weight increases over normal, when adipose tissue is the major component of body tissue added, the rate of increase in oxygen consumption declines. It is more accurate to have an estimation of BMR that accounts for these changes rather than one based on weight alone.

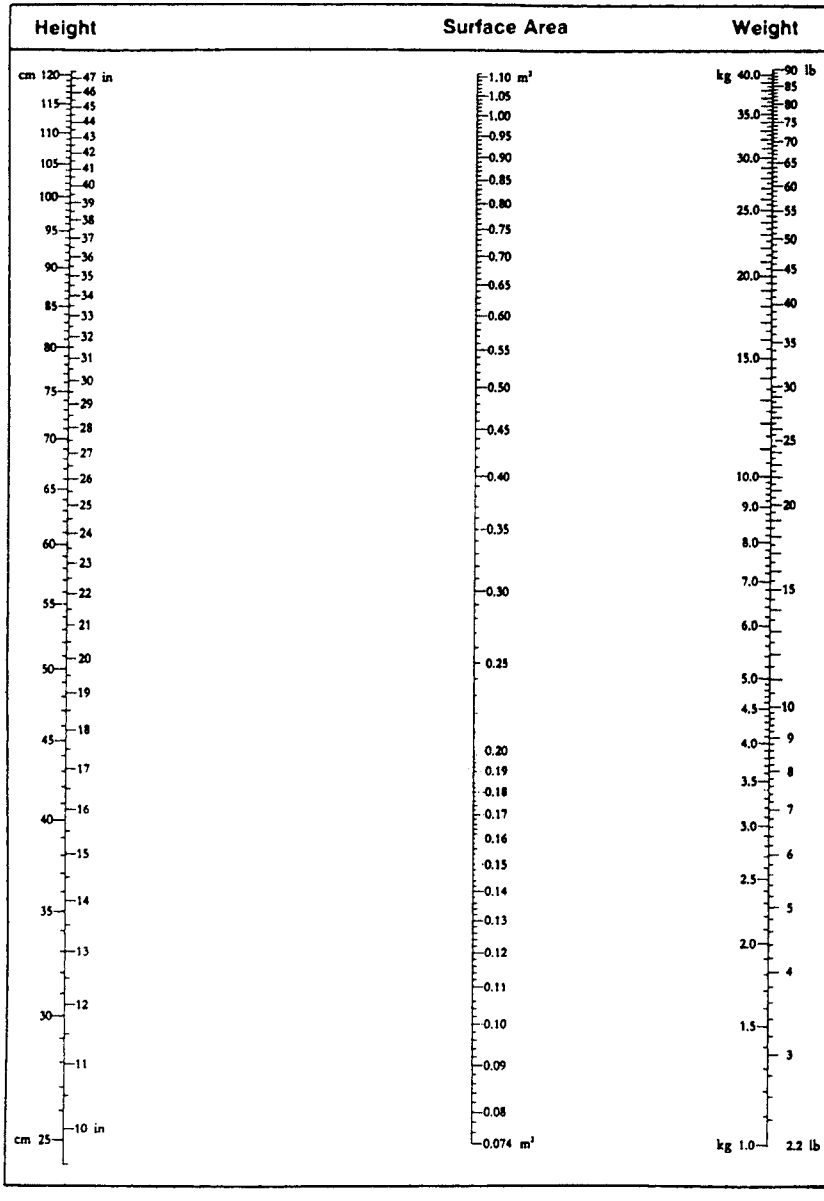
BMR Estimate Based on Body Surface Area

This estimate is made according to the following steps:

a. Determine body surface area (Figure 5-1). The BMR is expressed in square meters (m^2).
b. Identify the metabolic rate for any individual from predicted averages for age and sex (Table 5-2). These rates are given as kilocalories per square meter per day (kcal/m^2/day), an energy equivalent derived from the rate of oxygen consumption. The BMR is highest per square meter in the first few years of life and then steadily declines, although a slight increase occurs at puberty.
c. The BMR (kcal per day) equals the metabolic rate from Table 5-2 (kcal/m^2/day) times surface area (m^2). Basal metabolism may not be constant throughout the day, and the final calculated estimate does not account for such variations. Nonetheless, it provides a clinically useful guide.

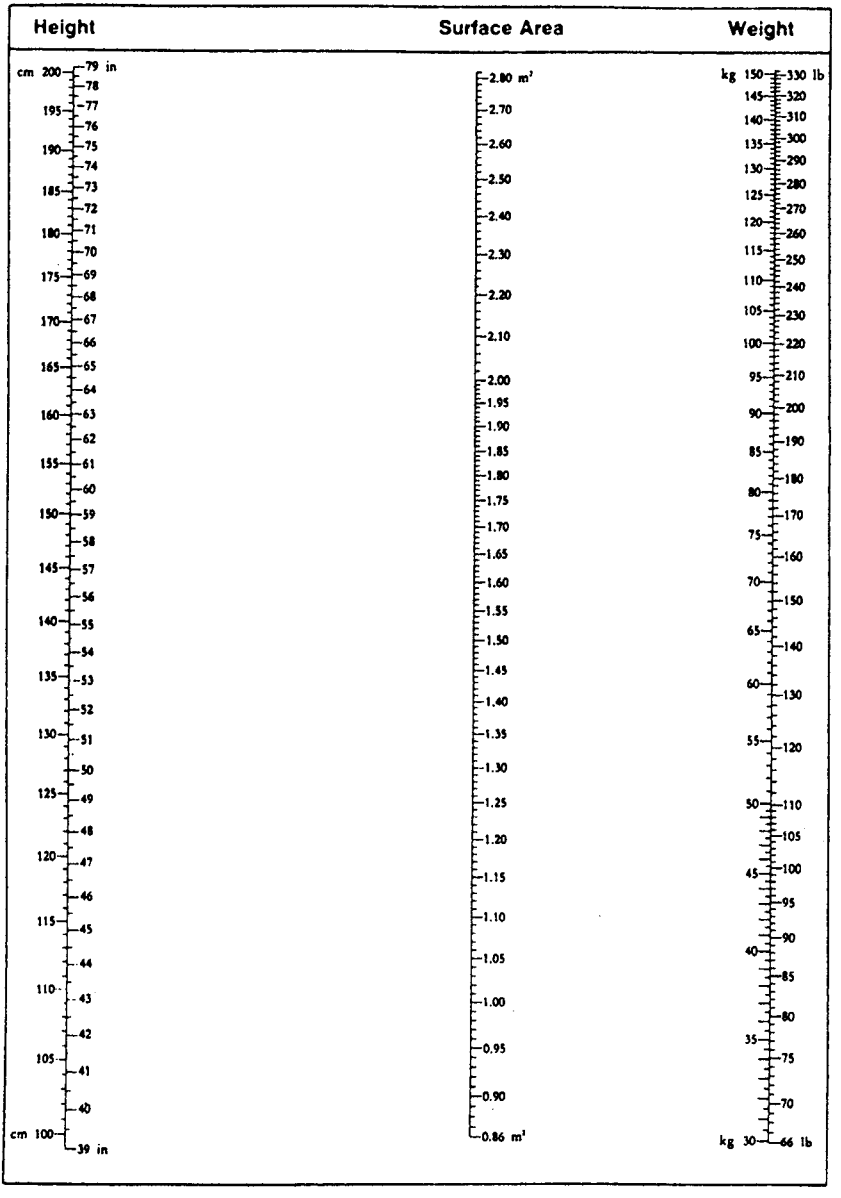
Method Based on Sex, Height, Age, and Weight (Harris–Benedict Equation)

An estimate based on indirect calorimetry was devised by J. A. Harris and F. G. Benedict (4). This method has gained wide acceptance because it requires no tables and is reasonably accurate in comparison with measurements of oxygen consumption (REE prediction is accurate to $\pm 14\%$). However, malnutrition is associated with an increase in



A

FIGURE 5-1. Nomograms for determining body surface area from height and weight. **A:** Body surface area of children. **B:** Body surface area of adults. (From the formula of DuBois D, DuBois EF. *Arch Intern Med.* 1916;17:863. $S = W^{0.425} \times H^{0.725} \times 71.84$, or $\log S = \log W \times 0.425 + \log H \times 0.725 + 1.8564$, where S = body surface area in square centimeters, W = weight in kilograms, and H = height in centimeters. Reproduced from *Scientific Tables, Documenta Geigy.* New York: Geigy Pharmaceuticals, 1962, with permission.) ***(continued)***



B

FIGURE 5-1. *(continued)*

TABLE 5-2. Standard Basal Metabolic Rates Based on Body Surface Area for Age and Sex

Age (y)	Metabolic rate (kcal/m^2 per day)	
	Men	Women
1	1,272	1,272
2	1,258	1,258
3	1,231	1,229
4	1,207	1,195
5	1,183	1,162
6	1,160	1,128
7	1,135	1,090
8	1,111	1,051
9	1,085	1,027
10	1,056	1,020
11	1,032	1,008
12	1,020	991
13	1,015	967
14	1,010	941
15	1,003	910
16	994	886
17	979	871
18	960	862
19	941	852
20	926	847
25	900	845
30	883	842
35	876	840
40	871	838
45	869	828
50	859	814
55	850	799
60	838	785
65	826	773
70	811	761
75 and over	797	751

Adapted from Fleish A. Le métabolisme basal standard et sa determination au moyen du "Metabocalculator." *Helv Med Acta.* 1951;18:23.

resting oxygen consumption, apparently only when it is expressed per predicted body mass (5). In malnutrition, a greater preservation of visceral than of skeletal components leads to an increase in REE (BMR) per body cell mass. The apparent hypermetabolism of cancer patients may just be malnutrition, most likely caused by a decrease in food intake (see Chapter 15). The underestimation of BMR by the Harris–Benedict equation in malnourished patients is about 20%, but no constant factor can be applied to all patients. This inaccuracy would be true for all methods of estimating BMR but has been examined most carefully for the Harris–Benedict equation. A similar overestimation occurs in obese patients (6).

For normally nourished persons the BMR can be calculated from the following formulas:

$$\text{BMR women} = 665 + (9.6 \times W) + (1.8 \times H) - (4.7 \times A)$$
$$\text{BMR men} = 66 + (13.8 \times W) + (5 \times H) - (6.8 \times A)$$

where W = actual or usual weight (kg),
H = height (cm), and
A = age (years).

The Harris–Benedict data have been reevaluated, and data for a wider age range, but still for normally nourished people, have been added (5).

For overweight persons, an adjusted body weight can be used, based on usual body weight (6) (see Table 5-3 or Table 13-2):

$$\text{Adjusted body weight} = [(\text{actual weight} - \text{ideal weight}) \times 0.25] + \text{ideal body weight}$$

Alternatively, ideal body weight may be estimated by using the Hamwi formula (7): For males, 106 lb for the first 60 in of height plus 6 lb for each additional inch; for females, 100 lb for the first 60 in. of height plus 5 lb for each additional inch. Add 10% for a large frame size; subtract 10% for a small frame size.

To determine frame size, wrist measurements are used (8). Small and large frames fall outside the ranges for a medium frame. A medium frame for males taller than 165 cm (65 in) is defined as a wrist circumference of 16.5 to 19 cm. Comparable figures for wrist circumference for females are 14 to 14.5 cm for a height of less than 157 cm (62 in), 15 to 16 cm for a height of 157 to 165 cm, and 16 to 16.5 cm for a height above 165 cm.

World Health Organization/Food and Agriculture Organization (FAO) Equations

These equations for REE (BMR) are simpler than those of Harris and Benedict and are based on more comprehensive data. The sample used includes persons who are thin (body mass index [BMI] < 20) or overweight (BMI > 25). People of the same weight but different heights have similar BMRs, but among adults of the same height but different weights, those with lighter weights have higher BMRs per kilogram because of the difference in body composition. For this reason, the simpler formula based only on body weight, age, and sex is reasonable. The equations to be used are as follows:

Age (y)	Male	Female
0–3	$(60.9 \times W^{a}) - 54$	$(61.0 \times W) - 51$
3–10	$(22.7 \times W) - 495$	$(22.5 \times W) + 499$
10–18	$(17.5 \times W) + 651$	$(12.2 \times W) + 746$
18–30	$(15.3 \times W) + 679$	$(14.7 \times W) + 996$
30–60	$(11.6 \times W) + 879$	$(8.7 \times W) + 829$
>60	$(13.5 \times W) + 987$	$(10.5 \times W) + 596$

[a] Weight in kilograms.

With such formulas, one can derive daily REE values for persons of different weights (Table 5-3). The values differ from the 1973 World Health Organization standards mostly for females, in whom an overestimation of weight above 40 kg reached nearly 18% by the end of the scale. For both sexes, the earlier standards underestimated values between 15 and 20 kg. The overestimation of BMR for healthy women over 40 kg was confirmed in a careful study of 44 women ages 18 to 65 years (9). This study found that other currently available tables and regression equations (including Harris–Benedict) overestimate the BMR of healthy women by 7% to 14%. The authors offered the following equations:

For persons who are not athletes:

$$\text{BMR} = 795 + 7.18 \times \text{W [kg]}$$

For athletes:

$$\text{BMR} = 50.4 + 21.1 \times \text{W [kg]}$$

The World Health Organization/FAO equations offer realistic and comprehensive estimates. One should remember, however, that the predicted BMR in nonathletes may overestimate or underestimate the measured values by 20% to 30% for any individual.

Method Based on Body Size and Age

The resting metabolic rate declines with age by almost 2% per decade in adults 20 to 75 years of age (10). The metabolic rate data compiled by Fleish (Table 5-2) can be converted to

TABLE 5-3. Basal Metabolic Rates According to Weight and Sex

Body weight (kg)	Metabolic rate (kcal/24 hr)	
	Males	Females
3.0	120	144
4.0	191	191
5.0	239	239
6.0	287	311
7.0	357	383
8.0	431	431
9.0	478	502
10.0	550	550
11.0	622	622
12.0	670	670
13.0	718	718
14.0	765	765
15.0	813	813
16.0	861	837
17.0	885	861
18.0	909	885
19.0	933	909
20.0	957	933
22.0	1,005	957
24.0	1,058	981
26.0	1,100	1,005
28.0	1,124	1,055
30.0	1,172	1,076
32.0	1,196	1,100
34.0	1,244	1,124
36.0	1,268	1,148
38.0	1,316	1,172
40.0	1,340	1,172
42.0	1,363	1,196
44.0	1,387	1,220
46.0	1,435	1,220
48.0	1,459	1,244
50.0	1,483	1,268
52.0	1,507	1,268
54.0	1,531	1,292
56.0	1,579	1,316
58.0	1,603	1,316
60.0	1,627	1,340
62.0	1,650	1,363
64.0	1,674	1,387
66.0	1,698	1,411
68.0	1,722	1,435
70.0	1,746	1,459
72.0	1,746	1,459
74.0	1,770	1,483
76.0	1,794	1,507
78.0	1,818	1,507
80.0	1,842	1,532
82.0	1,866	1,555
84.0	1,890	1,579

MJ/24 hr have been converted to kcal/24 hr as follows: 1,000 kcal = 4.18 MJ (Kleiber M. Joules VS. Calories in nutrition. *J Nutr* 1972;102:307). These figures are not applicable to the elderly. See text for a formula to use for persons older than 60 years.
Modified from James WPT. Basal metabolic rate: comments on the new equations. *Hum Nutr Clin Nutr.* 1985;39C[Suppl 1]:5.

Wilmore's equation, which allows the rate to be calculated without consulting the table (11). If one assumes a metabolic rate of 55 kcal per m^2 per hour at birth, then the following equations apply:

From birth to age 19 years:

$$\text{BMR (kcal/m}^2\text{/hr)} = 55 - \text{age [years]}$$

For age 20 years or more:

$$\text{BMR (kcal/m}^2\text{/hr)} = 37 - [(\text{age} - 20) + 10]$$

Estimated BEE for Most Hospitalized Patients

The goal for caloric intake for most patients is between 25 and 35 kcal/kg/day, or 125% to 175% of the BEE (BMR). The range of TEE for healthy nonelderly U.S. adults, by comparison, is 167 ± 14% of the BEE (2). To avoid excess provision of glucose, fat, or amino acids, reasonable goals for nonprotein kilocalories per day are as follows: glucose, ≤5 g/kg/day; lipid, ≤1 g/kg/day; and amino acids, 0.75 to 1.5 g/kg/day from a mixed protein diet, depending on the status of protein stores and the need to replace protein losses.

A simple method for estimating total daily energy requirements in hospitalized patients is based on the body mass index (BMI) (kg per m^2) (Table 5-4). Energy requirements are inversely proportional to the BMI. The lower range in each category should be considered in patients who are insulin-resistant or critically ill, unless they are depleted of body fat, to decrease the risk for hyperglycemia and infection associated with overfeeding.

The total energy requirement in illness in hospitalized patients on total parenteral nutrition (TPN) rarely exceeds by much the basal rate of the same patient in health. This is because both starvation and catabolic states (cachexia) lead to a relative conservation of body tissues. Starvation produces a fall in nearly all metabolic processes, whereas cachexia increases catabolism. But the net effect on TEE is minimal or even negative (see Table 1-21).

The basal caloric requirement of the usual patient rarely exceeds 2,100 kcal because as a rule such patients do not weigh in excess of 90 kg (200 lb). Thus, the total energy requirement for a patient with severe illness is generally less than 3,000 kcal per day. In fact, the earlier estimates of massively increased caloric requirements in sepsis have not been substantiated by studies of oxygen consumption. Because the energy of activity is quite low in immobilized patients, the total energy requirement in severe illness usually does not exceed the estimated BMR by more than 25% (12). Therefore, although the total energy requirement in patients with illness has been estimated by adding to the REE additional energy requirements for activity, stress, and fever, it is probably most accurate to base the REE on Harris–Benedict or WHO equations using actual body weight. Equations have been developed for use in estimating the REE of hospitalized patients when indirect calorimetry is not available and when more precision is desired than is provided by the

TABLE 5-4. Estimate of Energy Requirements for Patients Based on Body Mass Index[a]

	Energy requirements (kcal/kg/day)	
BMI (kg/m^2)	**Critically ill patients (RMR)**	**Other patients (RMR + TEF + TEA)**
<15	35–40	35–40 + 20%
15–19	30–35	30–35 + 20%
20–29	20–25	20–25 + 20%
≥30	15–20[b]	15–20

[a] Use Harris–Benedict or World Health Organization equations to estimate requirement for patients whose estimate by this method is <1,200 kcal/day.
[b] Do not exceed 2,000 kcal/day.
BMI, body mass index; RMR, resting metabolic rate; TEF, thermal effect of food; TEA, thermal effect of activity.

TABLE 5-5. Estimation of Resting Energy Expenditure in Hospitalized Patients

For ventilator-dependent patients:

REE(s) = 1784 − 11(*A*) + 5(*W*) + 244(*S*) + 239(*T*) + 804(*B*)

For spontaneously breathing patients:

REE(s) = 629 − 11(*A*) + 25(*W*) − 609(*O*)

REE, resting energy expenditure (kcal/d); *A,* age (y); *W,* body weight (kg); *S,* sex (male = 1, female = 0); *T,* diagnosis of trauma (present = 1, absent = 0); *B,* diagnosis of burn (present = 1, absent = 0); *O,* obesity (present = 1, absent = 0).
From Malone AM. Methods of assessing energy expenditure in the intensive care unit. *Nutr Clin Pract.* 2002;17:21.

Harris–Benedict equation (6,13). These equations were developed for both ventilator-dependent and spontaneously breathing patients by correlating indirect calorimetry results and other variables by means of multivariate regression analysis (Table 5-5). Increases above those determined for REE can be estimated, even for medically ill patients. For severely catabolic or malnourished hospitalized patients or for those with high fever or sepsis, an increase of 20% to 25% can be added. Overestimation should be avoided, however, because increased feeding with high-glucose infusions can cause hyperglycemia, hypokalemia, edema, and fatty liver.

THE ENERGY EXPENDITURE OF ACTIVITY/PHYSICAL ACTIVITY LEVEL

The energy expenditure of activity (EEA) can vary from 1.1 to 10.3 kcal/kg/hour. In fact, a correct calculation of energy requirement over 24 hours would include sleep time (about 90% of BMR) and the metabolic rate per hour of different types of work. In some types of work (e.g., gardening), certain muscle groups become fatigued without a large number of calories being used. Usually, any exercise in which the body leaves the ground (e.g., running) uses a large number of calories. However, one should not overestimate the contribution of sports to overall daily energy use because sports activities generally last for a short time and are followed by a much longer period of inactivity. Table 5-6 provides a more detailed analysis of activity-related energy expenditures. A number of methods are used to estimate or calculate the EEA.

Calculation Based on Level of Activity

A calculation, albeit imprecise, can be used if the typical activity pattern is known. An average daily activity factor can be calculated from the estimated level of activity, weighted for the time spent in each activity. Average estimates for different levels of activity are given in Table 5-7 as METs measured by the rate of oxygen consumption relative to basal conditions. The ΔPAL is calculated from the BEE using the reference body weights and heights for adults (Table 5-8). The difficulty with assigning a level of activity to individuals without a daily diary is due to the large variability in the duration and intensity of physical activity. The determination of the level of PAL (sedentary, low active, active, very active) is determined by the type of activity and how sustained it is. A truly valid estimate would consider activity patterns over days or weeks.

An accurate estimation of the BMR, or REE, of patients in intensive care units is important because both overfeeding and underfeeding may produce adverse effects. The calculation made from equations can be inaccurate in critically ill patients (14). Moreover, the effects of stress and infection are difficult to estimate. Therefore, other methods have been used to provide more accurate assessments. It is not yet certain whether this degree of accuracy is required for patients in intensive care units because the World Health Organization and Harris–Benedict equations are useful in determining the

TABLE 5-6. Calories Used for 10 Minutes of Activity

Activity	Body weight (lb)				
	125	150	175	200	250
Sedentary					
Sleeping	10	12	14	16	20
Sitting	10–15	12–18	14–21	16–24	18–30
Standing	12	14	16	19	24
Dressing or washing	26	32	37	42	53
Light office work	25	30	34	39	50
Standing (light activity)	20	24	28	32	40
Typing 40 words per minute	25	30	34	39	50
Locomotion					
Walking, downstairs	56	67	78	88	111
Walking, upstairs	146	175	202	229	288
Walking, 2 mph	29	35	40	46	58
Walking, 4 mph	52	62	72	81	102
Running, 5.5 mph	90	108	125	142	178
Running, 7 mph	118	141	164	187	232
Cycling, 5.5 mph	42	50	58	67	83
Cycling, 13 mph	89	107	124	142	178
Light work					
Domestic work	34	41	47	53	68
Weeding garden	49	59	68	78	98
Shoveling snow	65	78	89	100	130
Lawn mowing, power	34	41	47	53	67
Assembly work in factory	20	24	28	34	40
Auto repair	35	46	48	54	69
House painting	29	35	40	46	58
Heavy work					
Chopping wood	60	73	84	96	121
Pick and shovel	56	67	78	88	110
Dragging logs, lifting heavy materials	158	189	220	252	315
Recreation					
Baseball (except pitching)	39	47	54	62	78
Basketball	58	70	82	93	117
Dancing (moderate)	35	42	48	55	69
Football	69	83	96	110	137
Golfing	33	40	48	55	68
Racketball, squash	75	90	104	117	144
Skiing, downhill	80	96	112	128	160
Skiing, cross-country	98	117	138	158	194
Swimming, crawl (20 yd/min)	40	48	56	63	80
Tennis	56	67	80	92	115
Volleyball	43	52	65	75	94

Adapted from Brownell KD. *The Partnership Diet Program.* New York: Rawson-Wade, 1980.

REE in many cases. In addition, determinations must be made when the patient's clinical condition is stable. It is unlikely that the risk of providing too much (or too little) energy to critically ill patients will justify the expense of calorimetric measurements. The risks of nutrient provision more often involve fluid and electrolytes when given in excess. If calorimetry is available, it should be used only for selected patients who are very

TABLE 5-7. Impact of Various Activities on Physical Activity Level (PAL) Estimations

Activity	METs	ΔPAL/h	Activity	METs	ΔPAL/h
Mild → Moderate			**Vigorous**		
Lying quietly	1.0	0	Chopping wood	4.9	0.22
Riding in a vehicle	1.0	0	Tennis (doubles)	5.0	0.23
Light activity, sitting	1.5	0.03	Dancing (fast)	5.5	0.26
Playing piano	2.3	0.07	Skating, ice	5.5	0.26
Walking (2 mph)	2.5	0.09	Cycling, moderate	5.7	0.27
Watering plants	2.5	0.09	Dancing, aerobic	6.0	0.29
Golf (with cart)	2.5	0.09	Skating, roller	6.5	0.31
Dancing, ballroom	2.9	0.11	Skiing, water/snow	6.8	0.33
Volleyball, casual	2.9	0.11	Climbing hills	6.9	0.34
Walking the dog	3.0	0.11	Swimming	7.0	0.34
Loading/unloading car	3.0	0.11	Climbing w/load	7.4	0.37
Taking out trash	3.0	0.11	Walking (5 mph)	8.0	0.4
Mopping/vacuuming	3.5	0.14	Jogging (10 mph)	10.2	0.53
Lifting, raking lawn	4.0	0.17	Playing squash	12.1	0.63
Calisthenics, no weight	4.0	0.17			
Golf, no cart	4.4	0.19			
Swimming, slow	4.5	0.20			
Walking, 4 mph	4.5	0.20			

METs = multiples of resting oxygen uptake, based on 3.5 mL of O_2/min/kg body weight in adults.
PAL levels are: Sedentary 1.0–1.4, Low active 1.4–1.6, Active 1.6–1.9, Very Active 1.9–2.5
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids.* Food and Nutrition Board, Institute of Medicine, Washington, DC: The National Academies Press, 2005, pp. 885–886.

malnourished or who might tolerate the energy provision poorly, such as those in cardiac or respiratory failure.

Indirect calorimetry involves measuring oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) at the mouth. Most clinical equipment utilizes the open-circuit method, in which a set of one-way valves directs expired air into a collecting bag. At the end of a timed period, both the volume and composition of expired air are measured and the rates of oxygen consumption and carbon dioxide production are calculated by the difference between the concentrations in the inspired air and the gas collected. The REE is determined from these data by using the respiratory quotient, $\dot{V}CO_2/\dot{V}O_2$. This method requires the use of a metabolic cart and trained personnel but is generally quite accurate. Breath-by-breath systems now allow measurement of the REE even in ventilator patients receiving high levels (>40%) of inspired oxygen (15). If only oxygen consumption data are available, the REE can be estimated by multiplying the oxygen consumption in milliliters per minute by a factor of 7.

The Fick equation can be used to calculate energy expenditure in patients who have a pulmonary artery catheter in place (16). The calculation is based on $\dot{V}O_2$ alone, with use of the known caloric value of oxygen (4.86 kcal per L for an estimated respiratory quotient of 0.85). Oxygen consumption is calculated from the Fick equation with measurements of cardiac output (CO), hemoglobin level (Hb), and arterial (SaO_2) and mixed venous ($S\dot{v}O_2$) oxygen saturations.

$$\text{REE (kcal/day)} = CO \times Hb \times (SaO_2 - S\dot{v}O_2) \times 95.18$$

This method appears to be as accurate as indirect calorimetry and uses data available in most intensive care units. In mechanically ventilated nonsurgical patients without sepsis, the Harris–Benedict estimate was comparable (17). In patients with sepsis, an additional requirement of about 20% is appropriate.

TABLE 5-8. New Median Heights and Weights for Children and Adults in the United States

Gender	Age	Reference height [cm (in.)]	Reference weight [kg (lb)]	Body mass index (kg/m^2)
M, F	2–6 months	62 (24)	6 (13)	—
	7–12 months	71 (28)	9 (20)	—
	1–3 years	86 (34)	12 (27)	
	4–8 years	115 (45)	20 (44)	
Male	9–13 years	144 (57)	36 (79)	
	14–18 years	174 (68)	61 (134)	20.5
	19–30 years	177 (70)	70 (154)	22.5
Female	9–13 years	144 (57)	37 (81)	
	14–18 years	163 (64)	54 (119)	20.4
	19–30 years	163 (64)	57 (126)	21.5

Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids.* Food and Nutrition Board, Institute of Medicine. Washington DC: The National Academies Press, 2005, p. 35.

SPECIAL ENERGY REQUIREMENTS

There are additional energy requirements in illness. Heat production increases with inflammation and infection. Infection increases basal metabolism. The final caloric expenditure depends on the increase in oxygen consumption caused by fever or new cell production and the decrease in oxygen consumption caused by diminished calorie intake and immobility. An estimate for increasing the REE for fever is the following: (°F − 98.6) × 0.07 for Fahrenheit, and (°C − 37.0) × 0.13 for centigrade.

Fasting and malnutrition decrease the BMR, or BEE, approximately 25% by day 20. Although the calculations for BEE probably underestimate the REE for malnourished patients, the total REE falls significantly as weight falls.

Many conditions associated with weight loss have been thought to be associated with increased energy needs. However, daily energy expenditure is lower than expected in elderly patients with cachexia caused by heart failure and Alzheimer disease (18). This result is consistent with inadequate intake as the cause of weight loss because in the long term, the balance between daily energy expenditure and food intake must determine body composition.

Malabsorption is a special case of an increased energy requirement in which a loss of nutrients results from incomplete absorption of food. The most accurate way to assess caloric loss would be calorimetry of the feces. However, one can determine daily fat excretion more practically with a 72-hour fecal fat study. Fat accounts for about 40% of caloric intake. If one assumes that protein and carbohydrate are similarly malabsorbed, one then can estimate total calorie malabsorption by multiplying caloric loss from fat by 2.5. Carbohydrate probably is more efficiently absorbed than fat in diseases producing a short-bowel syndrome but not necessarily in diffuse mucosal disease. In practice, no distinction need be made between the proportion of macronutrients as caloric sources in the diet and as caloric losses in the feces.

$$\text{Fat excretion (g/day)} \times 9 \text{ kcal/g} = \text{fecal kcal loss from fat malabsorption}$$
$$\text{Fecal kilocalorie loss from fat} \times 2.5 = \text{total kcal lost from diet}$$

The energy requirement for a full-term pregnancy is estimated at 80,000 kcal. The WHO recommends an increased intake for pregnant women of 150 kcal per day over normal during the first trimester and 350 kcal per day over normal during the rest of the pregnancy. This estimate does not take into account any variation in physical activity or weight gain unrelated to gestation. Because the activity of pregnant women in Western

societies is usually decreased, an increase of 300 kcal per day is recommended for the second and third trimesters.

The production of 1 dL of human breast milk requires 67 to 77 kcal. Because the efficiency of converting nutrients to milk energy is 80% to 90%, the total energy requirement is 80 to 95 kcal per dL of milk. If 8.5 dL per day is the average rate of milk production for 3 months, the energy needed will be 750 kcal per day. However, extra fat stores are deposited during pregnancy, and it is estimated that these can provide the mother with 200 to 300 kcal per day for 3 months. Thus, the recommended additional caloric requirement for nursing mothers is 500 kcal per day.

ESTIMATION OF CALORIC INTAKE

The estimation of a patient's total daily intake of calories requires a careful dietary history. It is most helpful to use a reference in which the caloric contents of foods are listed according to common package limits or portion sizes (i.e., per ounce or per cup). Sources of such data are readily available in the health section of retail book stores, or from the U.S. Department of Agriculture *Food Composition Handbook 8* (www.nal.usda.gov/fmic/foodcomp). Table 5-9 lists the caloric content of some important common foods.

Sometimes, the type of food is known to be homogeneous, and the caloric content can be estimated from the volume ingested.

Nutrient	kcal/g	kJ/g
Carbohydrates		
Monosaccharide	3.75	16
Disaccharide	3.94	16
Starch and glycogen	4.13	17
Total carbohydrate	4	17
Protein	4	17
Long-chain triglyceride	9	37
Medium-chain triglyceride	8.3	34
Alcohol (specific gravity 0.79)	7	29
Intralipid 10% (specific gravity 0.91)	1.1 kcal/mL	4

The caloric content of alcoholic beverages can be calculated. The specific gravity of alcohol is 0.79 (rounded off to 0.8). Thus,

$$\text{Grams of alcohol} = (\text{proof of alcoholic beverage} \div 2) \times 0.8 \times \text{dL of beverage}$$

$$\text{kcal of beverage from alcohol} = \text{grams of alcohol} \times 7 \text{ kcal/g}$$

For example, three 2-oz drinks of 86-proof bourbon yields >400 kcal

$$(86 \div 2) \times 0.8 \times 1.8 = 62 \text{ g} \times 7 \text{ kcal/g} = 434 \text{ kcal}$$

or to approximate,

$$\text{kcal from alcohol} = 0.8 \times \text{proof} \times \#\text{ ounces}$$

Using the example above, three drinks (2 oz each) of 86-proof bourbon = $0.8 \times 86 \times 6 = 413$ kcal.

The alcohol content of a unit of common beverages is 10 to 13 grams.

Beverage	Unit	Alcohol content (g)	kcal/U
Distilled liquor	One jigger		
80 proof		10	70
90 proof		11	80
100 proof		13	90
3.6–4.0% beer	One 12-oz can	12.6–13.5	140–150
12.5–14.5% wine	3 1/2-oz glass	10.0–11.6	70–80

TABLE 5-9. Caloric Content of Common Foods

Food	Portion size	Kilocalories
Apple	1 (3/4 lb)	80
Baby foods		
Vegetables, fruits	4 3/4 oz	113–207
Meat	3 1/2-oz jar	99–136
Bacon, cooked	Yield from 1/4 lb	215
Beans, green, cooked	1 cup	35
Beef		
Sirloin steak, cooked	Yield from 1/2 lb	596
Ground beef, lean, cooked	Yield from 1/2 lb	497
Beverages		
Cola	12-oz can	144
Ginger ale, sweet mixers	12-oz can	113
40% Bran flakes	1 cup	106
Bread		
White	1 slice, regular	63–74
Whole wheat	1 slice, regular	56–61
Rye	1 slice, regular	61
Butter or margarine	1 tbs	322
Cake		
Chocolate, no icing	1 piece, 3 × 3 × 2 in	322
White, with chocolate icing	1 piece, 3 × 3 × 2 in	453
Candy		
Chocolate	1 oz	135–144
Chocolate with nuts	1 oz	159
Carrot	1	30
Cheese		
Cheddar	1 slice	96
American	1 oz	113
Cottage (regular)	1 oz	30
Swiss	1 slice	130
Chicken		
Broiled	Yield from 1 lb	273
Fried	Yield from 1 lb	565
	Breast, half	160
	Thigh	122
Cookies		
Brownies	1	97
Chocolate chip	1	52
Sugar	1	46
Corn, cooked	1 ear	70
Crackers		
Saltines	1 cracker	12
Graham	1 cracker	62
Doughnuts		
Raised	1	176
Cake	1	164
Eggs		
Extra large, fried	1	112
Cooking oil	1 tbs	111–120
Grapefruit	1	80–132
Ice cream		
Regular	1 cup	257
Frozen custard	1 cup	334
Rich (16% fat)	1 cup	329
Jam	1 tbs	54
Milk		
Whole	1 cup	159
Skim	1 cup	88
Low fat	1 cup	145

(*continued*)

TABLE 5-9. Caloric Content of Common Foods (*Continued*)

Food	Portion size	Kilocalories
Noodles, egg	Yield from 4 oz	440
Orange		
Navel	1	45–87
Juice	1 cup	112–122
Pastry, Danish	one 4-in-diameter pastry	274
Peanuts, out of shell	1 oz	166
Peanut butter	1 tbs	94
Peas, canned	1 cup	142
Pies		
Fresh, banana	one 31/2-in piece (1/8 pie)	253
Fresh, pecan		431
Frozen	one 31/2-in piece (1/8 pie)	187–282
Pizza		
Homemade, cheese	1/8 12-in pie	153
Frozen, cheese	1/8 12-in pie	139
Ham, roasted or baked	1/2 lb	848
Pork chops, lean	Yield from 1/2 lb	442
Potatoes		
Boiled with skin	1	173
Boiled without skin	1	122
French fried	ten 4-in strips	214
Chips	10 chips	114
Rice, white, cooked	1/4 cup	56
Salad dressing, Italian	1 tbs	83
Salmon		
Fresh, broiled	1/2 lb	364
Canned	1/2 lb	320–477
Sausage		
Bologna	1 slice	67–86
Hot dogs, cooked	1	134–170
Pork, cooked	1 link	62
Salami	1 slice	66–88
Spaghetti, cooked, from 21/2 oz dry	1/4 lb	168
Sugar, granulated	1 tsp	15
	1 cup	770
Tuna, canned	7 oz	570

To calculate the caloric content of cooking oil:

$$\text{kcal} = \text{mL} \times \text{specific gravity of cooking oil } (0.91) \times 9 \text{ kcal/g}$$

for example, 2 tbs of olive oil = $30 \times 0.9 \times 9 = 243$ kcal. To calculate the caloric content of dextrose infusions:

$$\text{kcal} = \text{nutrient \%} \times [\text{volume infused (mL)} \div 100] \times 3.4 \text{ kcal/g of hydrated dextrose}$$

for example, 3 L of 5% dextrose in water contains $5 \times (3{,}000 \div 100) \times 3.4 = 510$ kcal.

Methods for Assessing Dietary Intake

Even if one allows for the accurate translation of food units into calories, it is difficult to obtain a reliable dietary history with the methods available. The Committee on Food Consumption Patterns, Food and Nutrition Board, of the National Research Council has compiled many data on the methods for assessing food consumption and its relationship to nutritional status (19).

The 24-hour recall is the simplest method available in that it relies on the patient's ability to remember how much food was eaten in a 24-hour period. The 24-hour dietary recall requires a trained interviewer but has been used with success in the National Health and Nutrition Examination Surveys (NHANESs). It takes a minimum amount of time to

complete and can provide reproducible data. Although it is notoriously inaccurate in terms of the actual amount of food the patient has ingested (e.g., the intake of alcohol may be neglected), it is often the only technique available for assessing intake. The inaccuracy is compounded by not knowing the nutrient content of the ingested foods, and by the underreporting of intake in women in comparison with men.

The food history is also based on the patient's ability to recall, but the intake of food is averaged over a period of time. For example, the contents of a patient's average breakfast, lunch, or dinner, or all three, are calculated. The food history method is easy to use but suffers from the same inaccuracy of memory as 24-hour recall.

The patient can keep a written record of the amounts and types of food ingested. This method is accurate if the record is scrupulously maintained, but such thoroughness is rare. Also, people tend to alter their eating behavior during the test period to simplify the record. However, the energy content of foods eaten can be determined accurately, with only moderate overestimates, in a 5-day food record.

The calorie count is useful for the hospitalized patient because it requires the assistance of a dietitian, who understands the need for the calorie count. To ensure the accuracy of the count, no food is ingested by the patient other than what is reported to the dietitian. The dietitian observes the amount of food eaten at each meal and estimates its caloric content. Daily variations in food preparation and serving portions in the central kitchen can produce some inaccuracies. This method is the best of those available for estimating caloric intake. It combines some direct observation of the food actually ingested with a reasonable degree of control over its preparation. The major disadvantage is that it assesses intake of hospital food rather than home-prepared meals.

The weighed diet is very accurate, but it must be carried out on a metabolic ward where the portions of foods are weighed and most of the food is prepared on the floor. In this way, differences in the processing of foods are minimized, and the actual caloric content of foods is best estimated.

ENERGY BALANCE

Energy balance (kilocalories per day) equals kilocalories obtained minus kilocalories expended (BEE + EEA). *Calories obtained* refers to an estimate of dietary intake or to a calculation of calories fed enterally or parenterally (it can also refer to a combination of estimation and calculation). *Energy expended* includes that expended in basal metabolism and through physical activity or disease. When the intake of food exceeds the expenditure of energy, weight is gained. When the expenditure of energy exceeds the intake of food, weight is lost. When the energy balance is zero, weight is stable.

Although both water and carbohydrate stores are lost in the first few days of fasting, the loss of cell water is proportionally greater than the loss of glycogen. It is generally assumed that a loss of 1 lb of weight (0.45 kg) corresponds to a deficit of about 3,400 kcal. It is instructive to review the data on which this assumption is based. The mean composition of tissue lost during the first 11 weeks of semistarvation in otherwise healthy subjects is 40% fat, 12% protein, and 48% water. From weeks 12 to 23, the composition of tissue lost is 54% fat, 9% protein, and 37% water. The BMR per square meter falls an average of 31%, and the physical activity level drops by 55%. Thus, the rate of weight loss diminishes with time because expenditure decreases as intake remains constant. The average energy value of weight loss is about 1,900 kcal per lb during the first 11 weeks and about 2,500 kcal per lb during the next 12 weeks of semistarvation.

The mean composition of tissue lost from obese subjects is 78% fat, 5% protein, and 17% water. The energy value of each pound lost is about 3,400 kcal. It appears that obese patients use their adipose tissue reserves more efficiently than persons of normal weight because the percentage of calories available as fat from body stores is higher. In normal persons, weight loss often is associated with a decrease in activity, and total energy expenditure falls. The decrease in physical activity in obese patients during weight loss is less noticeable because they are less active initially. Therefore, weight loss is initially maintained better in very obese than in slightly obese patients because of their more efficient mobilization of fat (high-calorie source) from tissue stores and the fact that they continue to expend energy for a longer period of time at the same rate as before they began to lose weight.

Unfortunately, weight loss during starvation is not the same as controlled weight loss and may approach 50% fat and 50% fat-free mass. Thus, in a starving patient, the decrease in muscle mass and in BMR is larger. This accounts for the lower-than-expected BMR in severely ill hospitalized patients. It is also misleading to obese patients, who lose less fat while fasting completely than during slower, more controlled weight loss (20).

To calculate an estimated weight loss on a controlled diet, an allowance must be made for the decreased BMR and diminished level of activity noted in nonobese subjects. Because weight loss in normal subjects decreases the BMR by 31% and the energy expenditure of activity decreases by 55%, the average estimated decrease in expenditure is 40%. If this correction is applied to the caloric value per pound of weight loss in nonobese subjects (2,100 kcal per lb ÷ 0.6 = 3,500), the estimated weight loss by nonobese and obese subjects becomes virtually the same. Thus, the figure of 3,400 kcal per lb lost can be used to calculate weight loss for all subjects without any correction factor. An example of calculating tissue losses during weight loss is summarized below.

	Nonobese subject	Obese subject
Daily caloric intake (I)	2,000 kcal	3,000 kcal
Daily expenditure of energy (E)	2,800 kcal	3,800 kcal
Weekly caloric deficit ($E - I$) × 7	5,600 kcal	5,600 kcal
Predicted weekly weight change		
Weekly caloric deficit ÷ 3,400 kcal	1.6 lb/week	1.6 lb/week

Recommended Daily Energy Intake

Energy intake must be balanced according to the needs of age, sex, body size, and physical activity if a desirable body weight is to be maintained.

Despite attempts to estimate energy requirements for groups of adults, a wide range is seen within persons of the same body size and age that reflects differences in activity and individual metabolism. Moreover, it is not possible to establish desirable weights with certainty. For these reasons, the Committee on Dietary Reference Intakes of the Food and Nutrition Board has derived a table of mean estimated energy intakes that are related not only to the EER and the level of PAL, but also allows for a decline in these estimates with each year above 18 (Table 5-10). The data included are only for persons of average weight and height (as defined in Table 5-8) who are classified as 'active' in the PAL scale.

TABLE 5-10. Dietary Reference Intake Values for Energy by Active Healthy Americans[a]

	EER (kcal/d)[b]	
Life stage group	**Male**	**Female**
0–6 months	570	520 (3 months)
7–12 months	743	676 (9 months)
1–2 years	1,046	992 (24 months)
3–8 years	1,742	1,642 (6 years)
9–13 years	2,279	2,071 (11 years)
14–18 years	3,152	2,368 (16 years)
>18 years	3,067	2,403 (19 years)
>19 years	Subtract 10 kcal/day/year	Subtract 7 kcal/day/year
Pregnancy 19–50 years:	1st/2nd/3rd trimester	2,403/2743/2855 (19 years)
Lactation 19–50 years:	1st 6 mo/2nd 6 mo	2,733/2,803 (19 years)

[a] Applies to moderately active (active PAL group) residents of the United States and Canada.
[b] The intake is appropriate for individuals of the reference weight, height, and age who qualify for a PAL designation of "active."
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids.* Food and Nutrition Board, Institute of Medicine, Washington, DC: The National Academies Press, 2005, p. 5.

ESTIMATION OF PROTEIN REQUIREMENTS

Normally, nitrogen derived from amino acids, the catabolic product of proteins, is excreted in the urine and feces and lost from the skin. Unlike the energy that is retained and stored in triglyceride and glycogen, proteins and amino acids are not stored in the body. Therefore, protein or nitrogen requirements are often estimated by calculating nitrogen losses on a daily rather than a weekly basis. When excess protein is ingested, the amino acids not needed for new protein synthesis are transaminated so that the non-nitrogenous portion of the molecule can be used as a calorie source, as, for example, in pyruvate derived from alanine. The nitrogen that is not needed is converted to urea and excreted in the urine.

Urinary losses of nitrogen urea account for more than 80% of urinary nitrogen. Creatinine, porphyrins, and other nitrogen-containing compounds account for the remaining nitrogen.

$$\text{Urinary nitrogen loss} = [\text{urea } N_{\text{urine}} \text{ (mg/dL)} \times \text{daily urine volume (dL)}] \div 0.8$$

Urinary nitrogen excretion is related to the BMR. The larger the muscle mass in the body, the greater the number of calories needed to maintain it. Also, the rate of transamination is greater as amino acids and carbohydrates are interconverted to fulfill energy needs in the muscle. Between 1 and 1.3 mg of urinary nitrogen is excreted for each kilocalorie required for basal metabolism. Nitrogen excretion also increases during exercise and heavy work.

Fecal and skin losses account for a relatively constant proportion of nitrogen loss from the body in normal conditions, but these may vary widely in disease states. Thus, measurement of urinary nitrogen loss alone may not provide a reliable prediction of the daily nitrogen requirement when it is most needed. Fecal losses are a consequence of the inefficient digestion and absorption of protein (93% efficiency). In addition, the intestinal tract secretes proteins into the lumen from saliva, gastric juice, bile, pancreatic enzymes, and enterocyte sloughing. These sources contribute, respectively, about 3, 5, 1, 8, and 50 g of protein daily to the total protein secreted into the intestinal lumen.

Total nitrogen (N) losses include those from urine, feces, and skin. Fecal nitrogen averages 1 to 2 g per day in the absence of diarrhea. Skin losses average 0.3 g per day. The total fecal and skin losses can be estimated at about 2 g per day.

$$\text{Total N loss (g/day)} = N_{\text{urine}} + N_{\text{stool}} + N_{\text{skin}} \approx N_{\text{urine}} + 2$$

When fecal losses are measured, an estimated nitrogen loss of 1 g/day is used to cover losses in skin and other compartments.

Normal daily protein requirement is based on estimates of N loss and need (weight and extra requirements for growth and pregnancy). Obligatory losses of nitrogen are not altered by differences in age or sex, and urinary losses of nitrogen are proportional to body size and weight. The total losses from all sources are approximately 2 mg of nitrogen per basal kilocalorie. The best estimate of EAR of nitrogen in healthy adults is 105 mg N/kg/day, or 0.66 g/kg/day (21). This is the lowest amount of intake that achieved zero N balance, and was not apparently affected by climate, age, sex, or source of dietary protein. Women have a lower N requirement than men per kilogram of body weight, but they have a higher percent of fat mass (28%) compared to men (15%). There is no difference in protein requirements by gender when corrected for lean body mass (2). The RDA estimated by the DRI Committee was based on the meta-analysis by Rand (21). The amount of protein needed for zero balance in older adults was similar to that for younger adults (2). Minimal nitrogen loss per day has been estimated for adults. In a series of 11 studies reviewed by the World Health Organization (WHO), daily obligatory nitrogen losses averaged 53 mg per kg (range: 46 to 69 mg per kg). On the basis of short- and long-term balance studies, the WHO proposed a mean requirement of 0.6 g/kg/day for reference protein (highly digestible, high quality protein such as eggs, meat, milk, or fish) (22). If a value of 25% above the average is used to meet the needs of 97% of the population, 0.6×1.25, or 0.75 g/kg/day, was the RDA in 1989 for young male and female adults, and matches well with the current recommendation of 0.8 mg/kg/day (2) (Table 5-11).

Protein requirements are highest during infancy and adolescence. However, total body protein is lowest in infancy, and obligatory losses are greatest, so that protein deficiency is

TABLE 5-11. Dietary Reference Intake Values for Protein by Life Stage Group

Life stage group	EAR[a] (g/kg/day)		RDA[b] (g/kg/day)	
	Males	Females	Males	Females
0–6 months		1.52[c]		
7–12 months	1.0	1.0	1.2	1.2
1–3 years	0.87	0.87	1.05	1.05
4–8 years	0.76	0.76	0.95	0.95
12–13 years	0.76	0.76	0.95	0.95
14–18 years	0.73	0.71	0.85	0.85
>18 years	0.66	0.66	0.80	0.80
Pregnancy		0.88		1.1
Lactation		1.05		1.3

[a] EAR = estimated average requirement, the intake that meets the needs of half of the group
[b] RDA = recommended dietary allowance, intake that meets the needs of nearly all the group
[c] AI = adequate intake, the amount that sustains a defined health status, such as growth.
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids.* Food and Nutrition Board, Institute of Medicine, Washington, DC: The National Academies Press, 2005, pp. 12–13.

most common in infancy. A modified factorial procedure has been developed to calculate the protein needs of infants and children. Starting with a protein requirement of 1.1 g/kg/day for maintenance, an increment was added for growth and increased by 50% to allow for variability. Efficiency of utilization was assumed to be 70%, and a final calculated growth increment was added to the maintenance figure to recommend daily allowances for average U.S. dietary protein (Table 5-11). Another estimate is needed to convert the figures derived for reference proteins. The true digestibility of a mixed U.S. diet is estimated at greater than 90%, varying from 95% for milk, meat, eggs, peanut butter, and refined wheat, to 88% for polished rice, to 86% for oatmeal, whole wheat, corn, and soy flour, to 78% for beans (22).

About 925 g of protein is synthesized during a pregnancy by the mother for fetal and placental tissues. Protein needs increase as the pregnancy progresses. The amount of protein required for new deposition is 12.6 g per day, assuming that no additional protein is needed for the first trimester. Thus, the increased amount based on average body weight is 12.6 g per day ÷ 57 (reference adult female) = +0.22 g of protein/kg/day. When added to the EAR of a nonpregnant woman, one reaches an EAR of 0.88 g of protein/kg/day or an RDA of 1.1 g/kg/day. Based on the coefficient of variation of 12% seen in lactating women, an additional 0.2 g of protein/kg/day is recommended for lactating women.

CALORIE REQUIREMENT FOR PROTEIN

Nitrogen ingested as amino acids without other sources of energy is not efficiently incorporated into protein because the energy consumed in heat loss during metabolism (thermal effect) is especially high for protein. Moreover, the incorporation of amino acids into peptides requires three high-energy phosphate bonds, so that 10 kcal is used for each molecule derived from the hydrolysis of ATP. Any excess of dietary energy over basic needs improves the efficiency of dietary nitrogen utilization. To achieve a positive nitrogen balance when protein intake is barely adequate, a positive energy balance of about 2 kcal/kg/day is required (23). In other words, when energy intake is limited, protein balance is negative, even when protein intake seems adequate but is not excessive. The exact amount of extra calories required to produce a positive nitrogen balance depends on a large number of factors, including body energy stores, body protein mass, and the ratio of energy to protein sources in the food. To ensure positive nitrogen balance in the depleted patient, it is advisable

TABLE 5-12. Energy Intake Required to Maintain Positive Nitrogen Balance

Type of patient	Energy (kcal/kg/day)	Nitrogen (mg/kg per day)	kcal/g nitrogen	kcal/g protein
TPN postoperative	46.0	250	184	29
TPN septic	43.3	240	180	29
Ambulatory RDA	38.5	128	308	49

TPN, total parenteral nutrition; RDA, recommended daily allowance.
Data for postoperative patients from Hentley TF, Lee HA. *Nutr Metab.* 1975;19:201. Data for patients with septic disorders from Long CL, Crosby F, Geiger JW, et al. *Am J Clin Nutr.* 1976;29:380. Data for ambulatory patients from National Research Council. *Recommended Daily Allowances,* 10th ed. Washington, DC: National Academies Press, 1989, with permission.

to provide an amount of calories near the estimated energy requirement. Excessive calories may not lead to improvement in meaningful lean body mass.

A safe ratio (protein energy to total energy) that avoids protein–calorie malnutrition in children seems to be 1:20 (24)—that is, for every kilocalorie provided by protein, 19 kcal of nonprotein energy is needed to prevent protein–calorie malnutrition in children. Each gram of protein produces 4 kcal of energy, so 4 × 19 or 76 kcal of nonprotein energy is needed per gram of protein during the period of intense growth in children. When protein is present in excess of needs, even when nonprotein calories are limited, some of the protein is converted to energy that can be metabolized, and the 1:20 ratio is not required.

Relative requirements also have been estimated for energy and nitrogen in adult patients maintained in nutritional balance (Table 5-12). These estimates are, not surprisingly, somewhat lower than the estimates for children. Estimates of energy–protein requirements for normal, ambulatory 70-kg persons call for approximately 50 kcal from non protein sources per gram of protein, or about 300 kcal per g of nitrogen. This high ratio cannot usually be achieved with parenteral feeding because caloric intake is limited by the volume that must be infused. Therefore, acceptable figures for parenteral nutrition are about 25 to 30 kcal from nonprotein sources per gram of protein, or 150 to 180 kcal per g of nitrogen. These figures, however, should not be used as substitutes for independent estimates of energy and protein requirements. Especially in sick patients, energy and protein requirements may be dissociated to some extent. The protein–calorie ratios are important only insofar as they serve as a reminder of the need of calories along with protein replacement.

ESTIMATION OF PROTEIN IN ILLNESS

Obligatory loss of protein from the body (25 to 40 g per day) represents a small fraction of total protein synthesized by the body, which has been estimated to be from 285 to 340 g per day. Thus, the synthesis of protein can be decreased much more severely than is suggested by daily losses alone. Moreover, normal protein losses from the skin and gastrointestinal tract are only a fraction of what can be lost potentially. The average normal gastrointestinal protein loss is 1.7 g of nitrogen times 6.25, or 10.6 g of protein, some of which is recovered in the colon. The value of 6.25 is usually used for conversion of total nitrogen values to grams of protein because this is the factor for the high quality protein found in meat, fish, and eggs, and also in corn and beans. A lower factor (5.2 to 5.8) is used for other vegetable proteins, and higher values (~6.4) for dairy proteins.

Conditions Characterized by Excessive Protein Loss

Urinary Loss

Loss of protein occurs in nephrosis, chronic renal disease, and states of hypermetabolism with tissue breakdown. The losses from tissue breakdown are accounted for in the usual

TABLE 5-13. Estimate of Recommended Daily Protein Intake

Clinical condition	Protein requirements (g/kg IBW per day)
Normal	0.75
Metabolic "stress/illness/injury"	
Mild/moderate	1.0–1.25
Moderate/severe	1.25–1.5
Severe with extra losses (e.g., skin, urine)	>1.5
Renal failure, acute (undialyzed)	0.8–1.0
Hemodialysis	1.2–1.4
Peritoneal dialysis	1.3–1.5
Hepatic encephalopathy	0.4–0.6

IBW, ideal body weight.

estimate of urinary nitrogen loss. Estimating urinary urea nitrogen as the sole factor in urinary protein loss is the most logical determination for hypermetabolic conditions in which body proteins are degraded to urea. Protein loss can be estimated by multiplying urinary nonprotein nitrogen loss times 6.25. When protein *per se* is lost into the urine (e.g., in nephrosis or chronic renal disease), the protein itself is often measured.

Loss through Other Body Fluids

Nasogastric losses or losses through fistulae can be measured and added to the daily protein loss to allow a better estimate of total protein losses, especially if drainage volumes are large.

Loss through Gastrointestinal Tract, Skin, or Lungs

Nitrogen can be lost from organs with a large surface area of epithelial cells. These organs include the intestine, skin, and lungs. A limited number of observations have been made in illnesses involving these organs. Because the losses vary widely, no formula can be devised to estimate them. Intestinal losses are greatest in disorders associated with either decreased digestion or absorption of protein or increased loss of protein into the lumen. Because the small intestine has the largest surface area and the highest normal rate of protein loss of all the enteric organs (about 50 g of protein per day), diseases of the small intestine have the potential to cause the highest rate of protein loss from the body. These *protein-losing enteropathies* may or may not be accompanied by symptoms.

Estimation of Protein Requirements According to Severity of Illness

Nitrogen losses usually cannot be measured in clinical situations. For a hospitalized, adequately nourished adult receiving high quality protein intravenously, the basal requirements can be estimated to be about 0.4 to 0.6 g per kg. For an ambulatory patient consuming a standard diet of mixed-quality protein, the basal requirements should be estimated at 0.75 g per kg. The estimates in Table 5-13 are used to calculate protein requirements when excessive loss cannot be measured.

LONGITUDINAL MEASURES OF GROWTH OR BODY WEIGHT

Assessments are made to describe the nutritional status of populations and individuals. Normal values are descriptive of healthy subject groups and may not relate well to the individual patient undergoing evaluation. No single measure in routine use today can accurately reflect the protein–calorie status. Thus, many different anthropometric laboratory tests may be combined to formulate an overall impression. The advantages, disadvantages, and utility of the tests are described, but their routine use in nutritional therapeutics is not

necessarily endorsed. Longitudinal measures can be sensitive indicators of malnutrition before static body compartment measurements become abnormal. In the adult, maintenance of the usual body weight is generally expected. Therefore, weight loss with time is a helpful and simple longitudinal measurement in nutritional assessment. In the child, weight gain with growth is expected, and failure to maintain an expected growth rate similarly can be a simple indication of protein and calorie malnutrition. In addition to weight, increases in length and head circumference can be monitored in children because bone is growing.

Height should be measured without shoes in adults with the patient erect. Historical data are often erroneous by 1 to 2 in.

Weight is a simple measure of nutritional status. It can be compared with ideal weights or with usual weights corrected for height, derived from representative values of the adult U.S. population sampled in NHANES surveys.

$$\% \text{ Reference body weight} = (\text{actual weight} \div \text{reference body weight}) \times 100$$

To calculate weight change:

$$\% \text{ Body weight change} = [(\text{usual weight} - \text{actual weight}) \div \text{usual weight}] \times 100$$

A loss of 5% of body weight or less is not usually clinically important unless it occurs within a short time. Clearly, the rate of weight loss also must be considered in judging its significance. Weight changes cannot be an assessment of nutritive status in the face of increased extracellular fluid (edema, ascites, congestive failure) or during diuretic therapy. Despite these cautions, body weight is probably the best comprehensive estimate of protein–calorie status.

The definition of healthy weight has traditionally been set at the range of weights associated with the lowest mortality. However, many problems have arisen with this approach (25). A problem with standard weight guidelines is that a person can gain considerable weight (even 15 to 20 kg) and still remain within the recommended range. This has led to the concept that weight gain with age is acceptable. However, it is now clear that smaller gains in weight (e.g., 5 to 10 kg) during adult life are associated with an increased risk for chronic disease, including cancer, diabetes, hypertension, coronary artery disease, and cholelithiasis (25). Thus, it is important for adults to monitor their body weight, best corrected for height as in the BMI, as advocated by both the WHO and the International Obesity Task Force (see also Table 5-15).

BMI

The BMI is obtained by dividing weight (kg) by the square of the height (m^2) (see also Figure 5-2):

$$\text{BMI} = \text{W} \div \text{H}^2$$

This measure best predicts the percentage of body fat in groups of subjects, but not in individual persons. Because the height is squared, that contributing factor is minimized. A nomogram is useful for quickly determining the BMI (Figure 5-2). Overweight is now defined as a value greater than 25 (26). This figure is based on excess body weight of 15% or more, according to Metropolitan Life Insurance tables of 1983, which offer ideal weights somewhat lower than those found in the NHANES data for the average U.S. population (8). For children, different height–weight data must be used. The BMI may not be representative of some subsets of the population (e.g., elderly, medically ill), and it does not take into account frame size or distribution of fat. The National Institutes of Health Technology Assessment Conference Panel on Methods for Voluntary Weight Loss and Control endorsed use of the BMI to define overweight (27). Its use has been less well documented for identifying conditions associated with weight loss. Simple formulas for calculating the BMI from pounds and inches have been developed:

$$\text{BMI} = [\text{W (lb)} \div \text{H (in.)}] \div 0.0014192 \text{ (reference 28)}$$
$$\text{BMI} = \text{W (lb)} \div \text{H}^2 \text{ (in.)} \times 703 \text{ (reference 29)}$$

Tables 5-14 and 14-1 provide a quick conversion of height and weight into BMI for most patients. The advantage of the BMI over linear height and weight is that it provides a simple estimate of disease risk (Table 5-15).

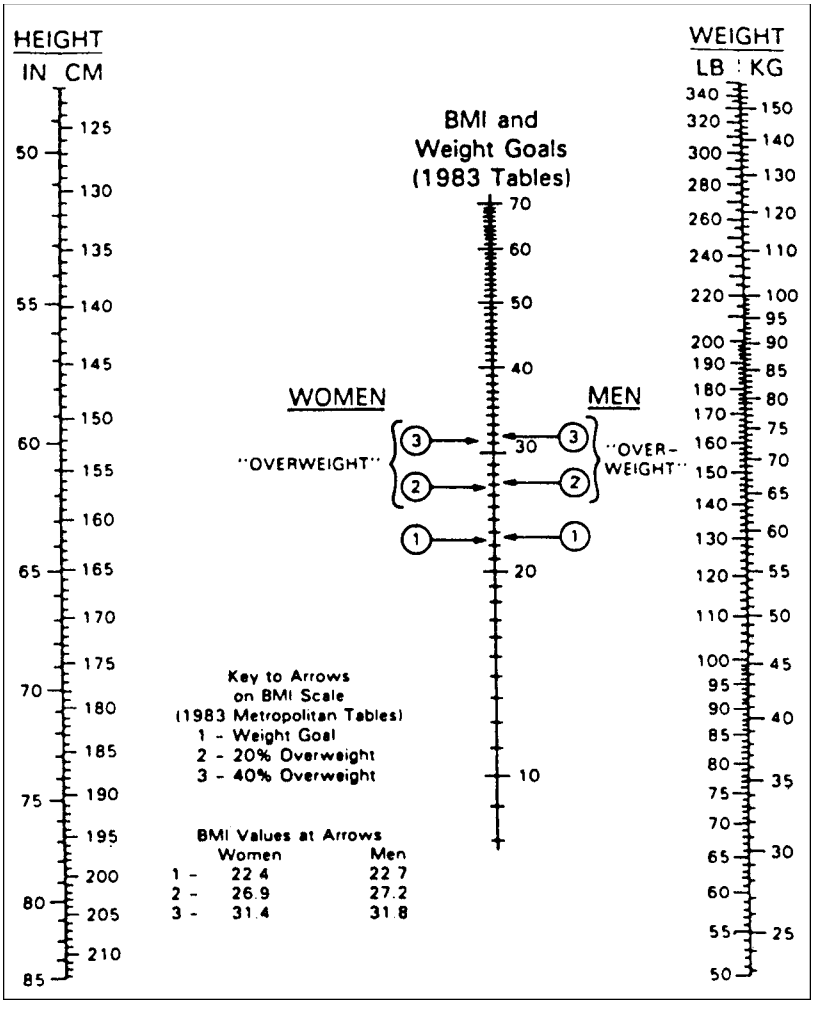


FIGURE 5-2. Nomogram for body mass index (kilograms per square meter) and weight goals (1983 tables). The ratio of weight to square of the height (metric units) is read from the central scale after a straight edge ruler is placed between the height and body weight. Weights and heights are without clothing. With clothing, add 5 lb (3.3 kg) for men or 3 lb (1.4 kg) for women, and add 1 in (2.5 cm) in height for shoes. (From Burton BT, Foster WR, Hirsch J, van Itallie TB. Health implications of obesity: NIH consensus development conference. *Int J Obesity.* 1985;9:155, with permission.)

MEASUREMENT OF BODY COMPONENTS

Fat Stores

Adipose tissue comprises about 25% of body weight. This calorie storehouse could theoretically provide more than 150,000 kcal in the average adult. Although reduction of the fat reserves in comparison with those of the normal population is not in itself detrimental, it does

TABLE 5-14. Body Mass Index for Overweight Patients

	Overweight						Obesity					
BMI	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**40**
Height (in)						**Weight (lb)**						
58	119	124	129	134	138	143	149	153	158	163	167	191
59	124	128	133	138	143	148	154	158	164	169	173	198
60	128	133	138	143	148	153	159	164	169	175	179	204
61	132	137	143	148	153	158	165	169	175	180	185	211
62	136	142	147	153	158	164	170	175	181	186	191	218
63	141	146	152	158	163	169	175	181	187	192	197	225
64	145	151	157	163	169	174	181	187	193	199	204	232
65	150	156	162	168	174	180	187	193	199	205	210	240
66	155	161	167	173	179	186	192	199	205	211	216	247
67	159	166	172	178	185	191	198	205	211	218	223	255
68	164	171	177	184	190	197	204	211	218	224	230	262
69	169	176	182	189	196	203	210	217	224	231	236	270
70	174	181	188	195	202	207	216	223	230	237	243	278
71	179	186	193	200	208	215	222	230	237	244	250	286
72	184	191	199	206	213	221	228	236	244	251	258	294
73	189	197	204	212	219	227	236	243	251	258	265	302
74	194	202	210	218	225	223	241	250	258	265	272	311
75	200	208	216	224	232	240	248	256	264	272	279	319
Height (cm)						**Weight (kg)**						
147.3	54.0	56.4	58.6	60.9	62.7	65.0	67.7	69.5	71.8	74.1	75.9	86.8
150	56.4	58.2	60.5	62.7	65.0	67.3	70.0	71.8	74.5	76.8	78.6	90
152.4	58.2	60.5	62.7	65.0	67.3	69.5	72.3	74.5	76.8	79.5	81.4	92.7
155	60.0	62.3	65.0	67.3	69.5	71.8	75.0	76.8	79.5	81.8	84.1	95.9
157.5	61.8	64.5	66.8	69.5	71.8	74.5	77.3	79.5	82.3	84.5	86.8	99.1
160	64.1	66.4	69.1	71.8	74.1	76.8	79.5	82.3	85.0	87.3	89.5	102.3
162.5	65.9	68.6	71.4	74.1	76.8	79.1	82.3	85.0	87.7	90.5	92.7	105.5
165	68.2	70.9	73.6	76.4	79.1	81.8	85.0	87.7	90.5	93.2	95.5	109.1
167.6	70.5	73.2	75.9	78.6	81.4	84.5	87.3	90.5	93.2	95.9	98.2	112.3
170.2	72.3	75.6	78.2	80.9	84.0	86.8	90.0	93.2	95.9	99.1	101.4	115.9
172.7	74.5	77.7	80.4	83.6	86.3	89.5	92.7	95.9	99.1	101.8	104.5	119.1
175.3	76.8	80.0	82.7	85.9	89.0	92.3	95.5	98.6	101.8	105.0	107.3	122.7
177.8	79.0	82.3	85.4	88.6	91.8	94.1	98.2	101.4	104.5	107.7	111.0	126.4
180.3	81.4	84.5	87.7	90.9	94.5	97.7	101.4	104.5	107.7	111.0	113.6	130
182.9	83.6	86.8	90.5	93.6	96.8	100.5	103.6	107.3	111.0	114.1	117.3	133.6
185.4	85.9	88.2	92.7	96.4	99.5	103.2	107.3	110.5	114.0	117.3	120.5	137.3
188	88.2	91.8	95.5	99.1	102.3	106.0	109.5	113.6	117.3	120.5	123.6	141.4
190.5	90.9	94.5	98.2	101.8	105.5	109.0	112.7	116.4	120.0	123.6	126.8	145

suggest inadequate calorie intake for a prolonged period of time and a concomitant protein compartment deficiency. Thus, normal fat reserves in comparison with population standards do not ensure that the protein compartment status is normal. Fat stores can be inferred from the body weight and estimated from subcutaneous fat measurements. The loss or gain of body mass leads to variable changes in lean body mass and fat mass. Older techniques such as subcutaneous fat (skinfold) measurement and mid arm muscle circumference do not allow for differences in distribution of fat or muscle in parts of the body other than the upper arm. There are now available noninvasive techniques that can measure fat-free mass (FFM) and fat mass (FM). Although these methods are to some extent driven by clinical investigation, they are so much more informative than the older methods that they should be the only ones considered for evaluation of overall body composition. There are still a few methods that can measure protein repletion status, and these will be discussed in the next section.

Dual-energy X-ray absorptiometry (DEXA) is considered the "gold standard" technique for body composition measurement, partly because of the increasing availability of

TABLE 5-15. Body Mass Index as a Measure of Associated Disease Risk

Weight category	BMI (kg/m^2)	Risk
Extremely underweight	<14.0	Extremely high
Underweight	14.1–18.4	Increased in smokers, chronic illness
Normal	18.5–24.9	Normal
Overweight	25–29.9	Increased
Obesity		
Class I	30.0–34.9	High
Class II	35.0–39.9	Very high
Class III	≥40.0	Extremely high

Adapted from National Institute of Diabetes and Digestive and Kidney Diseases. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res.* 1998;6:S53.

scanners. It can be used for both healthy subjects and for patients. Scanning time is now reasonably short (~5 min), and the results for a given machine are fairly reproducible. The accuracy of the measurement is more of a problem, as there has been little comparison to chemical analysis, due to the lack of appropriate direct measurements of body fat (30). The technique is based on the concept that photon attenuation *in vivo* is related to body composition, and that the three body components of fat, fat-free, or lean tissue and bone mineral can be distinguished from each other. The software containing the algorithms to produce the resulting information is different for each of the three major manufacturers of scanners, and is proprietary. Although the method assumes that soft tissue is well hydrated to accurately assess the fat and lean tissue masses, in practice fluid shifts seem to have only minor effects on the results. The major recent scanners are the QDR-4500 and Delphi from Hologic, and Prodigy from GE-Lunar. The estimates from these machines are different and were dependent on sex. At higher body fat levels (>25%) the differences were small but became larger, underestimating the fat mass, in lean individuals with <10% body fat. Abdominal (visceral) fat can be measured and correlates well with total body fat. These machines appear to be acceptable and sensitive for following longitudinal changes in body composition, and are being used to determine factors associated with clinical outcomes (31).

Bioelectrical impedence analysis (BIA) is even more commonly used than DEXA, in part because the equipment is more inexpensive and easier to use. The method does not measure body composition directly, but the electrical properties recored are calibrated against other methods to produce equations predicting components of body composition (32). A four-surface electrode is the most common method for BIA used currently. With this apparatus, total body water, extracellular water, FFM, and percent FM can be predicted from the impedence measurements. The method is valid in healthy young adults who are euvolemic. It is best used to determine estimates within groups, but because the results are derived from comparative equations, clinical applicability to individuals is limited. Like DEXA, the best clinical use for BIA may be in following individuals longitudinally over time. However, BIA is more limited than DEXA in producing data on regional body composition (e.g., visceral). There is yet no single agreed upon technology for multiple-frequency recordings, and there is still an abundance of instruments and equations in use for clinical research.

The *somatic protein compartment* largely represents muscle mass. Measurements of body weight also reflect the muscle mass because it constitutes approximately 30% of the total body weight. Protein–calorie malnutrition causes a decrease in the muscle mass as well as in body fat stores, both of which are reflected by a decrease in body weight. Comparison of body weight with values from a reference population can suggest somatic protein depletion, but single measurements can underestimate depletion in large patients and overestimate depletion in patients of small build. Recent weight change or weight as a percentage of usual body weight often better suggests protein depletion, even though these parameters do not measure the compartment directly.

Creatinine–Height Index

Endogenous creatinine production and excretion indirectly reflect the total body muscle mass. Creatinine is a dehydrated end-product of creatine, a complex molecule involved in supplying ATP to muscle cells; it is concentrated in the muscle mass. About 2% of the creatine phosphate in muscle is converted daily into creatinine in an irreversible reaction. Good correlation has been found between lean body mass measured by radioisotope labeling and by 24-hour creatinine excretion. For purposes of clinical assessment, a patient's creatinine excretion is compared with the expected excretion of a person of similar height and ideal weight. Actual population standards for this measurement do not exist. Calculated ideal values are derived from the average 24-hour creatinine excretions of healthy children and adults while on a creatinine- and creatine-free diet; adult values are given in Table 5-16. The creatinine-height index (CHI) compares the actual 24-hour creatinine excretion of a patient with the expected value for a person of the same height:

$$\text{CHI} = (\text{actual 24 hr creatinine excretion} \div \text{ideal 24 hr creatinine excretion}) \times 100$$

The CHI indicates mild or no protein depletion when it is above 80% moderate protein depletion is indicated at a CHI of 60% to 80%, and severe depletion is indicated by a CHI below 60%. The test is potentially useful when edema or obesity make the measurement of body weight or BMI unreliable as an estimate of malnutrition. Like other measurements that rely on comparison with reference population standards, the CHI relies on ideal body weight standards for adults and calculated reference standards for children. Estimates of muscle mass may be inaccurate in patients who do not fall into the midrange of ideal body weight for height. The test is not valid in patients whose urine output is impaired or who have undergone amputation. It requires 24-hour urine collection and a constant protein intake. Conditions that alter creatinine excretion include kidney failure, liver failure, sepsis, and trauma. Aging and consumption of a creatinine-free diet also reduce creatinine excretion. Creatinine excretion is increased by vigorous exercise, a diet rich in red meat, corticosteroid and testosterone therapy,

TABLE 5-16. Ideal 24-hour Urinary Creatinine Excretion by Adults of Various Heights (for use in calculation of the creatinine–height index)

Height		Ideal creatinine excretion (mg)	
in	cm	Adult women	Adult men
58	147.3	830	—
59	149.9	851	—
60	152.4	875	—
61	154.9	900	—
62	157.5	925	1,288
63	160.0	949	1,325
64	162.6	977	1,359
65	165.1	1,006	1,386
66	167.6	1,044	1,426
67	170.2	1,076	1,467
68	172.7	1,109	1,513
69	175.3	1,141	1,555
70	177.8	1,174	1,596
71	180.3	1,206	1,642
72	182.9	1,240	1,691
73	185.4	—	1,739
74	188.0	—	1,785
75	190.5	—	1,831
76	193.0	—	1,891

Adapted from Blackburn GL, Bistrian BR, Maini BS, et al. Nutritional and metabolic assessment of the hospitalized patient. *JPEN J Parenter Enteral Nutr.* 1977;1:11.

and administration of certain antibiotics (some aminoglycosides and cephalosporins). Because so many factors decrease creatinine excretion, the CHI often overestimates muscle mass depletion. For this reason, it is used less frequently than might be expected from its simplicity.

3-Methylhistidine Excretion

3-Methylhistidine is a biochemical degradation product of myofibrillar muscle protein metabolism. This amino acid is not recycled into protein and is excreted in the urine. However, 3-methylhistidine is not a breakdown product of sarcoplasmic protein, which constitutes about 35% of muscle protein. Like creatinine excretion, 3-methylhistidine excretion is decreased by old age, a decreased protein intake, trauma, or infection, and like the CHI, it overestimates muscle mass depletion.

Circulating Proteins

Serum levels of circulating proteins can be decreased and reflect protein depletion even when other measurements of the protein compartment appear to be normal. Proteins synthesized by the liver have been used as markers for assessing protein status. Presumably, decreased levels of these proteins reflect a decrease in both amino acid precursors and hepatic (and other visceral) mass. Serum levels of some of these protein markers are listed in Table 5-17. The assumption that decreased levels of these proteins are specific for malnutrition is obviously wrong. Levels of liver-dependent circulating proteins reflect not only on adequacy of nutrition but also the synthetic capacity of the liver (not simply in relation to nutrition but also in relation to hepatic disease), rate of metabolic utilization, status of hydration, and excretion. Therefore, no measurable circulating protein is or ever will be specific for assessing visceral protein nutritional status.

Albumin

Albumin is a single-chain polypeptide with 575 amino acid residues. The liver is the exclusive site of albumin synthesis, and the normal adult synthesizes 120 to 200 mg/kg/day (about 12 g per day for the average adult) as part of a total exchangeable pool of 3.5 to 5.0 g per kg of body weight. Only 40% of the pool is located intravascularly. Equilibration is slow between intravascular and extravascular albumin, about 5% per hour, so the entire mass of plasma albumin is exchanged daily with the extracellular component. Redistribution of the extravascular pool into the circulating compartment can help maintain normal levels despite protein deprivation.

Albumin represents about half the total exported protein synthesized by the liver. Many factors are involved in regulating albumin synthesis and secretion, and amino acid supply is only one. In short-term exogenous amino acid deprivation, albumin synthesis decreases, serum levels fall, and hepatic albumin degradation decreases such that a new steady state is reached. The total exchangeable albumin pool may decrease to one-third its normal level before a decreased serum albumin concentration is evident. Restoration of amino acid precursors in such cases allows for greater than normal synthesis rates and normalization of serum albumin levels. Long-term protein deprivation results in less rapidly

TABLE 5-17. Serum Proteins Used for Nutritional Assessment

Protein	Half-life (days)	Reference range	
		Conventional units	SI units
Albumin	18–20	3.3–6.1 g/dL	500–860 μmol/L
Transferrin	8–9	0.26–0.43 g/dL	28.6–47.3 μmol/L
Prealbumin	2–3	0.2–0.4 g/L	3.64–7.27 μmol/L
Retinol-binding protein	0.5	30–60 mg/L	1.43–2.86 μmol/L
Fibronectin, soluble	0.16–1	1.66–1.98 g/L	3.77–4.50 μmol/L

SI, Système International.

reversible decreases in the translational machinery of the hepatocytes. Providing amino acids only slowly normalizes the albumin-synthesizing capabilities of hepatocytes.

In health, the serum half-life of albumin is 20 days. This long half-life makes albumin a poor marker for rapid changes in metabolic states. Changes in synthesis and degradation rates in addition to body compartment shifts influence the serum level.

Because the serum albumin level correlates with morbidity and mortality in hospitalized patients, the concept has developed that such patients need nutritional support. Arbitrary levels of serum albumin have been suggested as indicators of protein malnutrition. A serum albumin level of 2.8 to 3.4 g per dL is associated with a mild degree of protein malnutrition; moderate depletion is suggested by a serum albumin level of 2.1 to 2.7 g per dL, and severe depletion by a level below 2.1 g per dL.

Albumin levels correlate with disease severity but not necessarily with nutritional status (33). Use of the serum albumin level as an indicator of the protein nutritional state assumes a steady state, which is seldom the case during acute or subacute illness. The long half-life of albumin in serum makes this protein a poor marker of acute changes in nutritional status. Interpretation varies depending on length of protein deprivation. The rapid loss of plasma proteins (e.g., postoperatively, from burns, from the gastrointestinal tract) reduces serum albumin levels but does not necessarily indicate a reduction in protein mass. Therefore, although the serum albumin level does reflect the size of the intravascular albumin pool, it is simplistic to assume that this measurement, especially during acute illness, always reflects the protein mass. Also, a shift away from the intravascular pool of as much as 16% of the total exchangeable pool can occur with a change in body position from sitting to reclining; this further influences longitudinal measurements. Inflammatory disorders can decrease albumin synthesis and degradation or increase capillary leak. Increased nutrition (e.g., total parenteral nutrition) often does not alter albumin levels (34). Thus, even when protein malnutrition is a component of an illness, restoration of a low serum albumin level to normal with protein or amino acid therapy can be slow, and generally lags considerably behind clinical impressions of successful nutritional therapy.

Reduced serum levels are seen in many conditions, including malnutrition, liver disease, ascites, idiopathic edema, nephrosis, protein-losing enteropathies, thermal burns, severe eczema, hypothyroidism, zinc deficiency, malignant diseases, congestive heart failure, acute stress, and age over 70 years.

Transferrin

Transferrin is a globulin (molecular weight of approximately 90,000) that binds and transports iron in the plasma. The liver is the principal but not the only site of transferrin synthesis; hepatic synthesis is probably modulated by ferritin within the hepatocytes. Serum levels are similar for men and women and decline only slightly in later life.

The synthetic rate appears to be the predominant factor in determining serum levels, although in acute illness, enhanced degradation can result in depressed levels. The body pool is only about 5 g, and the serum half-life of the protein is 8 to 10 days. Direct measurement of the protein is not always performed routinely, whereas serum total iron-binding capacity (TIBC) is often obtained when anemia is being investigated. Transferrin concentration can be estimated from the TIBC, but the relationship appears to be less constant at lower concentrations of transferrin, and the constants may vary from institution to institution. The attachment of iron to proteins other than transferrin when the latter is more than half-saturated further contributes to the inaccuracy of this estimate, and the readily measured transferrin is preferred.

Arbitrary levels of serum transferrin have been suggested as indicators of protein depletion. Serum transferrin levels of 150 to 200 mg per dL are associated with a mild degree of protein malnutrition; levels of 100 to 150 mg per dL are associated with moderate depletion, and a level below 100 mg per dL is associated with severe depletion.

Like serum albumin levels, serum transferrin levels depend on alterations in synthesis and degradation, both of which are affected by factors other than nutritional status. In particular, the degradation rate increases in acute illness, and synthesis increases in iron deficiency. *Decreased levels* are also seen in pernicious anemia, anemia of chronic disease, liver disease, starvation, burns, iron overload, nephrotic syndrome, and protein-losing enteropathies, and during steroid (glucocorticoid and androgen) therapy. *Increased levels* are observed during hypoxia, pregnancy, and treatment with estrogens or oral contraceptives.

Other Circulating Proteins

Two proteins that are also synthesized by the liver and secreted into the circulation are *retinol-binding protein* (RBP) and *thyroxine-binding prealbumin* (TBPA). Virtually all RBP is bound to TBPA in a 1:1 ratio. Because of their shorter half-lives (10 to 12 hours for RBP, 2 to 3 days for TBPA), and because of the particular amino acid content of TBPA, these two proteins rapidly reflect changes in hepatic protein synthesis. Any value less than the normal range for these proteins may indicate protein depletion.

Unfortunately, levels of both these proteins promptly drop with acute metabolic stress and the accompanying demand for protein synthesis. RBP and TBPA are both metabolized by the kidney, and levels increase in kidney failure. Because of the problems inherent in trying to use the measured level of serum protein to estimate the size and integrity of the organ where it is synthesized, it is unlikely that an ideal circulating protein to assess protein status will be found.

IMMUNOCOMPETENCE IN NUTRITIONAL ASSESSMENT

Abnormalities of the Immune System

Many aspects of the immune system are frequently abnormal in patients with generalized malnutrition. Decreased numbers of circulating T cells, decreased numbers of total circulating lymphocytes, and an impaired delayed cutaneous hypersensitivity response to skin test antigens in patients with protein depletion or protein–calorie malnutrition indicate concomitant impairment of cell-mediated immunity.

Depressed levels of various complement components (including C3), reduced amounts of secretory immunoglobulin A in external body secretions, and various abnormalities of the nonspecific cellular mechanisms of host resistance have been observed in malnourished laboratory animals and patients and have been reversed with nutritional repletion. Local nonspecific defenses (e.g., epithelial integrity, mucous production, cilial mobility) are also adversely affected by malnutrition. These adverse effects together make the malnourished patient a likely candidate for infection.

The precise nutritional deficiency that results in an immunocompromised state in the individual malnourished patient is generally unknown. Although the above-mentioned abnormalities are most frequently associated with protein malnutrition, most protein- and calorie-deficient patients have multiple nutritional deficiencies, not pure protein depletion. Almost any nutritional deficiency, if sufficiently severe, will adversely affect some aspect of the immune system. Therefore, the discovery of immunologic dysfunction does not necessarily imply protein malnutrition. However, if other indicators of macronutrient malnutrition are also present, then correction of protein nutritional status may normalize immune function.

Tests of Immune System

Many tests are available to assess immune function (Table 5-18). Two tests of the immune system have been employed most frequently as nonspecific clinical indicators of malnutrition in nutritional assessment: total circulating lymphocyte count and delayed cutaneous hypersensitivity to skin test antigens.

Total Lymphocyte Count

Circulating lymphocytes are mostly T cells. The thymus-dependent immune responses are very sensitive to malnutrition, and involution of tissues that generate T cells occurs early in the course of protein or protein–calorie malnutrition. Reduction in circulating T cells precedes and eventually leads to lymphopenia. The circulating total lymphocyte count (TLC) can be calculated from the peripheral white blood count (WBC) and the differential:

$$\text{TLC} = \text{WBC (cells/mm}^3) \times (\% \text{ of lymphocytes} \div 100)$$

Depression of circulating lymphocyte numbers below normal (200 cells per mm^3) is not specific for any particular nutritional deficiency. As a general indicator of malnutrition, the TLC tends to correlate best with other measures of protein status. A TLC of 1,200 to 2,000 per mm^3 correlates with mild malnutrition; a count of 800 to 1,200 is associated with moderate depletion, and a count below 800 is associated with severe depletion.

TABLE 5-18. Methods Used to Assess Nutrient–immune Interactions

Tissue tested	Function	Method	Relevance to nutrient status
Mononuclear cells	Disease status	Cell count	Nonspecific
	Proliferation	Cultured blood Culture cells	T-lymphocyte response
	Activation	Isolated cells	T- or B-cell response
	Subtypes	Flow cytometry	T- or B-cell subtypes
	NK cell	Cr release	Subtype of T cell
Cytokine	Serum content	ELISA, RIA	Ability to secrete
	IC content	ELISA, RIA	? Ability to synthesize
Delayed-type hypersensitivity	Cell-mediated	Skin test	Reflect *in vivo* immunity
Serum carnitine	Regulate immune cell function	Enzymatic assay	<30 μmol/L suggest deficiency
Serum amino acids	Glutamine and arginine affect immune cell function	Chromatography	Essential aa/Nonessential aa ratio ↓ d in severe protein deficiency

NK, natural killer; ELISA, enzyme-linked immunosorbent assay; RIA, radioimmunoassay; IC, intracellular; Cr, chromium.

Infections and immunosuppressant drugs alter the number of circulating lymphocytes. The reason for lymphopenia in chronic or severe disease is generally not specific or identified. The TLC *per se* does not indicate the adequacy of immune function. Its use is complicated in cases of infection, metabolic stress, malignancy, or treatment with corticosteroids or immunosuppressive drugs. In such cases, the TLC may correlate with disease severity but not with nutritional status.

Delayed Cutaneous Hypersensitivity Reactions

The erythematous, indurated skin response to recall antigens is the standard for studying the cell-mediated immune response *in vivo*. The delayed cutaneous hypersensitivity (DCH) reaction results from three sequential processes: (a) processing of antigen by macrophages results in the generation of both effector and memory T cells (the afferent limb); (b) recognition of antigen on rechallenge results in blast transformation, cellular proliferation, and generation of lymphokine-producing effector cells (efferent limb); and (c) local erythema and induration of the skin results from release of lymphokines and chemotactic factors at the antigen site.

A primary DCH response to new antigens requires that both afferent and efferent limbs be intact. Generally, the DCH response is tested by using antigens that the patient has previously encountered. Thus, presumably only the efferent aspects of the system are tested. Such antigens include purified protein derivative (PPD), streptokinase–streptodornase (SKSD), mumps virus, *Candida albicans, Trichophyton,* and coccidioidin.

Failure to react to recall antigens (anergy) has been well described in patients with protein depletion or protein–calorie malnutrition. Unfortunately, many other factors also influence the complex reaction sequence of the normal DCH response. When reactivity to a battery of skin test antigens is examined in relation to circulating liver-dependent proteins and to the TLC, the percentage of patients with anergy increases as protein levels and lymphocyte counts decrease, but anergy cannot be predicted accurately on the basis of any one variable.

The prevalence of nonreactivity to three recall antigens is about 50% in patients with serum albumin levels below 3.0 g per dL but is also reported up to 30% of the time when the serum albumin level is above 3.0 g per dL.

Normal response is represented by an induration greater than 5 mm after 24 to 72 hours to at least one of five skin test recall antigens (e.g., mumps virus, PPD, *C. albicans, Trichophyton,* SKSD).

Anergy is variably defined but usually implies a failure to respond to any of five skin test antigens (<5 mm of induration). Reactivity is interpreted as a normal DCH response; anergy, or failure of the DCH response, may be the result of protein–calorie malnutrition and reversible with nutritional repletion.

Recall response depends on prior exposure to the antigen. Because 60% or fewer of subjects respond to many of the antigens used, anergy cannot be assumed on the basis of no response to only one or two antigens. In addition, antigens vary in potency in different lots. A rapid response may occur in subjects tested serially with the same antigen (especially if at the same skin site). The reaction may fade by 48 hours, giving a false-negative test result. Sites should be examined at 24 and 48 hours. The primary illness (e.g., lymphoma, sarcoidosis, cancer, liver or kidney failure, immunosuppressive disease) and medications (e.g., immunosuppressive drugs, chemotherapeutic agents, corticosteroids, warfarin, cimetidine, aspirin) may influence the results. Edema interferes with the local response. Evidence of immune dysfunction on the basis of an impaired DCH response simply cannot be considered to indicate malnutrition.

Carnitine. Carnitine is synthesized from methionine and lysine, two essential amino acids, but healthy adults can make enough for their needs. The newborn infant has reduced stores of carnitine and a decreased ability to synthesize the compound, so newborns are at most risk for deficiency. The carnitine pool in humans is comprised of carnitine itself, acetylcarnitine, propionylcarnitine, and isovalerylcarnitine. A reduced pool of carnitine has been reported in serum or in tissues of patients whose immune responses appear to be impaired (35). These conditions include sepsis syndrome, infection with HIV, chronic renal disease, diabetes mellitus, and malnutrition. The significance of carnitine deficiency in estimating altered immune function is not clear at this time. Evidence for efficacy of supplemental carnitine in selected clinical conditions will be presented in Chapter 12 (Diets). Carnitine deficiency can be detected by measuring carnitine in blood and urine, usually by enzymatic assay kits. The congeners are not included in this determination. Normal values are ~28 to 70 μmol per L, and values <30 μmol per L probably indicate low carnitine status (36).

Glutamine and Arginine. Although neither of these amino acids is essential for growth, it has been suggested that in periods of stress, a state of relative deficiency may develop. Glutamine has been proposed as a protector of cell and gut barrier integrity, and it is an important fuel for immune cells (37). Arginine is a precursor of nitric oxide (NO), and has been proposed to help in seriously ill patients with cardiovascular disease (38). Although some studies conclude that supplemental glutamine or arginine plays an important clinical role, not all studies agree. These data will be reviewed in Chapter 12. Plasma amino acid levels have been examined in malnourished and normal infants and adults, but their usefulness as markers of protein deficiency and altered immune function has never been demonstrated. Plasma amino acid levels change rapidly during stress or by changes in protein intake. The ratio of essential to nonessential amino acids may be of some use in detecting extreme malnutrition, but neither this ratio nor glutamine or arginine levels are sensitive measures of malnutrition or altered immune function (36).

CLINICAL APPLICATIONS OF NUTRITIONAL STATUS ASSESSMENT

Selection of Malnourished Patients for Intensive Nutritional Therapy

A comprehensive assessment of protein and fat nutritional status may detect global malnutrition. However, none of the available tests is specific for malnutrition, and results can be abnormal in chronic or acute illness alone. Nutrition provision may be part of the reason for abnormal test results, but it is usually not possible to identify this factor among many others. No "gold standard" exists for determining nutritional status because no clinical definition of malnutrition is uniformly accepted. Most of the tests discussed below are judged according to their ability to predict clinical outcome. However, this does not necessarily imply that a poor outcome can be reversed by nutrient provision or nutrition support. Deficiencies of individual nutrients are discussed in Chapters 6 and 7.

Abnormalities in growth and weight maintenance are the most important clinical indicators of protein–calorie malnutrition in the ambulatory patient population. They are the most frequently used indicators because they are simple and inexpensive. For this reason, growth and weight are routinely monitored by physicians treating children and

adults, respectively. Weight loss as a predictor of outcome may be more significant when it is combined with other physiologic measurements in critically ill patients (39).

Subjective Global Assessment

The need for more comprehensive evaluation of protein and fat nutritional status in hospitalized patients is debated. An "eyeball" assessment of nutritional status with the use of routine clinical information from the history and physical examination provides an accurate estimation in more than 70% of patients (40,41). "Subjective" assessments can predict complications in hospitalized patients (42,43), but the findings correlate better with the severity of the underlying disease than with specific nutritional deficiencies of calories or protein. The Subjective Global Assessment (SGA) determines whether the nutrient status has been altered by decreased food intake or poor digestion/malabsorption, notes the effects on organ function and body composition, and evaluates the course of the patient's disease. The findings of the history and physical examination are then weighted to rank patients as well, moderately, or severely malnourished and predict the risk for medical complications (Figure 5-3).

A. History
   1. Weight change
      overall loss in past 6 months: _____kg
      change in past week: increase _____kg
      no change _____
      decrease _____kg
   2. Dietary intake change compared to normal
      no change _____
      change _____: duration of change _____weeks
      type of change: hypocaloric solid diet _____ full liquid diet _____
      hypocaloric liquids _____ starvation _____
   3. Gastrointestinal symptoms, persisting > 2 weeks
      none____ anorexia _____ nausea _____ vomiting _____ diarrhea ____
   4. Functional capacity
      no dysfunction _____
      dysfunction _____: duration _____weeks
      type of dysfunction: working suboptimally _____ ambulatory _____
      bedridden _____
   5. Disease and its relation to nutritional requirements
      primary diagnosis (specify) _____
      metabolic demand (stress): none _____ low _____ moderate _____
      high _____

B. Physical exam (for each trait specify: 0 = normal, 1+ = mild, 2+ = moderate, 3+ = severe)
   loss of subcutaneous fat (triceps, chest) _____
   muscle wasting (quadriceps, deltoids, temporals) _____
   ankle/sacral edema _____ ascites _____
   tongue or skin lesions suggesting nutrient deficiency _____

C. SGA rating (select one)
   _____A = well nourished (minimal/no restriction of food intake/absorption, minimal change in function, weight stable or increasing)
   _____B = moderately malnourished (food restriction, some functional changes, little/no change in body mass)
   _____C = severely malnourished (definitely decreased intake, function, and body mass)

FIGURE 5.3. Subjective global assessment of nutritional status. (From Detsky AS, McLaughlin JR, Baker JP. What is subjective global assessment of nutritional status? *JPEN J Parenter Enteral Nutr.* 1987;11:8. With permission.)

The SGA is not completely subjective because percentage of weight loss and serum albumin levels are taken into account. But hypoalbuminemia is a predictor of general risk, and is not specific for malnutrition (33). Although the SGA is highly sensitive (~100%) (44), it is much less specific (~66%), and misclassifies about 15% of patients (45). The SGA does classify patients better than anthropomorphic measurements (46). In general, the SGA performs well as a nutritional screening tool (31). Moreover, it correlates well with other screening instruments (45). A patient-generated version of the SGA (PG-SGA) has been developed (47). Other screening tools currently in use include the Malnutrition Universal Screening Tool (MUST) (www.bapen.org.uk/the-must.htm) (48), the Mini Nutritional Assessment (MNA) (www.mna-elderly.com) (See Table 1-21) (49), the DETERMINE check list (www.aafp.org/x17367.xml) (50), and the Nutritional Risk Screening (NRS-2002) (www.health.vic.gov.au/hacc/publications/nutrisk-rm.htm) (51). The European Society for Parenteral and Enteral Nutrition (ESPEN) has developed guidelines for nutrition screening suggesting the use of BMI as the initial observation, followed by MUST for adults, the NRS-2002 for hospitalized patients, and the MNA for the elderly (52). Each of these instruments is reproduced in Kondrup et al. (52). However, the American Society for Parenteral and Enteral Nutrition (ASPEN) does not endorse any screening system, feeling that none of them is sufficiently validated. ASPEN prefers to use the SGA, because this tool has been the most validated in a large number of clinical situations (53). More tools will surely be developed, as none of the available instruments is specific for malnutrition, but all serve as prognostic indicators of severity of illness.

Body Mass Index

The BMI can help to identify patients at increased risk for medical complications (Table 5-15). Therapy should be provided early for those patients who are extremely underweight (BMI <14 kg/m^2). The upper cutoff of 25 for increased risk for disease is well supported by data, but the much smaller population of underweight persons (BMI <19.0) who do not smoke or who have not lost weight from illness has never been studied. It is possible that such "underweight" persons with stable weight are not at increased risk for illness (22).

TABLE 5-19. Assessment for the Evaluation of Protein and Energy Nutritional Status

Measurement	Compartment best reflected by measurement	Normal values	Values suggesting malnutrition or severe disease
Weight (adults)	Fat/protein mass		
% loss in last month		<5%	>5%
% loss in last 6 month		<10%	>10%
Weight (children)	Fat/protein mass		
% drop on weight chart		<20th percentile	>20th percentile
DEXA	Fat-free mass (FFM) fat mass (FM)	Relative values depend on specific machine used	Decrease in FFM and FM with time suggests malnutrition
Creatinine/height index (%)	Protein mass	>90% (Table 5-18)	Mild = 80–90% Severe = <60%
Serum albumin (g/dL)	Protein mass	3.5–4.5	Mild = 2.8–3.5 Moderate = 2.1–2.8 Severe = <2.1
Serum transferrin (mg/dL)	Protein mass	220–350	Mild = 150–20 Moderate = 100–150 Severe = <100
Total lymphocyte count per cubic millimeter	Nonspecific	>2,000	Mild = 1,200–2,00 Moderate = 800–1,200 Severe = <800
Delayed cutaneous hypersensitivity to skin test antigens	Nonspecific	Reactive to >1/5 antigens	Anergy

Of course, a low BMI resulting from unexplained weight loss should signal a search for underlying causes.

Because the definition of clinically significant malnutrition based on the individual measurements described in this chapter is yet to be determined, a comprehensive evaluation incorporating many parameters often is of little practical clinical value. Weight change remains the most significant parameter and the one best correlated with nutritional status, but it also may reflect chronic illness in its late stages, when nutritional replacement may not be effective. Table 5-19 summarizes the available tests for protein and fat status discussed in this chapter.

Specific Indications for Nutritional Support

A consensus conference involving the National Institutes of Health, ASPEN, and American Society of Clinical Nutrition reviewed the data on nutritional support in gastrointestinal diseases, wasting diseases (especially cancer and AIDS), critical illnesses, and in the perioperative period (54). The conclusions are summarized in Tables 5-20 and 5-21. It is important to note that these conclusions identify issues for further study but are not recommendations or practice guidelines. In the use of nutritional support therapy, the

TABLE 5-20. Use of Nutrition Support in Gastrointestinal Diseases

Condition	Assumptions driving studies	Either EN or TPN	TPN alone
IBD	Bowel rest/EN helpful	Steroids > EN[b] therapy[a] EN possibly helpful[b] Mono/oligo/polymeric same outcome[a] Compliance limits use of EN formulations[a] EN/TPN promotes growth in children[b]	Not as primary[a]
Pancreatitis	Support helpful if oral intake limited Jejunal feeding >gastric/duodenal	No effect in mild, moderate disease[a] When course is prolonged, timing, route, and formulation unknown[c] EN can be safely given in mild/moderate disease[a]	IV lipid safe if TG 400 mg/dL[a]
Liver disease	Malnutrition can be identified in these patients	EN/TPN improves some parameters in ESLD[a] EN/TPN effect inconclusive in alcoholic ESLD[a]	
	BCAAs improve outcome	BCAA-enriched formulas improve protein intake in intolerant patients[a]	BCAA-rich aid recovery in hepatic encephalitis vs. glutamic acid,[a] untested vs. other amino acids

EN, enteral nutrition; TPN, total parenteral nutrition; IBD, inflammatory bowel disease; BCAA, branched-chain amino acid; ESLD, end-stage liver disease; TG, triglycerides.

[a] Supported by prospective randomized controlled trials of meta-analyses of prospective randomized controlled trial.

[b] Supported by well-designed nonrandomized prospective controlled trials, or by well-designed retrospective or case cohort studies.

[c] Supported by published experience, case reports, or expert opinion.

Modified from Klein S, Kinney J, Jeejeebhoy K, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. *JPEN J Parenter Enteral Nutr.* 1997;21:133.

TABLE 5-21. Use of Nutrition Support in Catabolic Conditions

Condition	Assumptions driving studies	Either EN or TPN	TPN alone
Cancer/AIDS	Reversing weight loss improves	Routine use doesn't ↓ morbidity/morality w/chemo-rad Rx[a] May maintain hydration/ nutrition, ↑ survival in pts who can't eat/drink[b] Restoring body composition/tissue mass probably good[c] Restores cell mass in AIDS pts w/ ↓ d food, no infection[b]	Infections ↑ w/chemo Rx[a] No ↓ morbidity/ mortality in pts w/BMT[a,d] Routine use doesn't ↓ mortality or QOL[b]
Critical illness	Hypermetabolic patients should improve w/ support Critical depletion of lean tissue occurs after 14 days	No good studies to support assumption[c] EN ↓ s complications in trauma pts (or ↑ d with TPN?)[b,e] Support should be started in 7–10 days in pts without oral feeding[c] No data available on special additives (e.g., Gln, Arg)	
Perioperative	"Malnourished" pts (weight loss, ↓ plasma protein, SGA) need nutrients for good outcome	EN after hip fracture ↓ s morbidity[a] Postop patients who can't eat need calories within 5–10 days[c]	7–10 days of preop Rx ↓ s complications by 10%[a] Routine postop TPN with no preop Rx ↑ s complications 10%[a,d]

EN, enteral nutrition; TPN, total parenteral nutrition; QOL, quality of life; BMT, bone marrow transplantation; SGA, subjective global assessment.

[a] Supported by prospective randomized controlled trials or meta-analyses of prospective randomized controlled trials.

[b] Supported by well-designed nonrandomized prospective controlled trials, or by well-designed retrospective or case cohort studies.

[c] Supported by published experience, case reports, or expert opinion.

[d] Supported by meta-analysis in AGA technical review on parenteral nutrition. *Gastroenterology.* 2001;121:970.

[e] Supported by Canadian Clinical Practice Guidelines for Nutrition Support in Mechanically Ventilated, Critically Ill Adult Patients. *JPEN*. 2003;27:355.

Modified from Klein S, Kinney J, Jeejeebhoy K, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. *JPEN J Parenter Enteral Nutr.* 1997;21:133.

integration of data from clinical trials, clinical experience in the illnesses being treated, and clinical expertise in nutrition and nutritional therapy will continue to be essential.

Overfeeding and Refeeding Syndromes

Although nutritional support is valuable in selected critically ill patients, it is not without risks. Metabolic complications resulting from overfeeding such patients can be serious (55). The clinical characteristics of the syndromes associated with overfeeding are listed in Table 5-22. Most of these are commonly recognized and are detected during the routine follow-up of patients on enteral or parenteral therapy (see Chapters 10 and 11). However, the refeeding syndrome is potentially very serious, can develop rapidly, and, because of its

TABLE 5-22. Clinical Characteristics of Overfeeding Syndromes

Syndrome	Patients at risk	Management
Azotemia	Age >65, protein intake >2 g/kg, BUN/Cr >15	Provide adequate energy, hydration, protein intake
Fat overload (respiratory distress, bleeding, jaundice)	Lipid intake >3 g/d, onset days to months	Hold lipids for TG >300 mg/dL, monitor PT, PTT, bilirubin
Hepatic steatosis	High CHO, very low fat during parenteral nutrition	Adjust energy and CHO intake, include fat daily
Hypercapnia	Poor ventilatory status	Decrease energy intake, esp. dextrose, add lipid, monitor pCO_2, pH
Hyperglycemia	On steroids, dextrose provision >4 mg/kg/min	Monitor hydration, blood glucose, replace dextrose with lipid
Hyperglycemic, hyperosmolar, nonketotic	High CHO load + diuresis	Monitor CVP, restore intravascular volume, add insulin and K
Hypertonic dehydration	High protein tube feed + fluid loss + old age	↓ Na and protein intake, use isotonic feeding and rehydration
Hypertriglyceridemia	Lipid intake >2 g/day, infection	Maintain TG <300 mg/dL, avoid overfeeding
Metabolic acidosis	Formulas with low kcal/g N ratio (<90:1), elderly	Monitor hydration, renal function, pH, ↓protein intake
Refeeding	Weight <70% of ideal, rapid replacement	Monitor cardiac status, P, Mg, K, ↓energy load, hydrate

BUN, blood urea nitrogen; Cr, creatinine; TG, triglyceride; PT, prothrombin time; PTT, partial thromboplastin time; CHO, carbohydrate; CVP, central venous pressure.
Modified from Klein CJ, Stanek GS, Wiles CE. Overfeeding macronutrients to critically ill adults: metabolic complications. *J Am Diet Assoc.* 1998;98:795.

relative rarity, may not be recognized early (56). The clinical characteristics of this syndrome are listed in Table 5-23. Cardiovascular and electrolyte abnormalities need to be carefully documented before critically ill patients are refed. Feeding should be restarted slowly, and it should be ascertained that all nutrients, especially nitrogen, phosphorus, potassium, magnesium, and sodium, are adequately provided. The daily intake should be about 20 kcal per kg and should contain about 150 g of carbohydrate and 1.2 to 1.5 g of protein per kilogram. Sodium should be restricted to about 1.5 g per day, but phosphorus, potassium, and magnesium should be liberally provided while weight, electrolytes, and cardiac function are monitored carefully.

TABLE 5-23. Clinical Characteristics of the Refeeding Syndrome

Nutrient/organ system	Clinical findings
Energy balance	Weight <70% of ideal weight
Cardiovascular system	↓ Cardiac mass, stroke volume, end-diastolic volume, heart rate, blood pressure ↑ Congestive failure, arrhythmias, QT interval
Kidney	↑ Sodium and water retention
Phosphorus	↓ Plasma P, leading to muscle weakness, seizures, acute respiratory failure, tachycardia, death
Potassium/magnesium	↓ Plasma K, Mg because each g of N used to form leads to retention of 3 mEq of K and 0.5 mEq of mg
Gastrointestinal tract	Diarrhea with oral feeding secondary to reduced epithelial mass

References

1. Pellett PL. Protein requirements in humans. *Am J Clin Nutr.* 1990;51:723.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids*. Food and Nutrition Board, Institute of Medicine, Washington, DC: The National Academies Press, 2005.
3. Foster GD, Knox LS, Dempsey DT, et al. Caloric requirements in total parenteral nutrition. *J Am Coll Nutr.* 1987;6:231.
4. Harris JA, Benedict FG. *A Biometric Study of Basal Metabolism*. Publication No. 279. Washington, DC: Carnegie Institution, 1919.
5. Roza AM, Shizgal HM. The Harris–Benedict equation reevaluated: resting energy requirements and the body cell mass. *Am J Clin Nutr.* 1984;40:168.
6. Ireton-Jones C. Adjusted body weight, con: why adjust body weight in energy-expenditure calculations? *Nutr Clin Practice*. 2004;20:474.
7. Hamwi TJ. Therapy: changing dietary concepts. In: Danowski TS, ed. *Diabetes Mellitus: Diagnosis and Treatment*. American Diabetes Association. 1964.
8. Metropolitan Life Insurance Company. Metropolitan Life Insurance Company Tables: Metropolitan Heights and Weights. *Stat Bull Metropol Life Ins Co*. 1983.
9. Owen OE, Kayle E, Owen RS, et al. A reappraisal of caloric requirements in healthy women. *Am J Clin Nutr.* 1986;44:1.
10. Keys A, Taylor HL, Grande F. Basal metabolism and age of adult men. *Metabolism.* 1973;22:579.
11. Wilmore DW. *The Metabolic Management of the Critically Ill.* New York: Plenum Press, 1977.
12. Baker JP, Detsky AS, Stewart S, et al. Randomized trial of total parenteral nutrition in critically ill patients: metabolic effects of varying glucose–lipid ratios as the energy source. *Gastroenterology.* 1984;87:53.
13. Ireton-Jones CS, Turner WW Jr, Liepa BU, et al. Equations for the estimation of energy expenditures in patients with burns with special reference to ventilatory status. *J Burn Care Rehabil.* 1992;13:330.
14. Mann S, Westenskow DR, Houtchens BA. Measured and predicted caloric expenditure in the acutely ill. *Crit Care Med.* 1985;13:173.
15. Makk LJ, McClave SA, Creech PW, et al. Clinical application of the metabolic cart to the delivery of total parenteral nutrition. *Crit Care Med.* 1990;18:1320.
16. Liggett SB, St John RE, Lefrak SS. Determination of resting energy expenditure utilizing the thermodilution pulmonary artery catheter. *Chest.* 1987;91:562.
17. Liggett SB, Renfro AD. Energy expenditures of mechanically ventilated nonsurgical patients. *Chest.* 1990; 98:682.
18. Toth MJ, Poehlman ET. Energetic adaptation to chronic disease in the elderly. *Nutr Rev.* 2000;58:61.
19. Standing Committee on the Scientific Evaluation of Dietary Reference Intake. *Dietary Reference Intakes: Applications in Dietary Assessment*. Food and Nutrition Board, Institute of Medicine, National Academies Press, Washington DC, 2000.
20. Garrow JS. Energy balance in man—a review. *Am J Clin Nutr.* 1987;45[Suppl 5]:1114.
21. Rand WM, Pellett PL, Young VR. Meta-analysis of nitrogen balance studies for estimating protein requirements in healthy adults. *Am J Clin Nutr.* 2003;77:109.
22. WHO/FAO Committee on Nutrition. *WHO Energy and Protein Requirements*. Technical report series 724. Geneva: World Health Organization, 1985.
23. Scrimshaw NS. Shattuck Lecture—strengths and weaknesses of the committee approach. An analysis of past and present recommended dietary allowances for protein in health and disease. *N Engl J Med.* 1976;294:198.
24. Waterlow JC, Payne PR. The protein gap. *Nature.* 1975;258:113.
25. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med.* 1999;341:427.
26. Schwartz LM, Woloshin S. Changing disease definitions: implications for disease prevalence. Analysis of the Third National Health and Nutrition Examination Survey, 1988–1994. *Eff Clin Pract.* 1999;2:76.
27. NIH Technology Assessment Conference Panel. Methods for voluntary weight loss and control. *Ann Intern Med.* 1992;116:942.
28. Frankel HM. Determination of body mass index. *JAMA.* 1986;255:1292.
29. Matz R. Calculating body mass index. *Ann Intern Med.* 1993;118:232.
30. Plank LD. Dual-energy X-ray absorptiometry and body composition. *Curr Opin in Clin Nutr Metab Care.* 2005;8:305.
31. Kyle UG, Genton L, Pichard C. Hospital length of stay and nutritional status. *Curr Opin Clin Nutr Metab Care.* 2005;8:397.
32. Buchholz AC, Bartok C, Schoeller DA. The validity of bioelectrical impedance models in clinical populations. *Nutr Clin Pract.* 2004;19:433.
33. Klein S. The myth of serum albumin as a measure of nutritional status. *Gastroenterology.* 1990;99:1845.
34. Gray GE, Megried MM. Can total parenteral nutrition reverse hypoalbuminemia in oncology patients? *Nutrition.* 1990;6:225.
35. Famularo G, de Simone C, Trinchieri V, Mosca L. Carnitine and its congeners: a metabolic pathway to the regulation of immune responses and inflammation. *Ann N Y Acad Sci.* 2004;1033:132.
36. Sauberlich HE. *Laboratory Tests for the Assessment of Nutritional Status*. 2nd ed., Boca Raton, FL: CRC Press, 1999.

37. Wilmore DW, Rombeau JL, eds. Glutamine metabolism: nutritional and clinical significance. *J Nutr.* 2001;131, Suppl 9S.
38. Morris SM, Jr, Loscalzo J, Bier D, Souba WW, eds. Arginine metabolism: enzymology, nutrition, and clinical significance. *J Nutr.* 2004;134 (Suppl 10S).
39. Windsor JA, Hill GL. Weight loss with physiologic impairment: a basic indicator of surgical risk. *Ann Surg.* 1988;207:290.
40. Detsky AS, McLaughlin JR, Baker JP. What is subjective global assessment of nutritional status? *JPEN J Parenter Enteral Nutr.* 1987;11:8.
41. Windsor JA, Hill GL. Nutritional assessment: a pending renaissance. *Nutrition.* 1991;7:377.
42. Baker JP, Detsky AS, Wesson DE, et al. Nutritional assessment: a comparison of clinical judgment and objective measurements. *N Engl J Med.* 1982;306:969.
43. Detsky AS. Predicting nutrition-associated complications for patients undergoing gastrointestinal surgery. *JPEN J Parenter Enteral Nutr.* 1987;11:440.
44. Mourao F, Amado D, Ravasco P, et al. Nutritional risk and status assessment in surgical patients: a challenge amidst plenty. *Nutr Hosp.* 2004;19:83
45. Pablo AM, Izaga MA, Alday LA. Assessment of nutritional status on hospital admission: a reevaluation. *J Am Diet Assoc.* 1992;93:27.
46. Planas M, Audivert S, Perez-Portabella C, et al. Nutritional status among adult patients admitted to a university-affiliated hospital in Spain at the time of genoma. *Clin Nutr.* 2004;23:1016.
47. Bauer J, Capra S, Ferguson M. Use of the scored patient-generated subjective global assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin Nutr.* 2002;56:779.
48. Malnutrition Advisory Group (MAG). *MAG-Guidelines for Detection and Management of Malnutrition.* Redditch, UK: British Association for Parenteral and Enteral Nutrition, 2000. www.bapen.org.uk/the-must.htm
49. Hudgens J, Langkamp-Henken B. The mini nutritional assessment as an assessment tool in elders in long-term care. *Nutr Clin Pract.* 2004;19:463.
50. de Groot LC, Beck AM, Schroll M, van Staveren WA. Evaluating the DETERMINE Your Nutritional Health Checklist and the Mini Nutritional Assessment as tools to identify nutritional problems in elderly Europeans. *Eur J Clin Nutr.* 1998;52:877. www.aafp.org/PreBuilt/NSI_DETERMINE.pdf
51. Kondrup J, Hojgaard Ramussen H, Hamberg O, et al. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr.* 2003;22:321.
52. Kondrup J, Allison SP, Elia M, et al. ESPEN guidelines for nutrition screening 2002. *Clin Nutr.* 2003;22:415.
53. ASPEN Board of Directors. Clinical Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients. Silver Spring, MD: ASPEN Publications, 2002.
54. Klein S, Kinney J, Jeejeebhoy K, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. *JPEN J Parenter Enteral Nutr.* 1997;21:133.
55. Klein CJ, Stanek GS, Wiles CE. Overfeeding macronutrients to critically ill adults: metabolic complications. *J Am Diet Assoc.* 1998;98:795.
56. Alpers DH, Klein S. Refeeding the malnourished patient. *Curr Opin Gastroenterol.* 1999;15:151.

6 VITAMINS

EVALUATION OF VITAMIN INTAKE AND DEFICIENCY

The intake of vitamins (and other nutrients) is calculated in three ways: (a) the amount an individual needs to avoid deficiency (daily requirement), (b) the average daily amount entire population groups should consume in a period of time to prevent deficiency [recommended dietary allowance (RDA) or adequate intake (AI)], and (c) the amount that can be safely ingested when the vitamin is taken to prevent chronic disease [tolerable upper intake level (UL)]. Statistically, the RDA is set 2 standard deviations above the mean requirement, so that it is sufficient for 97% of normal persons. RDAs therefore exceed the needs of many persons and furthermore are established only for healthy persons (1). The RDA takes into account the dietary form of the nutrient, the efficiency of absorption, and

other factors, in addition to the estimated daily requirement for the assimilated nutrient. Daily allowances thus may vary depending on whether the vitamin is to be administered parenterally (see Chapter 11) or by mouth. Discussions of controversial recommended dietary intakes of many vitamins and minerals are included in the publications of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine (2–4). RDAs and dietary reference intakes (DRIs) are not designed to provide guidelines for therapy. They should be used only as estimates for normal intake and perhaps as a starting point for therapy in cases of deficiency.

Requirements for Vitamin Nutrition in Selected Groups

These groups include physically active people, the elderly, and persons at increased risk for chronic diseases.

Physically Active People

Only about one-third of people in the United States engage in regular physical exercise—mostly walking, swimming, bicycling, running, and step aerobics. A deficiency of certain vitamins adversely affects physical performance (e.g., by causing anemia, muscle weakness, fatigue, or peripheral neuropathy). These include all the B vitamins. Exercise can increase the need for some nutrients, as in the gastrointestinal blood loss seen during prolonged exercise (5). In addition, some vitamins are considered to be important in reducing the risk for cardiovascular disease. These include vitamin E and the vitamins that lower serum homocysteine levels (vitamin B_6, folate, and vitamin B_{12}). The role of each of these vitamins is discussed later in the chapter.

Elderly People

The new DRIs include separate recommendations for persons over the age of 70 (6) (see Chapter 3). In the Survey in Europe on Nutrition and the Elderly, a Concerned Action (SENECA) Study, evidence of low vitamin intake/deficiency based on serum levels was found in 47% of European elderly persons for vitamin D, 23% for vitamin B_6, 2.7% for vitamin B_{12}, and 1% for vitamin E (7). Neurocognitive function can be decreased in deficiency states of vitamins B_6 and B_{12} and folate (8), the same vitamins that help to regulate homocysteine levels. The intake of these vitamins is often inadequate in the elderly. Because on average the elderly ingest only about 50% of the RDA for any vitamin, special care must be taken to ensure that the full RDA (or DRI) is taken.

Persons at Risk for Chronic Diseases

In addition to their potential role in preventing cardiovascular disease, vitamins may play a role in cancer chemoprevention (see Chapter 15) and in preventing cataracts, particularly the vitamins with antioxidant properties (vitamin A, β-carotene, and vitamin E) (4). The data are not yet sufficient to suggest that regular use of these vitamins prevents cancer or nuclear cataracts or cardiovascular disease (9, 10). If vitamins and minerals are effective in these settings, guidelines from professional societies and the U.S. government recommend obtaining the micronutrients from food (11). Small amounts of regular and enriched foods improve vitamin concentrations in frail, elderly patients, so deficiency is not a problem of malabsorption (12). In physically active people without deficiency, there is no effect of supplemented vitamins and minerals if they are ingesting a balanced diet (13).

Bioavailability of Vitamins

Bioavailability of vitamins differs in various foods. *Bioavailability* refers to the fraction of total dietary vitamin that is absorbed and functions in an organism. The assessment of bioavailability involves assays of tissue content and biologic activity. The accuracy of dietary requirements depends on information about food content and its bioavailability. Nutrient content listed under each vitamin is usually well established. Where data exist concerning bioavailability, they are given.

Vitamin Deficiency

A variety of factors other than dietary intake are related to vitamin deficiency. These are listed in Table 6-1. Dietary deficiency is uncommon in the case of the vitamins that are

TABLE 6-1. Pathophysiology of Vitamin Deficiency

Physiologic factor	Vitamins affected	Comments
Dietary intake	All except K, B_6, biotin	K, B_6, and biotin probably produced by enteric bacteria
Endogenous synthesis	D (skin), K, B_6, biotin	
Enterohepatic circulation	A, polar metabolites of vitamin D, folic acid, cobalamin	
Decreased storage capacity	Cobalamin, A	Stored in liver
Increased utilization	Folic acid	Used in increased amounts during pregnancy, hemolysis
Increased loss from body	All	During malabsorption

produced endogenously. Enterohepatic circulation of a vitamin is associated with an increased rate of loss during malabsorption because some portion of the body stores must be reabsorbed each day, along with what is derived from the diet. An enterohepatic circulation of vitamins other than those listed in Table 6-1 is possible, but such data are not available at this time. Hepatic stores of vitamin A and cobalamin are decreased most frequently in cirrhosis. All vitamins may be needed in larger amounts during pregnancy and growth, but folic acid is especially important because body stores are small.

Onset of Clinical Vitamin Deficiency

The onset of clinical vitamin deficiency varies depending on the rate of loss and the size of available body stores. In general, the body stores of water-soluble vitamins are smaller, whereas fat-soluble vitamins are stored in adipose tissue or liver, so that the body stores are larger. Thus, clinical deficiency of fat-soluble vitamins is usually delayed and may take 2 years or more to develop.

Clinical Manifestations of Deficiency of a Given Water-soluble Vitamin

The clinical manifestations of deficiency of a given water soluble vitamin are relatively late consequences (Table 6-2). Blood levels fall early in the course of deficiency and are thus useful in detecting changes in body stores of the vitamin. This event is followed by altered cell function and finally clinical symptoms. This sequence is not often seen in deficiencies of the fat-soluble vitamins. Vitamin D must be converted to active forms. Thus, even though body stores of the parent vitamin may be normal, activation to the hydroxylated forms may be inadequate. Vitamins A and D are carried in plasma by specific binding proteins, and alterations in the levels of these binding proteins can lead to an erroneous estimate of body stores. The intracellular content of a vitamin sometimes correlates better with body stores than do plasma levels. Thus, the vitamin content of white or red cells is sometimes used to assess body stores.

Therapeutic Supplementation

In many instances, only one or two vitamin deficiencies exist at one time in a patient. However, when generalized malabsorption occurs, extra vitamins are needed each day to prevent deficiencies. This is often best accomplished with one of the multivitamin and mineral preparations. When feeding is only or largely parenteral, multivitamin supplements must be given. (Doses and administration of parenteral therapy are discussed in Chapter 11.) Most of this chapter is devoted to a separate discussion of each vitamin.

Treatment of Vitamin Deficiency. Most healthy people in the United States do not need vitamin supplements. However, supplements should be given to certain groups of patients at high risk for vitamin deficiency. Details are provided in the sections on the individual vitamins.

Infancy.

(a) Vitamin K once (0. 5 to 1.0 mg IM or 1 to 2 mg orally) to prevent hemorrhagic disease of the newborn.

(b) Vitamin E (500 mg per kg daily) to premature infants weighing less than 1.5 kg to prevent hemolytic anemia.

TABLE 6-2. Summary of Vitamin Functions and Deficiency States

Vitamin	Functions	Results of deficiency	Major food sources
Thiamine B_1	Transketolase coenzyme, muscle tone, appetite	Moderate: fatigue, apathy, nausea, irritability, numbness	Enriched grains, most animal and vegetable products
Riboflavin/B_2	Part of FAD, FMN that accept/donate $[H^+]$ equivalents	Severe: beriberi with CHF, polyneuritis, edema	Organ meats, enriched cereals/flours, cheese, eggs, lean meat
Niacin	Part of NAD, NADP that accept/donate $[H^+]$ equivalents	Angular stomatitis, cheilosis, glossitis, seborrheic dermatitis	Meat, nuts, dairy products, eggs
Vitamin B_6	Coenzyme in transamination, decarboxylation, transsulfuration	Dermatitis (light-exposed), diarrhea, swollen tongue, delirium, depression	Grains, seeds, organ meats, lean meats
Pantothenic acid	Part of CoA/acyl carrier protein	Seborrheic dermatitis, red tongue, irritability, weakness, convulsions, neuritis	Organ meats, cereals/ flours, nuts, eggs
Biotin	Coenzyme in decarboxylation, deamination	Anorexia, nausea, fatigue, numbness, insomnia	Organ meats, eggs, soy flour
Folate	Formation of purines, pyrimidines, heme, tyrosine, glutamate	Scaly dermatitis, anorexia, glossitis, muscle pains	Organ meats, green vegetables, legumes, eggs, fish, nuts, whole wheat products, enriched flour/cereals
Vitamin B_{12}	Transfer of single carbon units, synthesis of CH_{3-}	Megaloblastic anemia, glossitis, diarrhea	Organ meats, muscle meats, eggs, dairy products, fish
Vitamin C	Collagen formation, iron absorption, metabolism of folate	Sore tongue, weakness, neuropathy, mental changes, pernicious anemia	Citrus fruits, other fruits, green peppers, leafy vegetables
Vitamin A	Visual adaptation, body/bone growth, gene expression	Weight loss, fatigue, sore gums/joints, petechiae, bone fractures	Organ meats, eggs, dairy (fortified)
Vitamin D	Calcium/phosphorus absorption, bone mineralization	Night blindness, xerosis, xerophthalmia, follicular dermatitis, abnormal teeth	Carotene: yellow vegetables, fruits
Vitamin E	Antioxidant against free radicals	Rickets, osteomalacia, tetany	Vitamin D-fortified foods (cereals, dairy), fish oils
Vitamin K	Synthesis of clotting factors, glutamate	Hemolysis, ophthalmoplegia, peripheral neuropathy Delayed blood clotting, hemorrhagic disease of the newborn	Vegetable oils, nuts, seeds, eggs, meats Widely distributed (dairy, meat, eggs, fruit, vegetables)

CH_{3-}, methyl groups; CHF, congestive heart failure; FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate.

(c) Vitamin D (400 IU per day) to breast-fed infants if not exposed to sunlight.
(d) Cobalamin (vitamin B_{12}) to breast-fed infants of strict vegetarian mothers.

Pregnancy. Folic acid requirements are increased. A dosage of 400 μg per day is recommended for all pregnant women to decrease the incidence of neural tube defects.

Low-calorie intake/diets. If less than 1,200 kcal is ingested per day, a multivitamin preparation may be used. This is especially true for alcoholics, elderly persons who are poor or homebound, and patients with anorexia nervosa or severe depression.

Gastrointestinal disorders. Patients with fat malabsorption may require vitamins A and D or, rarely, E. Following ileal resection, vitamin B_{12} is needed (100 µg per month). Folic acid (1 mg per day) is often required, and all water-soluble vitamins must be administered to patients with short-bowel syndrome. The micronutrients often needed in patients with inflammatory bowel disease (IBD) include folate, vitamin D, calcium, magnesium, iron, and zinc, and vitamin B_{12} in Crohn disease (www.nih.gov/health/digest/digest.htm#pubs). A proprietary medication has been formulated for IBD patients. Forvia contains vitamin D 800 IU, vitamin E 150 IU, vitamin K 80 µg, vitamin B_{12} 1 mg, other water soluble vitamins, zinc 22.5 mg, and iron 30 mg (www.forvia.com).

Osteodystrophies. Patients in whom activation of vitamin D is defective may require vitamin D, calcifediol (hepatic disease), or calcitriol (renal disease). In otherwise normal subjects, data are accumulating that suggest the need for a larger daily dose of vitamin D to prevent osteoporosis and to prevent fractures. A dose of 800 IU per day (twice the DRI) prevents ~30% of hip and nonvertebral fractures in adults >65 years, corresponding with 25-hydroxy-vitamin D concentrations >74 nmol/L (14).

Human immunodeficiency virus (HIV) disease. Supplemental vitamin A, carotene, B complex, C, and E were provided to pregnant women with HIV disease in a double-blind controlled study and led to a reduced death rate (25% vs. 31%), as well as decreased progression to stage 3 disease or greater, improved CD4+ counts, and lower viral load (15). Vitamin A alone reduced mortality and improved growth in a single hospital sample of HIV-infected children, and reduced diarrhea-associated mortality in another trial in infants (16). However, there was no evidence that micronutrient supplementation reduced morbidity and mortality in HIV-infected adults.

Vitamin therapy in conditions other than deficiency. Vitamins are administered in many conditions in which deficiencies are not demonstrated, or where the DRI is felt to be inadequate to counter true deficiency (e.g., vitamin D). In most instances, either no effect of the vitamin has been documented, or the data are insufficient to warrant a strong recommendation for their use. Table 6-3 lists some of the clinical areas in which vitamin supplementation has been suggested, along with references that review the accumulated data. Discussions of some of these uses not related to deficiency are included in the sections on the individual vitamins, especially vitamins A and E. Accepted uses of vitamins in states other than deficiency are the administration of pyridoxine to treat pyridoxine-dependent inborn errors of metabolism, and the administration of vitamin A derivatives to treat skin diseases and acute promyelocytic anemia, and niacin for hyperlipidemia.

Assessment of Vitamin Status

Guidelines are given for the interpretation of test results (see Table 1-19 in Chapter 1). However, the precise values vary among laboratories. The reader should ascertain the exact normal values of the laboratory providing the information.

WATER-SOLUBLE VITAMINS

The B-complex vitamins are often considered together because deficiency frequently produces overlapping symptoms. All of these vitamins form coenzymes in metabolic processes. Some characteristics of the vitamins are listed in Table 6-2.

Thiamine (Vitamin B_1)

Requirements

Relation to Energy Intake. Thiamine pyrophosphate is important in key reactions in energy metabolism (e.g., the decarboxylation of pyruvic acid). Therefore, the requirement for thiamine is usually related to energy intake and more specifically to carbohydrate ingestion. The Food and Nutrition Board recommends 0.5 mg per 1,000 kcal for adults, and the same ratio for infants and children, although fewer data are available for them. Allowances are based on the effects of varying dietary thiamine and the relationship of thiamine intake to signs of clinical deficiency and to urinary excretion of thiamine and serum erythrocyte

TABLE 6-3. Proposed uses of Vitamins at Higher than Recommended Doses and/or in Nondeficiency States

Vitamin	Condition	Reference
Riboflavin	Migraine	Modi S, Lowder DM. *Am Fam Physician* 2006;73:72.
Niacin	Hyperlipidemia	Berra K, *J Am Acad Nurse Pract* 2004;16:526.
Vitamin B_6	Carpal tunnel syndrome	Aufiero E, et al. *Nutr Rev* 2004;62:96.
	Premenstrual syndrome	Fugh-Berman A, Kronenberg F. *Reprod Toxicol* 2003;17:137.
	Immune response	Huang YC, et al. *Nutrition* 2005;21:779.
	Cognition	Malouf R, et al. *Cochrane Database Syst Rev* 2003;(4):CD004393.
Folate	Depression	Taylor MJ, et al. *Cochrane Database Syst Rev* 2004;(4):CD003390.
	Prevention of colon cancer	Strohle A, et al. *Int J Oncol* 2005;26:1449.
Vitamin B_{12}	Cognition	Malouf R, et al. *Cochrane Database Syst Rev* 2003;(3):CD004326.
Coenzyme Q	Mitochondrial dysfunction	Littarru GP, Tiano L. *Curr Opin Clin Nutr Metab Care* 2005;8:641.
Vitamin C	Common cold	Douglas RM, et al. *Cochrane Database Syst Rev* 2004;(3):CD000980.
	Asthma	Ram FSF, et al. *Cochrane Database Syst Rev* 2004;(3):CD000993.
	Chronic diseases	Jacob RA, Soutoudeh G. *Nutr Clin Care* 2002;5:66.
Vitamin A	Cancer/leukemia	Njar VC, et al. *Bioorg Med Chem* 2006;14:4323.
	Measles	Huiming Y, et al. *Cochrane Database Syst Rev* 2005;(4):CD001479.
Vitamin E	Cardiovascular disease	Pham DQ, Plakogiannis R. *Ann Pharmacother* 2005;39:1870.
	Premenstrual syndrome	
	Cataracts	
	Tardive dyskinesia	Soares KVS, McGrath JJ. *Cochrane Database Syst Rev* 2004;(3);CD000209.
	Alzheimer disease	Tabet N, et al. *Cochrane Database Syst Rev* 2004;(3):CD002854.
Antioxidants (Vitamins C, E, and/or β-carotene)	Cancer prevention	See Chapter 15
	Atherosclerosis	Aviram M, et al. *Handb Exp Pharmacol* 2005;170:263.
Vitamin D	Cardiovascular disease	Holick MF. *Mayo Clin Proc* 2006;81:353.
	Cancer prevention	Garland CF, et al. *Am J Public Health* 2006;96:252.
Vitamin K	Childhood bone health	Cashman KD. *Nutr Rev* 2006;81:353.

transketolase activity. The requirements are listed in Table 6-4. A minimum of 1.0 mg per day is recommended for all adults, even those consuming fewer than 2,000 kcal daily.

Higher Requirement in Pregnant and Lactating Women. This pattern is repeated for all the vitamins for which data are available. The lactating mother secretes about 0.1 to 0.2 mg per day in milk, which is available for the suckling child.

Food Sources

Thiamine is abundant in all foods and is added to many commercial breads and cereals. Rather small quantities of food provide the needed daily requirement. Thiamine is easily removed during the processing of grains or destroyed (10% to 30%) during heating. Because thiamine is water-soluble, much of the content of the vitamin (up to 80%) is extracted in cooking liquid. The method of food preparation must be considered when lists of food content are consulted. Table 6-5 lists the thiamine content of various foods.

Assessment

Intake or Absorption. Thiamine in the urine is assayed either chemically by the thiochrome method or microbiologically with *Lactobacillus viridescens* (10). When thiamine intake

TABLE 6-4. Thiamine Dietary Reference Intakes[a]

Life stage group	Thiamine (mg/day)	Life stage group	Thiamine (mg/day)
Infants		**Females**	
0–6 months	0.2[b]	9–13 years	0.9
7–12 months	0.3[b]	14–18 years	1.0
		19–30 years	1.1
Children		31–50 years	1.1
1–3 years	0.5	51–70 years	1.1
4–8 years	0.6	>70 years	1.1
Males		**Pregnancy**	
9–13 years	0.9	≤18 years	1.4
14–18 years	1.2	19–30 years	1.4
19–30 years	1.2	31–50 years	1.4
31–50 years	1.2		
51–70 years	1.2	**Lactation**	
>70 years	1.2	≤18–50 years	1.4

[a] Estimate based on recommended dietary allowances (RDA).
[b] Recommendation given as adequate intake (AI).
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academies Press, 1998.

equals the requirement of 0.3 to 0.35 mg per 1,000 kcal, the urinary excretion is 40 to 290 mg per day. When intake is less than 0.2 mg per 1,000 kcal, the urinary excretion falls below 25 mg per day. To correct for variations in the collection of urine and allow random samples to be utilized, excretion is usually reported as micrograms of thiamine per gram of creatinine. When expressed in this way, urinary thiamine is quite sensitive in the detection of low intake. However, this measurement does not assess body stores of the vitamin. Table 6-6 provides some guidelines for interpreting the results of this test.

Body Stores. Assessment is either by the direct measurement of thiamine in blood or serum or more commonly by determining the activity ratio of transketolase with and without added thiamine.

High-pressure liquid chromatography (HPLC) with fluorescent detection is most often used (17). Enzymatic degradation of derivatives produces free B1, which is converted to a fluorescent form and separated by HPLC. Mean values in normal adults are 11 to 19 nmol/L in serum, 101 to 191 nmol/L in whole blood, and 132 to 284 nmol/L in erythrocytes. Levels of phosphorylated thiamine in whole blood of infants and adults range from a mean of 120 to 177 nmol/L. Erythrocyte thiamine diphosphate levels correlate well with erythrocyte transketolase measurements (Table 6-6).

Erythrocyte transketolase is a thiamine-requiring enzyme that catalyzes the following reactions in the pentose phosphate pathway:

$$\text{xylulose-5-PO}_4 + \text{ribose-5-PO}_4 \rightarrow \text{sedoheptulose-7-PO}_4 + \text{glyceraldehyde-3-PO}_4$$

$$\text{xylulose-5-PO}_4 + \text{erythrose-4-PO}_4 \rightarrow \text{fructose-6-PO}_4 + \text{glyceraldehyde-3-PO}_4$$

When thiamine intake is stable for a period of time, the activity of this enzyme correlates with urinary excretion of thiamine. However, a single determination of urinary excretion detects intake only at one time, whereas transketolase activity (and erythrocyte thiamine diphosphate concentration) assesses cumulative intake and therefore body stores.

The assay is performed on hemolyzed whole blood with ribose-5-phosphate as substrate in the absence and presence of added thiamine. Values obtained without added thiamine reflect the amount of coenzyme present in tissues. The stimulated value gives a

TABLE 6-5. Approximate Thiamine Content of Selected Foods

Food	Portion	Thiamine (mg)	Percentage of RDI (1.5 mg)
Grain products			
White bread[a]	Slice	0.131	5–12
Whole wheat bread	Slice	0.1	5–12
Shredded wheat[b]	Biscuit	0.06	
Spaghetti, enriched, cooked	1 cup	0.286	10–24
Rice, white, enriched, cooked	1 cup	0.334	15–30
Meats			
Beef, rib roast, cooked	3 oz	0.056	1–5
Pork center loin chops, cooked	4 oz	0.52	>40
Chicken, roasted			
Breast	4 oz	0.065	1–5
Dark meat, thigh	4 oz	0.042	1–5
Sausage, pork, cooked	2-oz patty	0.2	10–24
Ham, roasted	3 oz	0.551	>40
Vegetables			
Peas, cooked from fresh	1/2 cup	0.207	10–24
Peanuts or almonds			
Roasted	1 cup	0.364	10–24
Dried	1 cup	0.969	>40
Potato, baked	2 1/3 in	0.164	10–24
Tomato, raw	2 2/3 in	0.073	5–12
Milk and eggs			
Whole milk	1 cup	0.093	5–12
Eggs, large	One	0.05	1–5
Beverages			
Beer	12 oz	0.021	1–5

RDI, recommended dietary intake.
[a]Thiamine is added to all-purpose flour.
[b]Ready-to-eat cereals may be fortified with thiamine; check the label.
Derived in part from Hands ES. *Food finder,* 2nd ed. Salem, OR: ESHA Research, 1990.

measure of the apoenzyme present that lacks coenzyme. Guidelines for interpretation of the test results are as follows (17):

Body Stores of Thiamine	Thiamine Stimulation	Activity Coefficient
Normal	0–15%	1.0–1.2
Marginal	16–24%	1.2–1.25
Low	>25%	>1.25

Physiology

Function. Thiamine pyrophosphate is a coenzyme in the oxidative decarboxylation of α-ketoacids to aldehydes, and is closely linked with magnesium. Lipoic acid, nicotinamide adenine dinucleotide (NAD), and coenzyme A (CoA) are also requirements for the reaction in animals. The reaction yields acetyl CoA and succinyl CoA. Thiamine also catalyzes transketolase activity in the pentose phosphate cycle. This function results in the production of pentose phosphates used for nucleotide synthesis and supplies NAD phosphate (NADP) for synthetic pathways (i.e., fatty acid synthesis). In thiamine deficiency, blood pyruvate levels rise. Because the vitamin plays such an important role in carbohydrate metabolism, the requirement is increased when carbohydrate intake is increased.

TABLE 6-6. Guidelines for the Interpretation of Thiamine Status

Age of subjects (years)	[RBC thiamine pyrophosphate] (nmol/L)	Thiamine urinary excretion (μg/g creatinine)	
		Deficient intake (<0.3 mg/1,000 kcal)	Very low intake
1–3	—	<175	<120
4–6	—	<120	<85
7–9	—	<180	<70
10–12	—	<180	<60
13–15	—	<150	<50
15+	>150 (normal) 120–150 (marginal) <120 (deficient)	<65	<27

RBC, red blood cell.
Adapted from Sauberlich HE. *Laboratory tests for the assessment of nutritional status,* 2nd ed. Boca Raton, FL: CRC Press, 1999.

Metabolism. Thiamine is synthesized by plants, is abundant in all foods, and is added to many commercial baked products and cereals. Although intestinal bacteria may make some thiamine, mammals are dependent on dietary intake. The vitamin is rapidly absorbed from the upper small intestine by transporters of the SLC19 folate/thiamine family, specifically the A2 and A3 types, located both apically and basolaterally in polarized cells such as enterocytes (18). At low concentrations absorption is sodium dependent, but at higher concentrations passive diffusion is the major mechanism. Absorption efficiency is greater than 80%, although efficiency decreases at higher doses. Thiamine phosphorylation probably occurs in the intestinal mucosa. Thiamine accumulates in all body tissues, and no storage site is preferred. About 1 mg is degraded in the tissues daily. At low intake (≤1 mg), much of the vitamin is excreted in the urine as pyrimidine metabolites; at high intake, unmetabolized thiamine is excreted.

Deficiency

Mechanisms. Deficiency may develop from a decrease in intake, an increase in tissue utilization (e.g., pregnancy), or a combination of the two factors. The clinical settings most commonly associated with thiamine deficiency include chronic alcoholism, malabsorption syndromes, and nausea and vomiting of pregnancy. The total amount of thiamine in the human body is about 30 mg, with half of this in muscle, largely as thiamine pyrophosphate. With requirements in excess of 1 mg per day, deficiency can develop rapidly within a period of weeks or a few months.

Anti-Thiamine Factors. Anti-thiamine factors in foods can alter thiamine activity and be a cause of vitamin deficiency. The thermolabile factor found in the viscera of freshwater fish and shellfish and the thermostable factor in tea leaves have both been reported to cause deficiency when coupled with low thiamine intake.

Signs of Deficiency. Signs of deficiency depend on the duration and severity of the defect, but all degrees of deficiency affect muscle and nerve function. Mild deficiency may result in anorexia, weakness, paresthesias, edema, and lowered blood pressure and body temperature. The infant with acute onset of thiamine deficiency presents with abdominal distension and tenderness, colicky pain and vomiting, and a decreased appetite.

Usual Presentation. The usual presention of chronic deficiency in the Western world is associated with alcoholism or malabsorption. In these cases, multiple deficiencies may be present that can alter the signs and symptoms of pure thiamine deficiency. The features of thiamine deficiency are cardiac failure, peripheral neuropathy, subacute necrotizing

encephalomyelopathy, cerebellar signs, and Wernicke encephalopathy (19). This presentation can accompany any condition with persistent vomiting, malnutrition, or severe gastrointestinal or liver disease, as well as those with decreased dietary intake and reduced thiamine stores (19). Severe deficiency (beriberi) is characterized by neuritis and heart failure (acute mixed type), congestive failure and emaciation (wet type), or polyneuritis and paralysis (dry type). Signs of deficiency may worsen if glucose is administered without thiamine. If lactic acidosis accompanies thiamine deficiency, acute and severe cardiac failure can occur (20). Thiamine deficiency often is neglected as a cause of lactic acidosis, especially in the setting of cardiac failure (dyspnea, palpitations, cardiomegaly, gallop, increased venous pressure, and a prolonged QT interval). Neuropathy and myelopathy are accompanied by aching and burning and decreased muscle strength, more so in the legs than in the arms. Alcoholic myopathy may complicate the effects of thiamine deficiency. There is no recognized syndrome of marginal thiamine deficiency.

Treatment

Deficiency. Thiamine hydrochloride is available in tablets (5 to 1,000 mg), in injectable form (100 or 200 mg per mL), and as an elixir (2.25 mg per 5 mL). Mild deficiency may be treated with 15 mg per day parenterally (or 25–50 mg orally) for 1 week, followed by a maintenance oral dose. Benfotiamine (S-benzolythiamine-O-monophosphate) is a lipid soluble thiamine analogue that reaches plasma levels 5 times those of comparable thiamine doses (21). There is no known clinical benefit derived from these higher plasma levels. Severe deficiency may require somewhat larger doses up to 100 mg twice daily for 3 days, followed by oral supplementation of 5 to 30 mg per day until a normal diet is resumed. The amount of thiamine that enters the cerebrospinal fluid is limited; thus, larger doses must be given when the central nervous system is involved. Because thiamin deficiency is often associated with deficiencies of other B vitamins, it is reasonable to provide thiamine as part of a multivitamin preparation.

Inborn Errors. A few, rare thiamine-responsive inborn errors of metabolism have been described in which the enzyme involved uses thiamine pyrophosphate as a cofactor. The defective enzymes/transporters implicated include branched chain α-ketoacid dehydrogenase (maple syrup urine disease), pyruvate decarboxylase (Leigh disease), and α-ketoglutarate dehydrogenase, thiamine pyrophosphokinase, or thiamine transporter SLC 19A2 (megaloblastic anemia, diabetes mellitus, and deafness) (22). These disorders require pharmacologic doses for therapy (50 mg per day or more).

Preventive Therapy. Preventive therapy should be given to patients whose intake is limited and to those with malabsorption or increased requirements lasting more than 2 weeks. The dose required depends on need but is usually 1 to 2 mg per day.

Nondeficiency States. It has been suggested that thiamine improves energy levels during exercise and in the elderly, and increases cognition in patients with Alzheimer-type dementia, but the small number of studies do not support these uses (23). Low levels of thiamine have been reported in patients with recurrent aphthous mouth ulcers, and in a single trial, replacement therapy with vitamins B_1, B_2, and B_6 led to sustained improvement, but only in those patients with detectable deficiency (23).

Toxicity

Excess thiamine is rapidly cleared from the circulation by the kidneys. The UL has not been set because of a lack of suitable data (3). Reported side effects have included headache, irritability, insomnia, tachycardia, and weakness (24). Occasionally, an anaphylactic reaction has been noted after thiamine injection, probably a consequence of hypersensitivity in patients who received the vitamin previously.

Riboflavin (Vitamin B_2)

Requirement

Riboflavin is the 10-D-ribityl derivative of the 3 ring polyphenolic red pigment, flavin. Other dietary flavonoids result from reduction of C-C double bonds (flavanones), reduction of ketones (flavonols), or hydroxylation of various points on the ring structure (25).

The color of the pigment depends on pH, so riboflavin and flavonoids are components of foods that are red, blue, or purple. Riboflavin forms the active portion of the coenzymes involved in biologic oxidation reactions. Therefore, requirements have been linked to protein or energy intake. Requirements have been determined by following the urinary excretion of riboflavin and by monitoring for signs of deficiency. Table 6-7 lists the daily allowances at all ages. In contrast to thiamine requirements, those for riboflavin do not seem to change as energy requirements are increased at any given age. For adults older than 51 years with a low caloric intake, a minimum riboflavin requirement of 1.2 mg per day (women) or 1.4 mg per day (men) is suggested. Otherwise, allowances for all ages have been computed as 0.6 mg per 1,000 kcal. For persons engaged in strenuous exercise, the allowance has been estimated as high as 1 to 6 mg per 1,000 kcal. The requirement to avoid deficiency symptoms is probably 0.4 to 0.5 mg per 1,000 kcal.

Food Sources

Riboflavin is widely distributed, especially in all leafy vegetables and in the flesh of mammals. The best sources are yeast, milk, egg whites, kidney, liver, and leafy vegetables. Fish, meat, and poultry are good sources. Other vegetables and legumes are not as good. Milk, eggs, meat, grains, and green leafy vegetables are the usual dietary sources in Western countries. Table 6-8 lists the riboflavin content of specific foods. Enrichment accounts for much of the riboflavin in dairy products and grains. Flavonoids also are prominent in a large variety of foods, flavonols (in teas, red grapes, and many foods), flavanones (citrus foods), flavones (green leafy spices), isoflavones (soybeans, legumes), and anthocyanidins (red, purple, and blue berries) (25). Intake of flavonoids varies from <1 mg per day for flavones to ~30 mg per day for flavonols. The role of flavonoids (other than riboflavin) in health is uncertain, but they have been linked to cancer prevention (see Chapter 15).

Effects of Processing. Much riboflavin in milk and grains is free, but in other sources, it is conjugated to protein. It is heat stable but unstable in UV light. It leaches out into cooking water, with average losses of 15% to 20%. If food is exposed to light during cooking, losses can be as great as 50% of the amount in uncooked food. However, exposure of

TABLE 6-7. Recommended Riboflavin Intakes

Life stage group	Riboflavin (mg/day)
Child	
0–0.5 year	0.3[a]
0.5–1.0 year	0.4[a]
1–3 years	0.5
4–8 years	0.6
Male	
9–13 years	0.9
14–>70 years	1.3
Female	
9–13 years	0.9
14–18 years	1.0
19–>70 years	1.1
Pregnant	1.4
Lactating	1.6

[a] Estimate based on adequate intake (AI). All others based on recommended dietary allowance (RDA). Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academies Press, 1998.

TABLE 6-8. Approximate Riboflavin Content of Selected Foods

Food	Portion	Riboflavin[a] (mg)	Percentage of RDI[b]
Grain products			
White bread	Slice	0.087	5–12
Whole wheat bread	Slice	0.059	1–5
Frankfurter rolls	Roll	0.132	5–12
Spaghetti, cooked	1 cup	0.137	5–12
Rice, cooked	1 cup	0.027	1–5
Meats			
Beef, ground, lean	3 oz	0.176	10–24
Beef liver	3 oz	3.52	100
Chicken, light meat, roasted	3 oz	0.098	5–12
Hot dog, beef	One	0.058	1–5
Pork, center loin chop, broiled	4 oz	0.217	10–24
Tuna, canned, water	4-oz can	0.194	10–24
Bacon, cooked	3 pieces	0.054	1–5
Vegetables			
Asparagus, cooked from fresh	1/2 cup	0.104	5–12
Spinach, cooked from fresh	1 cup	0.425	10–24
Cabbage, raw	1 cup	0.022	1–5
Corn on cob, boiled	1 in	0.08	1–5
Potato, baked	4.75 × 2.3 in	0.067	1–5
Tomatoes	2.4 in	0.059	1–5
Dairy products and eggs			
Milk, whole	1 cup	0.395	10–24
Eggs, large	One	0.265	10–24
Cheese, cheddar	1 oz	0.106	5–12
Cheese, cottage, low fat <2%	1 cup	0.416	10–24
Ice cream	1 cup	0.329	10–24

[a] Data from Hands ES. *Food finder,* 2nd ed. Salem, OR: ESHA Research, 1990.
[b] Recommended dietary intake is 1.7 mg.

processed milk to light does not affect its riboflavin content. Little riboflavin is lost during the pasteurization of milk, but canning of foods can cause up to 30% of the vitamin content to be lost into the water. The riboflavin values listed in Table 6-8 are those of the unprocessed foods in most cases. Riboflavin is lost during the processing of grain and is added back to white flour, corn meal, and rice. The average Western diet contains about 2.7 mg per day, in excess of the RDA. Decaffeination decreases the flavonol levels of teas. Storage and cooking reduces some, but not all flavonoids.

Colonic Bacteria. Colonic bacteria produce riboflavin, but this is not available for absorption in sufficient quantity to fulfill daily need. The bacteria must be lysed or killed for the vitamin to be available.

Assessment

Intake. Riboflavin is unique among vitamins in that it is minimally metabolized or stored by the body. Thus, urinary excretion correlates well with intake during normal conditions. Urinary levels of riboflavin are measured by means of HPLC with fluorometric detection (17). During fasting or prolonged bed rest, urinary excretion can be falsely elevated. Because urinary levels reflect the recent dietary intake of riboflavin, variations can be considerable. The values are reported as micrograms of riboflavin per gram of creatinine to correct for body size and allow random sampling in 2-hour collections. Samples are usually obtained

in the fasting state to avoid the variations caused when the subject consumes a meal near the time of collection. However, a deficient patient retains most of the ingested vitamin, and such variations are minimal in patients whose body stores are depleted. Table 6-9 provides guidelines for the interpretation of this measurement.

Body Stores. The riboflavin-dependent enzyme erythrocyte glutathione reductase catalyzes the following reaction:

$$NADPH + H^+ + GSSG \rightarrow NADP^+ + 2GSH$$

where GSSG = oxidized glutathione and GSH = reduced glutathione.

This assay is performed on whole blood with and without the addition of flavin adenine dinucleotide. Normally, no stimulation is noted, but when body stores of the vitamin are decreased, activity is markedly stimulated. The activity coefficient value is independent of age and sex. An activity coefficient above 1.40 is diagnostic of severe deficiency. This sensitive assay is the procedure of choice (17).

Physiology

Coenzyme Function. Riboflavin forms a part of the two coenzymes flavin mononucleotide and flavin adenine dinucleotide. The prosthetic group is bound to the enzyme, accepts an H^+ ion, and then is reoxidized by interacting with another H^+ acceptor, usually a cytochrome of the mitochondrial electron transport chain (26). Flavins participate in both one- and two-electron transfers. Enzymes that require these coenzymes include succinic dehydrogenase; oxidases of fatty acids, glucose, and glycine; and xanthine oxidases. Thus, the richest sources of the vitamin are metabolically active tissues, not storage tissues. The highest concentrations of the vitamin are in the liver, heart, and kidneys. Riboflavin circulates in the blood largely bound to proteins (75%). The mean concentration in blood is 32 μg/L.

Absorption and Excretion. Riboflavin is absorbed rapidly in the intestine by a site-specific and saturable system that is energy- and sodium-dependent; however, the capacity for absorption is limited to ~30 mg per day. The intestine, along with liver and other tissues, also phosphorylates the vitamin. The vitamin enters plasma as free flavin mononucleotide, is bound to albumin and immunoglobulins, and then is excreted as riboflavin or its metabolites (27). Urinary excretion is increased by a negative nitrogen balance and by large amounts of thiamine. Excretion is decreased by low-carbohydrate diets, exercise, and pregnancy. Riboflavin is excreted in milk, up to about 10% of the daily intake (i.e., 300 μg per day). Excretion in sweat is much lower.

Deficiency

Signs and Symptoms. Early symptoms are related to oral and ocular lesions. Soreness and burning of the lips, mouth, and tongue develop along with photophobia, tearing, burning, and itching of the eyes. Angular stomatitis is characteristic but not specific. This lesion is characterized by maceration and bilateral transverse fissures of the mucocutaneous

TABLE 6-9. Guidelines for Interpretation of Assessment of Riboflavin Status

Age (years)	Marginal (moderate risk)	Deficient (high risk)
	Riboflavin excretion (μg/g creatinine)	
All adults	40–119	<40
	Erythrocyte glutathione reductase (activity coefficient)	
All ages	1.2–1.4 (20–40% ↑)	>1.4 (>40% ↑)

Adapted from Sauberlich HE. *Laboratory tests for the assessment of nutritional status,* 2nd ed. Boca Raton, FL: CRC Press, 1999.

junction at the angle of the mouth. Lesions of the vermilion of the lips, termed *cheilosis,* frequently occur along the line of closure in riboflavin deficiency. Geographic tongue and denudation of papillae may occur. Desquamation of the skin and seborrheic dermatitis may be seen, especially in the nasolabial fold and scrotum. Corneal vascularization develops around the entire circumference. Hypochromic anemia is associated with erythroid hypoplasia. Growth and appetite are poor. Some of these symptoms also occur in vitamin B_6 deficiency because the oxidase required to produce the functional form of vitamin B_6 is riboflavin-dependent (18). Thus, the symptoms specifically caused by riboflavin deficiency are not known with certainty. Patients at risk include pregnant or lactating women, infants and school children, and groups that have high utilization and partially depleted stores.

Associated Deficiencies. Riboflavin-containing foods often contain other B vitamins. Moreover, riboflavin is required for the metabolism of vitamin B_6, folate, niacin, and vitamin K. Thus, multiple other deficiencies often accompany riboflavin deficiency (Table 6-2). The usual settings in which deficiency develops are conditions characterized by poor intake, such as alcoholism or malabsorption. Hemodialysis can lead to losses of water-soluble vitamins, and deficiency can develop if they are not replaced. Drugs can prevent conversion to the active coenzyme; chlorpromazine, imipramine, amitriptyline, and quinacrine have been implicated.

Differential Diagnosis. The differential diagnosis of lip lesions includes poorly fitting dentures with malocclusion; sensitivity to lipsticks, toothpaste, and similar substances; and iron-deficiency anemia. Similar tongue lesions can be seen with iron deficiency, smoking, pernicious anemia, pellagra, and antibiotic therapy.

Treatment

Deficiency States. Deficiency states should be treated with 5 to 10 mg per day by mouth. Often, other B-complex vitamin deficiencies accompany riboflavin deficiency, and some (e.g., niacin deficiency) cannot be distinguished easily on clinical grounds. When malabsorption is present, prophylactic use of the vitamin at a dose of about 3 mg per day is useful. Tablets are available in doses of 5 to 100 mg, and an injectable solution is available at a concentration of 35 mg per mL.

Nondeficiency States. Riboflavin is used in rare genetic disorders in which the formation of specific flavoproteins is deficient and as a supplement during phototherapy for neonatal jaundice. During the photosensitized oxidation of bilirubin to more polar derivatives that can be excreted, riboflavin is destroyed, and additional vitamin needs to be provided. Migraine-like headaches occur in the syndrome of mitochondrial encephalopathy, in which riboflavin therapy appears to be effective. In a randomized, double-blinded, placebo-controlled trial of high-dose (400 mg per day) riboflavin, the frequency of migraine attacks was reduced during a period of 3 months (28). However, the severity of the attacks was not affected, and the benefit of riboflavin was apparent only at the end of the study. More such trials are needed to demonstrate the effectiveness of riboflavin therapy in this condition.

Toxicity

Up to 10 mg per kg can be given without any apparent toxic effects. However, insufficient data are available to recommend an UL (3). Riboflavin may cause a yellow-orange discoloration of the urine.

Niacin (Vitamin B_3)

Requirement

The term *niacin* is used for both nicotinic acid and nicotinamide. Estimates of requirement are complicated by the fact that some tryptophan is converted to nicotinic acid in humans. On the basis of three studies in adults, a Food and Nutrition Board task force estimated that 60 mg of ingested tryptophan is equivalent to 1 mg of niacin—that is, from 60 mg tryptophan enough is oxidized to provide about 1 mg of niacin. Niacin is required for the function of respiratory enzymes, and therefore allowances are based on energy expenditures.

Estimates of the requirement are usually reported in terms of niacin equivalents (NE) (i.e., 1 mg of niacin or 60 mg of tryptophan). The availability of tryptophan for niacin synthesis also depends on the presence of other essential amino acids. Table 6-10 gives the daily requirements and allowances for adults and children.

Most data on deficiency are for adults, but estimates have been made for children. Daily allowances are based on an intake of 6.6 mg NE/1,000 kcal. A minimum for adults over the age of 18 years is 15 (female) or 19 (male) mg NE per day. During lactation, about 1.6 mg of niacin is lost daily in 850 mL of milk.

Food Sources

Nicotinic acid is present in most foods except fats and oils, mainly as the pyridine nucleotides NAD and NADP. It is removed during grain processing but is added back during enrichment. It is particularly abundant in meat, fish, and grain products. It is sometimes present in a form that is not absorbable (e.g., in corn). It is stable in foods and can survive a reasonable amount of heating, cooking, and storage. Average diets in the United States supply 6 and 24 mg of niacin and 700 and 1,100 mg of tryptophan per day for women and men, respectively. This intake amounts to a total of 16 to 24 mg NE per day. Animal proteins provide more tryptophan than vegetable proteins (1.4% on average vs. 1.0%). Human milk contains about 0.17 mg of niacin and 22 mg of tryptophan per deciliter and is adequate to supply the needs of an infant. Table 6-11 lists the niacin content of various foods. However, food tables based on niacin content alone are not helpful unless the content is linked to energy, ingested tryptophan, or both.

Assessment

Intake or Absorption Measured by Urinary Excretion. Normally, adults excrete 20% to 30% of niacin as *N′*-methylnicotinamide and 40% to 60% as the 2-pyridone metabolite. Values for these metabolites fall as intake decreases. HPLC procedures provide a rapid and sensitive method for determining the levels of both metabolites. The level is usually reported per gram of creatinine to allow for random sampling; however, this method is available only for adults. In children, the level of creatinine excretion is more variable, and good guidelines for the interpretation of excretion have not been worked out. The measurement of 2-pyridone in plasma may be a more reliable assay than the ratio of the

TABLE 6-10. Recommended Dietary Intakes of Niacin

Life stage group	Niacin equivalent (mg/day)	Life stage group	Niacin equivalent (mg/day)
Infants		**Females**	
0–6 months	2[a]	9–13 years	12
7–12 months	4[a]	14–>70 years	14
Children		**Pregnancy**	
1–3 years	6	≤18–>50 years	18
4–8 years		**Lactation**	
Males		≤18–>50 years	17
9–13 years	12		
14–>70 years	16		

[a] Estimate based on adequate intake (AI). All others based on recommended dietary allowance (RDA). Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academies Press, 1998.

TABLE 6-11. Approximate Niacin Content of Selected Foods

Food	Portion	Niacin content (mg)	Percentage of RDI[a]
Grain products			
White or whole wheat bread	Slice	1.05	5–12
Corn bread	Muffin	0.850	1–5
Frankfurter roll	One	1.58	5–12
40% bran flakes[b]	1/2 cup	2.1	5–12
Puffed wheat	1 cup	1.2	5–12
Rice, cooked	1 cup	3.03	10–24
Meats			
Beef, ground, lean	3 oz	4.23	10–24
Pork, center loin chop	4 oz	4.35	>40
Chicken, light meat, roasted	3 oz	10.6	25–39
Fish (e.g., halibut), broiled	3 oz	6.06	>40
Liver, beef	3 oz	12.3	>40
Tuna in water	4-oz can	12.3	10–24
Vegetables and fruits			
Green beans, cooked fresh	1 cup	0.768	1–5
Cauliflower, cooked	1/2 cup	0.342	1–5
Peas, frozen, cooked	1/2 cup	1.18	5–12
Potato, baked	4.75 × 2.3 in	3.32	10–24
Tomato, fresh	2.6 in	0.772	1–5
Apple	2.75 in	0.106	<1
Banana	8.75 in	0.616	1–5
Peanuts	1 cup	20.6	100
Peanut butter	2 tbs	4.23	10–24
Milk and eggs			
Milk, whole	1 cup	0.205	1–5
Egg, large	One	0.033	<1

[a] Recommended dietary intake is 20 mg.
[b] Most cold cereals are enriched; check labels.
Data from Hands ES. *Food finder,* 2nd ed. Salem, OR: ESHA Research, 1990.

two niacin metabolites in the urine (17). Table 6-12 provides guidelines for interpreting urinary excretion data.

Body Stores. The levels of 2-pyridone and *N′*-methylnicotinamide in plasma have been reported in a few small studies to be a more reliable indicator of these metabolites than their urinary concentrations. In addition, the measurement of pyridine metabolites in red cells may be useful and more reliable (Table 6-12). Thus, it is possible that as HPLC methods become more widely available, one of these plasma/red cell measurements may identify patients with low body stores of niacin.

Physiology

Nicotinic acid is an essential component of the coenzyme nicotinamide adenine dinucleotide and its phosphate (NAD^+ and $NADP^+$). These coenzymes function to carry hydrogen from a substrate through the mitochondrial electron transport system. They are really cosubstrates rather than coenzymes because they join and leave the enzyme along with the substrate. Many dehydrogenases are NAD- and NADP-dependent. Perhaps the most important pathway is that of oxidation of glucose-6-phosphate. The products of oxidation, NADH and NADPH, are then used for other metabolic processes, such as fatty acid synthesis. Nicotinic acid is produced from tryptophan in the liver by a series of enzymes.

TABLE 6-12. Guidelines for Interpretation of Niacin Status

Patient	Acceptable	Deficient intake	Low intake
	Urinary excretion: ratio of mg N′-methylnicotinamide/g creatinine to 2-pyridone-N′-methylnicotinamide		
Males and nonpregnant, nonlactating females	1.6–4.29	<0.5	0.5–1.50
Women, pregnant			
1st trimester	1.6–4.29	<0.5	0.5–1.59
2nd trimester	2.0–4.99	<0.6	0.6–1.99
3rd trimester	2.5–6.49	<0.8	0.8–2.49
	Plasma N′-methylnicotinamide-2-pyridone (μg/dL)		
Young men[a]	16.3 ± 5.9 (28 NE/day)	3.7 ± 0.9 (10 NE/day)	1.2 ± 2.3 (6 NE/day)
	Erythrocyte NAD/erythrocyte NADP ratio		
Young men[a]	<1.0		

NE, niacin equivalent; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate.
[a] Based on a single study of niacin-deficient diets.
Adapted from Sauberlich HE. *Laboratory tests for the assessment of nutritional status,* 2nd ed. Boca Raton, FL: CRC Press, 1999.

NAD^+ and $NADP^+$ inhibit the first enzyme of this synthetic pathway, tryptophan oxygenase, thus regulating the production of nicotinic acid. The fourth enzyme in this pathway, kynureninase, requires pyridoxal phosphate, so that deficiencies of these two vitamins are linked. NAD^+-dependent protein deacetylases (sirtuins or Sir2-like proteins) are important regulators of many biological processes, including deacetylation of histones (29). The NADPH complex includes NADPH oxidase that produces superoxide, and may be implicated in vasculopathy in humans (30).

Nicotinic acid, but not nicotinamide, exhibits two pharmacologic properties—peripheral vasodilation and a plasma lipid-lowering effect. The latter effect is more marked when cholesterol levels are high. Nicotinic acid is used to decrease levels of triglycerides and of total and low-density-lipoprotein (LDL) cholesterol, and to increase levels of high-density-lipoprotein (HDL) cholesterol. The receptor for nicotinic acid has been identified as the G_1-coupled receptor HM74A, present on adipocytes, dermal dendritic cells and macrophages, and immune cells in other organs (31). Activation of this receptor on adipocytes may account for the antilipolytic effects of nicotinic acid. Activation of immune cells in the skin probably accounts for the flushing response, probably related to mobilization of arachidonic acid and production of vasodilatory prostaglandins PGD_2 and PGE_2.

Deficiency

Pellagra. The classic deficiency syndrome, pellagra, is associated with skin, gastrointestinal, and central nervous system changes. Dermatitis, which occurs in exposed areas, is symmetric and exacerbated by trauma. Cracking and crusting develop over thickened areas of skin. Soreness is common in the mouth, with a red, swollen, and painful tongue and mucous membranes. Angular stomatitis is often seen but is probably caused by associated riboflavin deficiency. Diarrhea is a common feature of niacin deficiency and may be related to mucosal atrophy. Early neurologic symptoms include headache, sleep disturbances, anxiety, depression, and thought disorders. The peripheral neuropathy seen with pellagra cannot be distinguished from thiamine deficiency, and does not respond to niacin alone, so is

likely due to multiple vitamin deficiencies (19). Psychomotor retardation and stupor may ensue. As the deficiency progresses, confusion, hallucinations, and agitation develop, and finally seizures or catatonia alternating with lucid spells.

Associated with Vitamin B_6 Deficiency. Tryptophan and niacin deficiencies are often compounded by vitamin B_6 deficiency because B_6 is required in the conversion of tryptophan to nicotinic acid. Isoniazid therapy can lead to pellagra because hydrazine drugs form adducts with pyridoxal phosphate. If vitamin B_6 is provided and tryptophan is available, exogenous niacin is not needed. Isoniazid resembles nicotinic acid chemically and acts as an inhibitor. However, other hydrazine drugs that are more potent inhibitors than isoniazid do not cause pellagra. Thus, inhibition of the vitamin alone may not explain the clinical deficiency.

Hartnup Disease. Hartnup disease is a rare inherited condition of neutral amino acid malabsorption that produces a clinical syndrome mimicking pellagra. Dermatitis with photosensitivity, ataxia, and psychiatric changes are common. Decreased intestinal and renal tubular absorption of tryptophan may explain in part the relative tryptophan deficiency associated with this condition. Protein synthesis seems adequate, but sufficient extra tryptophan is not available for nicotinic acid synthesis. The fact that the disorder responds to oral niacin confirms the role of tryptophan in daily niacin production.

Carcinoid Syndrome. Carcinoid syndrome often presents with low blood levels of tryptophan, probably a result of increased synthesis of serotonin from tryptophan. Rarely, pellagra occurs in the carcinoid syndrome and may be overcome by oral niacin.

Treatment

Deficiency. Isolated niacin deficiency is uncommon, and usually other B-complex vitamins must also be given. Niacin (nicotinic acid) is available in immediate release tablets (20 to 500 mg), as sustained release/long acting (100, 500, and 750 mg), as extended release (Niaspan) capsules (500, 750, and 1,000 mg), and as an injectable solution (10, 50, and 100 mg per mL). Nicotinamide is also available in comparable doses. Nicotinamide does not have hypolipidemic or vasodilating effects. The glossitis, dermatitis, diarrhea, and mental symptoms of pellagra respond to oral doses of 100 to 500 mg per day, depending on the severity of symptoms. The peripheral neuritis seen in pellagra responds to niacin or B_6 replacement, depending on the vitamin deficiency responsible for the syndrome.

Pharmacologic Effects

Cardiovascular disease. Nicotinic acid (1 to 3 g per day in three or four divided doses), but not nicotinamide, lowers serum levels of triglyceride, total cholesterol, and LDL cholesterol (32). Most randomized, placebo-controlled trials show significant decreases in recurrent myocardial infarction, cerebrovascular events, total mortality, and angiographic progression of atherosclerosis in patients on nicotinic acid monotherapy (3 g per day) (33). Combination therapy with a statin appears to be more potent for lowering LDL-c than monotherapy alone (34).

Diabetes mellitus. Despite a protective effect on beta cells in animals and an increase in C-peptide levels as a measure of beta-cell function in humans, C-peptide secretion is not altered in humans, but intensive insulin therapy with nicotinamide added appears to improve diabetic control in patients with type 1 diabetes (35).

Osteoarthritis. One preliminary study suggests an effect on joint mobility and the use of anti-inflammatory drugs (22).

Hair and skin conditioners. Both nicotinamide and niacin are present in cosmetics (shampoos, hair tonics, skin moisturizers, cleansing preparations) at concentrations from 0.0001% to 3% (36). They appear to be safe to the skin at these low concentrations.

Toxicity

The UL for niacin intake has been set at 35 mg per day for subjects over 18 years of age. Large doses of nicotinic acid (>1 g per day) cause flushing secondary to histamine release, with burning of the hands and face. This effect may wear off with time. Taking the drug

with meals in divided doses or with aspirin may diminish the flushing (37). At doses of 3 g per day or more, nausea, vomiting, diarrhea, and arrhythmias may occur. Symptoms of dyspepsia can be aggravated by the large acid load. Hyperuricemia secondary to competition for excretion occurs in about 40% of patients. Gout occurs less frequently (7%). Cardiac arrhythmias occur uncommonly. About one-fourth of patients note rash, pruritus, hyperkeratosis (especially at higher doses of >3 g per day), and glucose intolerance. Laboratory evidence of hepatic injury may be found. Elevations of aspartate aminotransferase and bilirubin are common (30% to 50%), even at doses as low as 750 mg per day. These elevations are more likely with the use of long acting or sustained release niacin, as these form the active metabolite nicotinamide (38). The dose of 2 g per day should not be exceeded. Cholestatic jaundice and submassive necrosis have been reported, again at high doses. Rarely, acanthosis nigricans can be seen that is not associated with occult neoplasm. Toxicity is more common with timed-release preparations taken at high doses. A new timed-release preparation may be safer, delivering up to 2,000 mg per day (39).

Pyridoxine (Vitamin B_6)

Requirement

The term *vitamin* B_6 encompasses three naturally occurring pyridines—pyridoxine, pyridoxal, and pyridoxamine. These are all interrelated functionally, and a quantitative requirement would depend on knowledge of the intake and activity of all three. Such data are not readily available in humans. The estimates of requirement are based on production or cure of clinical signs of deficiency or, more often, on production or reversal of abnormal biochemical test results (e.g., excretion of tryptophan metabolites after a tryptophan load). Requirements are increased during intake of large amounts of protein.

The vitamin B_6 allowance has been estimated according to a ratio of 0.016 mg of the vitamin per gram of protein ingested. Thus, the estimates for women and men are based on the lower rates of protein intake in women than in men (Table 6-13). These figures slightly exceed the estimated requirement based on repletion studies. In the elderly, the incidence of biochemical pyridoxine deficiency was nearly 50% (40), but there is little evidence to indicate that this deficiency is based on differences in energy intake (41). Thus, the recommendations are higher in the older aged population. The protein requirements of pregnant and lactating women are increased; in addition, they must supply the fetus or newborn with vitamin B_6. The additional allowances suggested for these stresses have been made without much quantitative data to support the recommendations. The vitamin B_6 content of human milk is low in the first few weeks. Oral contraceptive intake for more than 30 months before pregnancy can decrease vitamin B_6 levels.

Food Sources

Dietary intake of the vitamin comes from vegetables as pyridoxine, and from meat in the form of pyridoxamine. These forms are oxidized to pyridoxal-5-phosphate by pyridoxamine oxidase. Vitamin B_6 is produced by intestinal microorganisms, but it is not thought that much of this is absorbed. The three forms of the vitamin are present in low concentrations in all plant and animal tissues. For this reason, dietary deficiency is uncommon. Bound forms of the vitamin are found as β-D-glucosides in plants; about 60% of this is bioavailable. Most vitamin B_6 is associated with glycogen phosphorylase, and this source accounts for much of the storage pool of the vitamin. Table 6-14 lists the content of the vitamin in various foods. Pyridoxal represents 80% of the B_6 vitamins in human milk. This abundance of pyridoxal is needed because the premature infant (<29 weeks) cannot utilize pyridoxine to any extent. Losses of vitamin B_6 have been observed during the heating and storage of some foods as Schiff base forms between pyridoxal phosphate and the ε-amino lysines in proteins. Bioavailability can be as low as 40% but usually ranges from 60% to 80%. Losses occur during processing, often exceeding 50%. Sometimes, the availability of vitamin B_6 is increased during food processing.

Assessment

Intake or Absorption. The vitamin is excreted in the urine mainly as pyridoxal and to a lesser extent as pyridoxamine. About 20% to 50% is excreted as the metabolite *4-pyridoxic acid*. The excretion of free vitamin B_6 correlates closely with intake. Dietary protein

TABLE 6-13. Recommended Daily Dietary Intakes of Vitamin B_6

Life stage group	Vitamin B_6 (mg/day)	Life stage group	Vitamin B_6 (mg/day)
Infants		**Females**	
0–6 months	0.1[a]	9–13 years	1.0
7–12 months	0.3[a]	14–18 years	1.2
Children		19–50 years	1.3
1–3 years	0.5	50–>70 years	1.5
4–8 years	0.6	**Pregnancy**	
Males		≤18–50 years	1.9
9–13 years	1.0	**Lactation**	
14–50 years	1.3	≤18–50 years	2.0
51–>70 years	1.7		

[a] Estimate based on adequate intake (AI). All others based on recommended dietary allowance (RDA). Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academies Press, 1998.

does not affect urinary excretion. Urinary excretion reflects recent dietary intake but may not reflect the degree of deficiency. Random samples provide as good data as do 24-hour excretion studies. Chromatographic (HPLC) methods are very reliable for all metabolites, especially 4-pyridoxic acid. Low intake correlates with excretion of less than 5.0 μg of 4-pyridoxic acid per day. Urinary excretion is probably not a reliable measure of pyridoxine status in patients being treated with vitamin B_6 antagonists, such as isoniazid. Table 6-15 provides guidelines for the interpretation of urinary levels.

Body Stores

Transaminases. Transaminases are enzymes requiring vitamin B_6. Because the level of transaminase activity is greater in red cells than in serum and is less variable, erythrocyte transaminases are used for this determination. The assay is performed with and without the addition of pyridoxal phosphate. However, in contrast to what occurs in the stimulatory tests for thiamine and riboflavin, transaminase activity in normal subjects is increased by the addition of pyridoxal. Activity is reported as a ratio of stimulated to unstimulated activity, termed the *erythrocyte transaminase (E-AST or E-ALT) index*. Normal subjects have an E-AST index of less than 1.7 and an E-ALT index of less than 1.25. Deficiency is correlated with an E-AST index of more than 2.2. Ratios between 1.8 and 2.2 are marginal. This test remains the best readily available functional assessment of vitamin B_6 status.

Pyridoxal-5′-phosphate. Pyridoxal-5′-phosphate (PLP) is also a sensitive measure of vitamin status and correlates with body stores. However, plasma levels can be modified by physical exercise, pregnancy, and by plasma alkaline phosphatase activity. PLP can be measured in whole blood (50 to 120 nmol/L) and in plasma (17±7 μg/L), with ranges of 30 to 134 nmol/L and 5 to 33 μg/L, respectively (17). If the 95% reference limits for PLP derived from white populations are used, many blacks have low levels of pyridoxine. Thus, low PLP levels in blacks do not necessarily indicate deficiency (42). The assay is currently performed with tyrosine apodecarboxylase as the apoenzyme. HPLC has also been used, but the assay is not so widely available. In some situations, stores are not correctly assessed by PLP measurement. Patients with cirrhosis metabolize PLP more rapidly than normal persons do. However, metabolism is not to pyridoxic acid, so excretion of that metabolite does not assess depletion. PLP is also elevated in hypophosphatasia (43). Thus, its level may vary with alkaline phosphatase activity. The difficulty with assessing body stores is that multiple forms of the vitamin exist and must be measured (17).

TABLE 6-14. Approximate Vitamin B_6 Content in Selected Foods

Food	Portion	Vitamin B_6 content (mg)	Percentage of RDI (2.0 mg)
Grain products[a]			
Bread			
White	1 piece	0.009	<1
Whole wheat	1 piece	0.052	1–5
Rice, cooked	1 cup	0.283	10–24
Spaghetti, enriched	1 cup	0.049	1–5
Corn flakes	3 oz	0.060	1–5
Meats			
Beef, ground, lean	3 oz	0.210	10–24
Pork, center loin chop	4 oz	0.348	10–24
Salmon	3 oz	0.186	5–12
Chicken			
Dark meat, roasted	3 oz	0.304	10–24
White meat, roasted	3 oz	0.510	25–39
Fruits and vegetables			
Banana	8.75 in	0.659	25–39
Apples	2.75 in	0.066	1–5
Grapes	10 each	0.060	1–5
Cauliflower, cooked	1/2 cup	0.125	5–12
Peas, green, cooked	1 cup	0.250	5–12
Potatoes, baked	1 each	0.701	25–39
Tomatoes, fresh	1 each	0.098	5–12
Peanuts	1 cup	0.367	10–24
Peanut butter	2 tbs	0.124	5–12
Dairy products and eggs			
Milk, whole	1 cup	0.102	5–12
Cheese, cottage, 27% fat	1 cup	0.172	5–12
Egg	One	0.060	1–5

RDI, recommended dietary intake.
[a] Cereals are sometimes fortified with B_6; check label.
Data from Hands ES. *Food finder,* 2nd ed. Salem, OR: ESHA Research, 1990.

Xanthurenic acid excretion. Xanthurenic acid excretion following a 2- or 4-g tryptophan load is also a sensitive functional assay of vitamin B_6 status, perhaps even more sensitive than the transaminase ratio (17). The HPLC assay is reproducible, but because of the convenience of sampling blood or plasma, it has not been used as much as the transaminase ratio and PLP concentrations.

Homocysteine. Vitamin B_6 is one of three vitamins important in the metabolism of homocysteine, and levels of this metabolite are elevated when the vitamin is deficient. Detection is very accurate by HPLC. Homocysteine is elevated to ≥12 μmol/L fasting and ≥38 μmol/L after methionine load. When homocysteine is elevated, plasma levels of PLP are significantly lower than in people with normal levels. However, elevation of homocysteine is not specific for pyridoxine deficiency (Table 6-15). Folic acid is probably the main determinant of the homocysteine increase associated with coronary artery disease (see sections on folic acid and vitamin B_{12}).

Physiology

The forms of vitamin B_6 are rapidly absorbed in the small intestine by a pH-dependent, sodium-independent carrier-mediated mechanism (44). The absorbed vitamin is distributed among enzyme proteins as the coenzyme pyridoxal phosphate. Most enzymes use this

TABLE 6-15. Guidelines for Assessment of Vitamin B_6 Status

Parameter	Acceptable values		
Plasma pyridoxal-5′-phosphate	>30 nmol/L		
Urinary 4-pyridoxic acid	>3.0 μmol/day		
Erythrocyte AST activity coefficient	<1.80		
Erythrocyte ALT activity coefficient	<1.25		
Urinary xanthurenic acid excretion	<65 μmol/day (2 g L-tryptophan load)		
		Plasma [homocysteine][a]	
		<16.3 μmol/L	>16.3 μmol/L
Pyridoxal-5′-phosphate	≥30 nmol/L	83 ± 76	56 ± 50
Plasma folate	≥5 nmol/L	6.7 ± 3.6	5.5 ± 2.9
Plasma cobalamin	±200 pmol/L	275 ± 148	202 ± 61

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a] Values from reference 46.
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academies Press, 1998.

form, although transaminase can also use pyridoxamine. The ability of the human fetus (up to 30 weeks of age) to convert pyridoxine phosphate to pyridoxal phosphate via pyridoxine oxidase is limited. Enzymes that require vitamin B_6 are involved in the synthesis and catabolism of all amino acids. Thus, the requirement is linked to protein intake. Most of the transaminases require vitamin B_6, as do many amino acid decarboxylases. Important among this latter group are the enzymes that convert histidine to histamine, ornithine to polyamines, aromatic amino acids to dopamine, and serotonin and glutamate to γ-aminobutyric acid. The enzymes serine deaminase, which produces pyruvic acid, and threonine deaminase, which produces 2-oxybutyrate, both require vitamin B_6. The synthesis of CoA, which is the first step in porphyrin (heme) synthesis, the conversion of linoleic to arachidonic acid, and the production of nicotinic acid from tryptophan via kynurenine are all B_6-dependent steps. The vitamin binds to a nuclear steroid hormone receptor and thus acts as a negative control of steroid hormone action.

Deficiency

Because the vitamin is widely distributed in food and is also made by intestinal bacteria, dietary restriction rarely leads to deficiency. The usual clinical situations in which deficiency arises include malabsorption, old age, alcoholism, and treatment with vitamin B_6 antagonists. The deficiency syndrome is not well defined in humans. The major findings include seborrhea-like lesions about the eyes, nose, and mouth; cheilosis; glossitis; hypochromic anemia; and peripheral neuropathy (19). Nausea, vomiting, dizziness, irritability, insomnia, and convulsions can occur. Vitamin B_6 deficiency can impair interleukin-2 production and lymphocyte proliferation in elderly adults. Most of these symptoms are induced by the use of vitamin B_6 antagonists and may not reflect symptoms of the true deficiency state. Deficiency of pyridoxamine oxidase produces fetal distress with intractable seizures by preventing production of the active form of the vitamin, pyridoxal-5-phosphate (45).

Hyperhomocysteinuria. Hyperhomocysteinuria has been identified as an independent risk factor for vascular disease and may be associated with a deficiency of cystathionine synthase, the B_6-dependent enzyme that catalyzes the conversion of homocysteine to cystathionine. Significantly lower levels of PLP, cobalamin, and folic acid were found in patients with moderately elevated levels of homocysteine (≥16.3 μmol/L) (46). Most studies implicate folic acid as the major factor related to hyperhomocysteinemia (see section on folic acid in this chapter). However, when pyridoxine alone has been used to lower

homocysteine levels, rather low doses were used (2–10 mg per day) (47). These are doses in the range of the DRI for vitamin B_6, but most patients with hyperhomocysteinemia do not have plasma pyridoxine levels in a range that would be considered deficient, so the implication of the vitamin's role in homocysteine levels in humans is still unresolved. It is premature at present to recommend the widespread use of these supplements to alter atherogenesis in this subset of patients with hyperhomocysteinemia.

Vitamin B_6 Antagonists. The most common antagonists are isoniazid, hydralazine and other hydrazines, oral contraceptives, dopamine, and penicillamine. Cycloserine also can act in this way. These compounds increase urinary excretion (e.g., isoniazid) or combine with pyridoxal or pyridoxal phosphate to form inactive drugs (e.g., hydrazones are derived from hydrazines and a thiazolidine derivative from penicillamine). These effects can be reversed with vitamin B_6 supplements, usually in the range of 2 to 5 mg per day (48). Large doses of the vitamin have also been used to treat Gyromitra mushroom (monomethylhydrazine) poisoning. Some experts advocate prophylaxis for all patients on isoniazid; others suggest supplements only for those at risk for neuropathy. Large doses (600 mg bid) have been used to treat neuroleptic-induced akathisia (restlessness) and tardive dyskinesia, presumably due to its effects on neural transmission (49).

Pyridoxine-Dependent Syndromes. These syndromes have been reported, in which tissue levels of the vitamin are normal but binding of the cofactor to the enzyme is impaired. These inherited disorders respond to larger doses of vitamin B_6 than are required to treat deficiency states (21). Table 6-16 lists the syndromes.

Venous Thromboembolism. An association of low serum vitamin B_6 levels with increased risk of venous thromboembolism has been reported (50). This risk was not associated with serum homocysteine levels. The results of intervention studies are not sufficiently clear to allow a recommendation for routine use.

Therapy

Deficiency. Pyridoxine hydrochloride is available as 5-, 10-, 25-, 50-, 100-, 200-, 250-, and 500-mg tablets and as a solution for injection containing 50 or 100 mg per mL. It is a component of many multivitamin tablets at doses of about 2 mg. In treating deficiencies, it is often advisable also to give other B-complex vitamins because multiple deficiencies frequently occur simultaneously. For *prophylactic* use with isoniazid to prevent peripheral neuropathy, 5 mg per day is probably sufficient, but doses up to 25 mg are used. Treatment of established neuropathy requires 50 to 300 mg per day. Pyridoxine is sometimes given to patients with sideroblastic anemia, dystonia, or Parkinson disease treated with L-dopa, and to newborns with seizure disorders.

Pharmacologic Doses. The vitamin has been used to treat a variety of disorders that may or may not be associated with decreased intake, but little evidence of efficacy has been provided by properly conducted trials (51). Pyridoxine has been used in carpal tunnel syndrome (52), asthma, and autism, with no clear evidence of efficacy from available studies (13). A meta-analysis of 10 randomized, controlled trials of premenstrual syndrome found efficacy in doses of 50 mg once or twice a day (53), although the quality of the studies was questioned and was considered relatively poor. Depressive symptoms were helped more than others, and no side effects were noted. However, a systematic review of double-blinded placebo-controlled trials using vitamin B_6 supplements found no evidence for short-term benefit in improving mood (depression, fatigue, tension) or cognitive function (54).

Toxicity

When pyridoxine is ingested in large amounts (0.5 to 6 g per day), a peripheral sensory neuropathy can occur (55) that is completely reversible when treatment is stopped. Possible explanations include neurotoxicity directly caused by pyridoxine, neurotoxicity caused by a minor contaminant, or inhibition of the formation of pyridoxal phosphate by unconverted pyridoxine. The UL for adults has been established at 100 mg per day (3).

TABLE 6-16. Pyridoxine-dependent Errors of Metabolism

Disorder	Enzyme	Clinical findings	Laboratory findings
Infantile seizures, B_6-dependent	Glutamic acid decarboxylase	Convulsions	None
Chronic anemia, B_6-dependent	δ-aminolevulinic acid (ALA) synthase	Hypochromic anemia	Increased serum iron
Homocystinuria	Cystathionine β-synthase	Mental retardation, severe collagen disease involving vessels, eye problems, osteoporosis	Homocystinemia, homocystinuria, hypermethioninemia
Cystathioninuria	γ-cystathionase	Mental retardation, blood dyscrasia, heart disease	Cystathionuria
Xanthurenic aciduria	kynureninase	Urticaria, mental retardation	Xanthurenic aciduria
Gyrate atrophy of choroids and retina	Ornithine aminotransferase	Chorioretinal degeneration, blindness	None diagnostic
X-linked sideroblastic anemia	Erythroid specific δ-ALA synthase	Anemia	Ringed sideroblasts
Primary hyperoxaluria	Alanine-glyoxylate aminotransferase	Renal stones	Hyperoxaluria
Developmental delay	Aromatic-L-aminoacid decarboxylase	Hypotonia, oculogyric crises	Elevated 5-hydroxytryptophan in CSF, plasma, and urine
Cohen syndrome	β-alanine α-ketoglutarate transaminase	Hypotonia, obesity, mental retardation, facial/oral/ocular/limb anomalies	None diagnostic

CSF, cerebrospinal fluid.
Adapted from Frank T, Bitsch R, Maiwald J, Stein G. High thiamine phosphate concentrations in erythrocytes can be achieved in dialysis patients by oral administration of benfotiamine. *Eur J Clin Pharmacol* 2000;56:251.

Folate (Folic Acid, Folacin, Ppteroylglutamic Acid)

Requirement

Difficulty of Estimation. Estimating the folate requirement is complex. *Folacin* is a generic term denoting compounds with a structure and function similar to those of folic acid (pteroylglutamic acid), and more than 150 forms are known to exist in foods. The forms differ in the degree of reduction of the double bonds in the ring structure (e.g., tetrahydrofolate), the presence of 1-carbon groups (e.g., methyltetrahydrofolate), and the number of glutamyl residues in the peptide chain (e.g., folate pentaglutamate). Moreover, individual compounds are variably absorbed and retained by the body. Dietary folates are mostly in the polyglutamate form, which is not quite as available as the unconjugated vitamin. Absorption does not necessarily correlate with retention in the body because more of the monoglutamate form of pteroylglutamic acid is excreted in the urine after ingestion than of other forms.

Folacin is variably available in foods because of the presence of binders, inhibitors, and other factors. Enterohepatic recirculation of 5-methyltetrahydrofolic acid is important in the retention of body stores, but the relative importance of this factor in individuals can only be guessed at. An exact determination of total body pools of folacin is not available because the data are based on few determinations. The form of folate used commercially,

pteroylglutamic acid, is a relatively poor substrate for dihydrofolate reductase; consequently, the rates of tissue utilization and retention for this form are much lower than those for the natural methylated or reduced folates found in food. However, folacin requirements have been assessed by replacement with pteroylglutamic acid.

Dietary References Intakes. The recommendations for folate intake have been modified dramatically (3) since the RDA of 200 μg per day for adults was offered in 1989 in the 10th edition of *Recommended Dietary Allowances*. Subsequently, the need for extra folate to reduce the incidence of neural tube defects was recognized (56), as was the role of folate intake and elevated serum homocysteine concentrations in cardiovascular disease (57). The recent report of the Institute of Medicine expresses dietary folate as folate equivalents, adjusted for the apparently greater bioavailability of synthetic folic acid in comparison with naturally occurring folate, and for the estimated amount of ingested folate needed to maintain folate levels in red blood cells (i.e., body stores) in long-term metabolic studies (3). The resulting recommendations are all higher by 100–200 μg per day than previous estimates (Table 6-17). Pregnant and lactating women require extra folate to build red blood cells and produce milk, respectively.

Food Sources

The folacin content of selected foods is given in Table 6-18. Major sources are orange and other citrus juices, white bread, dried beans, green salads, liver, eggs, and enriched breakfast cereals. However, much dietary folate comes from food sources that are frequently consumed but in which the vitamin is not especially concentrated, and from cereals and grain foods (flour, pasta, rice, cornmeal) that are fortified with folate.

Polyglutamate versus Monoglutamate Forms. Folacins occur in food largely as polyglutamates. The pentaglutamate form predominates, although forms with four and six residues also are common. The assessment of polyglutamate forms in foods is difficult because of rapid breakdown to the monoglutamate form in mammalian tissues. This problem is relevant to estimates of the availability of folacins in foods because they must be deconjugated to the monoglutamate form for absorption. Moreover, the microorganisms used to assay folacin content differ in how they use the monoglutamate and oligoglutamate

TABLE 6-17. Dietary Reference Intakes for Folate

Life stage group	Folate (μg/day)	Life stage group	Folate (μg/day)
Infants		**Females**	
0–6 months	65[a]	9–13 years	300
7–12 months	80[a]	14–50 years	400 SGA + diet
		51–>70 years	400
Children			
1–3 years	150	**Pregnancy**	
4–6 years	200	≤18–50 years	600 (400 as SGA)
Males		**Lactation**	
9–13 years	300	≤18–50 years	500
14–>70 years	400		

SGA, synthetic folic acid. Because it is more readily available than dietary folate and is the form shown to prevent some neural tube defects, this form is recommended during the childbearing years and pregnancy.
[a] Estimate based on adequate intake (AI). All others based on recommended dietary allowance (RDA).
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academies Press, 1998.

TABLE 6-18. Approximate Folacin Content of Selected Foods

Food	Portion	Total folacin (μg)	Percentage of RDI (400 μg)
Meat			
Beef or pork, cooked	3 oz	3–4	1–5
Liver, beef, cooked	3 oz	123	25–39
Liver, chicken, cooked	1 each	204	>40
Vegetables			
Asparagus	1 cup	86	10–24
Spinach, cooked	1 cup	164	25–39
Beans, green, cooked	1 cup	41	10–24
Cauliflower	1 cup	42	10–24
Turnip greens	1 cup	52	10–24
Lettuce, head or leaf	1 cup	20	5–12
Lettuce, romaine	1 cup	98	10–24
Nuts			
Walnuts	1 cup	66	10–24
Peanuts	1 cup	153	25–39
Peanut butter	1 tbs	13	1–5
Almonds	1 cup	136	25–39
Breads and cereals			
Bread			
White	1 slice	10	1–5
Whole wheat	1 slice	16	1–5
Rice	1 cup	20	1–5
Eggs			
Egg	1 each	29	5–12
Beverages			
Wine, spirits	8 oz	None	0
Beer	12 oz	21	5–12
Milk, whole	1 cup	12	1–5
Orange juice, fresh or frozen	1 cup	136	25–39

RDI, recommended dietary intake.
Source: An extensive list of folacin content of foods is given by Perloff BP, Britrum RR. Folacin in selected foods. *J Am Diet Assoc* 1977;70:161.

forms. *In situ* deconjugation in the tissues affects the assessment of nutritional folacin availability. Estimates of folacin available as the monoglutamate form vary from 30% in orange juice to 60% in cow's milk.

Folacin Availability. Most dietary folacins are reduced and methylated forms; 5-methyl pteroylglutamic acid accounts for 60% to 95% of dietary folacin, 10-formyl pteroylglutamic acid for 14% to 40%, and other reduced forms for 10% to 20%. The 5-methyl and *N*-10-formyl folacins are heat-stable, whereas unsubstituted, reduced pteroylglutamic acids are unstable. Some dietary folates are bound to specific binding proteins (e.g., in milk). In steaming and frying, as much as 90% of the food content can be lost. Boiling for 8 minutes causes a loss of about 80% of folacin activity from most vegetables. Boiling destroys heat-labile folacin in cow's milk; during boiling, the folacin content of milk falls from about 54 μg/L to less than 10 μg/L. Thus, infants fed with boiled milk formulas must receive supplements. Some foods are judged to contain highly bioavailable folacins, such as bananas, lima beans, liver, and yeast. Foods in which the folacin bioavailability is low include orange juice, lettuce, egg yolk, cabbage, soybean, and wheat germ.

Folacin Content of Average Diets. The new DRIs use the concept of dietary folate equivalents (DFEs) to calculate estimates, and DFEs are used to estimate dietary content. The DFE converts all forms of dietary folate, including synthetic folate in fortified foods, to an equivalent of food folate (58). The estimated equivalent of food folate for synthetic folate is 50%, and the estimated equivalent for synthetic folate added to food, as opposed to synthetic folate by itself, is 85%. Thus, synthetic folic acid added to food is 85/50 or 1.7 times more available than synthetic folate alone. The diets of adults in the United States and Canada contained 262 to 2,807 μg of DFEs per day, with mean daily intakes of 708 and 718 μg for adult men and women, respectively (in the second National Health and Nutrition Examination Survey, 1988–1994), and of 718 and 644 μg, respectively (in the Continuing Surveys of Food Intakes by Individuals, 1994–1996) (59). With allowances made for the increased availability of foods fortified with folate and the increased use of supplements, it was estimated that 67% to 95% of the U.S. population was meeting the new estimated average requirement (58). However, 68% to 87% of women of childbearing age still had intakes of synthetic folate below the recommended level of 400 μg per day, and about 20% of children under the age of 8 had intakes over the newly established UL of 400 μg per day for that age group (1,000 μg per day for adults).

Assessment

Intake or Absorption. Only small amounts of folacin are excreted in the urine (about 1% of dietary intake) (17). Moreover, not all dietary forms are excreted in the same proportions. Thus, urinary excretion is not useful in assessing intake. Oral folic acid tolerance tests have been described, but they do not clearly distinguish between folate and vitamin B_{12} deficiencies because folate utilization is decreased in vitamin B_{12} deficiency. The serum folate level is quite sensitive to changes in dietary folate intake and is a measure of the status at the time of assay (60). A low serum level (2 or 3 to 6 ng/mL) reflects only a recent low dietary intake and may not reflect tissue stores (Table 6-19). Continued low levels

TABLE 6-19. Guidelines for Interpreting Folate Status

Test	Folate deficiency	Low recent folate intake[a]	Normal	Vitamin B_{12} deficiency
Serum folate (ng/mL)	<2 or 3	3–6	>6	High
Red cell folate (ng/mL)	<140	150–160	>160	<150
Bone marrow	Megaloblasts	Normocytic, normochromic	Normocytic, normochromic	Megaloblasts
Peripheral blood smear	Multilobed polymorphonuclear leukocytes,[b] macrocytosis	Normal	Normal	Multilobed polymorphonuclear leukocytes, macrocytosis
	Moderate/ severe risk	**Low risk**	**Normal**	
Serum homocysteine (μmol/L)	>30	>16	<12–15 (40+ years M) <10–12 (40+ years F)	

[a] Low serum levels also may reflect hypoproteinemia or the ingestion of drugs that alter folic acid metabolism or binding, such as folate antagonists, phenytoin, alcohol, and oral contraceptives. Hemolysis may falsely elevate the serum values.
[b] Multilobed: >3.5 lobes per cell on average, or >5% of cells have five lobes, or >1 six-lobed leukocyte per 100 cells.

(<2 or 3 ng/mL) are usually associated with megaloblastic anemia and decreased tissue reserves. Folate is assayed microbiologically with *Lactobacillus casei*, which uses the 5-methyl vitamers, the only circulating form of folacin. Alternatively, measurements based on binding assays or radioimmunoassays are used. Although the microbiologic assay is the reference method, binding assays are simpler and faster, avoid interference from antibiotics in serum samples, and allow simultaneous measurement of serum B_{12} levels. Results are quite variable with the microbiologic assay, especially as different pH extraction methods are used (61). Variability was only 9% to 11% for folic acid-fortified foods, but much more so (>45%) for natural foods. As a result of this variation, the Association of Official Analytical Chemists (AOAC International) recommends using a trienzyme extraction to recover folic acid from food (62). In addition the results of radioassays are quite variable between laboratories, and the radioassays require more expensive reagents and equipment. Single-stage (competitive) and two-stage (noncompetitive) assay kits are available, with the latter providing slightly better sensitivity.

Most circulating folacin is in the form of 5-methyltetrahydrofolic acid. About 90% is loosely attached to albumin and 10% to specific binding proteins. Therefore, hypoalbuminemia can lead to a low total serum folic acid level, and this result does not necessarily imply a deficiency of the vitamin. Aspirin, at a dose of 650 mg every 9 hours, can produce a reversible decrease in total and bound folate (63). Other albumin-binding drugs produce the same effect. Low values are also associated with decreased intake, malabsorption, or ingestion of drugs that affect folate absorption or utilization. These drugs include folate antagonists, phenytoin, prednisone, alcohol, and oral contraceptive agents. Alcohol lowers serum folate levels by increasing urinary folate excretion (64). Because both red and white cells contain much larger amounts of folacin than serum does, hemolysis or a very high white blood cell count, especially when the white cells are abnormal, falsely elevates serum folate levels. One-third of hospitalized patients may have low folate levels, which implies a recent negative folic acid balance. However, few of these patients require long-term supplementation.

Tissue Stores. Although serum and red cell folate levels decline in parallel, the red cell folate level is a more accurate reflection of tissue stores. It is less variable and reflects the folate status at the time of red cell formation. However, the red cell contains monoglutamate and polyglutamate forms of folic acid, so that the dose–response curves are altered in binding assays. Folate is measured in both serum and whole blood, and the folate level in red cells is calculated based on the hematocrit. In primary vitamin B_{12} deficiency, folate is not well utilized. Thus, in 15% to 25% of cases of vitamin B_{12} deficiency, serum folate levels rise and red cell levels fall. When both the serum and red cell levels are low, folate deficiency is the cause, although the red cell folate level falls after the serum folate level. Table 6-19 outlines the guidelines used for interpreting folate levels.

Other Assays. The presence of hypersegmented lobes can be helpful, but the determination is somewhat subjective. Macrocytosis (mean corpuscular volume >97) may be present but is not specific. Urinary excretion of formiminoglutamic acid after an oral 20-g load of histidine (normal rate, >50 mg per 12 h) is a functional assay, as is the deoxyuridine suppression test. These tests are not routinely available and are not clearly more discriminating than the red cell folate level in detecting deficiency.

Serum Homocysteine. Serum homocysteine (but not methylmalonic acid) levels are elevated in folate deficiency (see section on vitamin B_{12}). However, they also reflect inadequacies of vitamin B_6 and vitamin B_{12}. Other causes of elevated serum homocysteine concentrations include renal insufficiency, hypovolemia, hypothyroidism, psoriasis, and inherited metabolic defects (65). A common cause of hyperhomocysteinemia is a genetic predisposition secondary to a polymorphic substitution in the methylenetetrahydrofolate reductase gene. In interpreting elevated homocysteine levels, it is best to obtain serum methylmalonic acid levels simultaneously (Table 6-20). Part of the problem in identifying hyperhomocysteinemia is the variability in assay results and normal values. This variability is partly a consequence of the multiple forms of homocysteine in serum (reduced, oxidized, protein-bound), and partly a consequence of the different and noninterchangeable results of HPLC, enzyme immunoassay, and fluorescence polarization immunoassay (66).

TABLE 6-20. Interpretation of Serum Methionine Metabolite Assays

	Folate deficiency	Vitamin B_{12} deficiency
Metabolite(s)	(% in patients with deficiency)	
Methylmalonic acid (MMA) ↑	12	98
Homocysteine (Hcy) ↑	91	96
MMA ↑, Hcy normal	2	4
Hcy ↑, MMA normal	80	1
MMA, Hcy normal	7	0.2

Adapted from Savage DG, Lindenbaum J, Stabler SP, et al. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. *Am J Med* 1994;96:239.

Reference values for total serum homocysteine increase with age and are higher for men than for women at all ages (67).

Physiology

Absorption. Absorption takes place through a pH-dependent active process in the proximal intestine, with maximum transport occurring after deconjugation to the monoglutamate form. Some, but not all, dietary folate is nutritionally available. Polyglutamate forms of folate in food are hydrolyzed by folyl poly-γ-glutamate carboxypeptidase; the products of hydrolysis, which contain decreased numbers of glutamate residues, include the monoglutamate form, found in small amounts in human salivary, gastric, pancreatic, and jejunal juice. The activity of this ubiquitous carboxypeptidase is also increased in intestinal mucosa, liver, pancreas, kidney, and placenta. Both brush border and lysosomal sites of folate conjugase activity have been reported in human jejunum. The brush border enzyme is necessary for the hydrolysis of dietary folates.

The intestinal transporter for folate is the same as the reduced folate carrier found in red cells, the SLC19A1 sodium/folate co-transporter (68). Folate receptors exist as α and β isoforms with different tissue distribution, and a soluble form exists in plasma and milk (69). The folate receptor-α is present in the epithelium of the intestine, kidney, choroids plexus, and epididymis, bound to the membrane by a glycosylphosphatidylinositol (GPI) structure. Deficiency of the receptor in mice leads to decreased reabsorption of folate in the renal tubule, and confirms the importance of this receptor in folate uptake in vivo (70). Megalin, a large member of the LDL receptor family, mediates soluble folate receptor uptake in the renal tubule, but its role in regulating uptake of the membrane bound receptor is still unclear (69).

Reduced folates are better absorbed than oxidized forms. Pteroylglutamic acid, used in tablets, is not as good a substrate for dihydrofolate reductase and must be reduced before it can be maximally utilized. Methyltetrahydrofolic acid is absorbed rapidly and not changed. Other forms are converted in enterocytes to reduced formylated and methylated derivatives. Some vitamin escapes unreduced and is metabolized in the liver. The reduced methylated form is delivered to all tissues. Folate absorption may be decreased in elderly patients with gastric atrophy, a situation that can be corrected by administering hydrochloric acid to lower the gastric and intestinal pH.

Reabsorption. After conversion in the liver to 5-methyltetrahydrofolic acid, the vitamin can enter the plasma as the monoglutamate, be stored in tissue as the polyglutamate, or be reexcreted in bile and reabsorbed. The rate of enterohepatic circulation is estimated to be 100 μg per day. This figure is comparable with the amount of daily tissue folate utilized (50 to 100 μg). Thus, folate deficiency develops more rapidly in malabsorption than in dietary deficiency alone. During deficiency states, the concentration of folate in the bile

decreases, so the enterohepatic circulation does not contribute to losses at a constant rate. The large intestine contains an efficient carrier-mediated transport mechanism for folate (presumably the reduced folate receptor-α), raising the possibility that the colon might participate in folate reabsorption (71).

Intracellular Metabolism. Natural forms of folic acid are converted to coenzymes by reduction of the pyrazine ring (two possible sites), elongation of the peptide chain with glutamyl residues (six possible additions), and addition of a one-carbon fragment in position 5 or 10 (six possible fragments). Thus, a large variety of folate coenzymes exist. The tetrahydro form is frequently involved, and it is thought that a polyglutamate form is the active coenzyme. These coenzymes function in many reactions involving one-carbon transfers, including purine and thymidylate synthesis, metabolism of several amino acids (especially serine and homocysteine), methylation of biogenic amines, and initiation of protein synthesis by formylation of methionine. The coenzymes are quite unstable in cells because peptidases degrade the polyglutamyl chain. For mobilization of the storage form in the liver and release into the blood, hydrolysis to the monoglutamate form is required.

Protein Binding. Two-thirds of plasma folate is protein-bound because it is negatively charged at physiologic pH. This binding, largely to α_2-macroglobulin and albumin, is loose. In addition, folate is tightly bound to a specific binder that recognizes reduced folates. The role of this binder is unclear.

Deficiency

"Classic" Deficiency. Because folate coenzymes are active in RNA, DNA, and protein synthesis, conditions of rapid growth or metabolic utilization (pregnancy, lactation) are associated with a high risk for deficiency. Acute symptoms of folate deficiency have been noted after the administration of antagonists. These include anorexia, nausea, diarrhea, mouth ulcers, and hair loss. Thrombocytopenia occurs frequently. Chronic deficiency is characterized by fatigue, a sore tongue, and anemia, with few neurologic signs. If folate stores are normal at the start, deficiency takes about 4 months to develop. If stores are depleted initially, the symptoms of deficiency can develop in 2 to 3 months. Not all clinical deficiency can be defined by serum folate levels, because 10% to 20% of populations in Western nations may have low levels. Some of these are related to low recent intake. If prolonged, a decreased intake leads to deficiency (decreased body stores). Malabsorption of any cause can lead to deficiency. Diseases that are frequent causes of folate deficiency include tropical sprue, gluten-sensitive enteropathy, and alcoholism (72). In this setting isolated folate deficiency is rarely seen, but is associated with other vitamin deficiencies. Neurologic manifestations are rare and mild, so any attribution of these presentations should encourage a search for other causes, e.g., vitamin B_{12} or B_6 deficiency (19).

Neural Tube Defects. The results of randomized trials show that at least half of neural tube defects could be prevented if women consumed adequate amounts of folic acid early in pregnancy (56, 73, 74). The data have been repeated in areas with a high and low incidence of neural tube defects (3, 75). Based on the results of these trials and on uncontrolled observations of the effects of lower doses of folic acid, the U.S. Department of Health and Human Services published *Recommendations for the Use of Folic Acid to Reduce the Number of Cases of Spina Bifida and Other Neural Tube Defects*, with the suggestion that 400 μg of folic acid be ingested daily by all women capable of becoming pregnant. High doses were not recommended because they can mask B_{12} deficiency. These recommendations have been confirmed by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (3). Not all neural tube defects can be prevented, and folate should be ingested before conception as well as after. Some experts advise women who have had a prior pregnancy in which the fetus had a neural tube defect to take 4.0 mg of folic acid per day. At this dose, folic acid may interfere with anticonvulsant therapy in epilepsy. The synthetic form of folate is recommended. To derive an equivalent intake from the diet, about 10 servings of fruits and vegetables a day would be required, and the folate in foods is less bioavailable.

Folic acid is clearly a vitamin essential for reproductive health. Despite all the evidence that supplementation has been beneficial, the amount of folate in commercial breads in the United States declined after 2001 (76). Moreover, educational efforts to promote daily folic acid supplementation by women of reproductive age have not led to increased supplement use (77). The groups most vulnerable to not following the recommendations are women who are young, poor, or have unplanned pregnancies (78). In addition, some countries have not yet decided to mandate folic acid fortification.

Bottle-fed Infants. Bottle-fed infants are susceptible to folate deficiency because heating can destroy milk folacins. Total serum homocysteine level appears to be a sensitive indicator of folate deficiency in children on a poor diet, with HIV infection, and with antifolate drug treatment (79).

Pregnancy. Pregnancy is associated with low serum folate levels because of hemodilution and increased requirements. Anemia is often secondary to iron deficiency also. One-third of pregnant women have low serum folate levels at delivery (see Chapter 4).

Folate Receptor Antibodies. These antibodies can produce a cerebral folate deficiency syndrome in infants, older children, and occasionally in adults, resulting from blocked folate transport into the brain (80). Serum and red blood cell folate and serum homocysteine levels are normal, but 5-methyltetrahydrofolate in the cerebrospinal fluid is low, consistent with the regional (brain) folate deficiency. If folate stores are normal in the mother and infant, symptoms will appear initially at about 4 months.

Anticonvulsant Drugs. Anticonvulsant drugs (especially phenobarbital, phenytoin, and primidone) cause macrocytosis in 40% of patients, but only half of these patients have low serum and red blood cell levels of folate. Most patients have normal levels of vitamin B_{12}. Thus, the mechanism is not entirely clear. Some alteration in absorption of folates is postulated.

Increased Utilization. Folate deficiency occurs in disorders in which utilization is increased, such as hemolytic anemia, chronic myelofibrosis, leukemia, sideroblastic anemia, and chronic exfoliative dermatitis.

Alcohol Ingestion. Alcohol ingestion in excess of 80 g of ethanol per day is associated with macrocytosis (>80%) and low serum levels of folate.

Sulfasalazine. Sulfasalazine can cause deficiency by decreasing folate absorption. The same effect is not caused by 5-aminosalicylic acid.

Inhibition of Dihydrofolate Reductase. Inhibition of dihydrofolate reductase impairs the conversion of folates to the active coenzyme. Dihydrofolate reductase inhibitors include methotrexate, trimethoprim, pyrimethamine, and triamterene. The frequency of clinical deficiency is greatest with methotrexate.

Smokers with Bronchial Metaplasia. Plasma levels of folate are decreased in smokers who have bronchial metaplasia in comparison with smokers who do not have metaplasia. The issue of whether folate deficiency can develop and cause tissue damage is not resolved.

Hyperhomocysteinemia. Hyperhomocyteinemia can be the result of folate deficiency when there is no elevation of methylmalonic acid, a feature of vitamin B_{12} deficiency. Three inborn errors of metabolism can produce elevated homocysteine levels associated with atherosclerosis: deficiency of cystathionine synthase, methionine synthase, and methylenetetrahydrofolate reductase (81). These cases, along with data in animals, led to the proposal that homocysteine was a significant risk factor for atherosclerosis in the general population. Homocysteine levels are correlated with an increased risk of myocardial infarction in about 10% of patients (57). It is not clear whether the metabolite itself is sufficient or whether it is a cofactor. Folate levels are usually normal, but feeding supplemental folate can reduce the hyperhomocysteinemia. A 400 μg/day dose provides a maximal effect (~20%–25%) (82). Other factors, including vitamins B_2, B_6, betaine, and choline, may have some effect, the latter two particularly in the presence of high methionine intake (83).

Other dietary factors, such as, tea, coffee, high-protein meal, and methionine, elevate homocysteine levels, but these postprandial rises can be transient. It is generally felt that folate intake has the largest effect in reducing these elevations, postprandial or otherwise, but it is not clear whether lowering homocysteine levels reduces the risk of cardiovascular disease or risk for stroke (82).

Hyperhomocysteinemia is considered by many to be an independent risk factor for cardiovascular disease and mortality (84), including the large prospective Women's Health Study (85). However, there are other factors that are associated with an increased risk of vascular disease, including C-reactive protein, lipoprotein (a), and fibrinogen (86). Where these factors fit into a screening and risk stratification strategy along with homocysteine is not clear. Strong epidemiological associations implicating homocysteine as a risk factor for heart disease continue to appear (87, 88), but folate status is not always associated with elevated total homocysteine levels, perhaps due to the presence of other confounding risk factors (89). Another reason for the lack of confirmation of epidemiologically determined risk factors is the accrual of larger numbers. For example, the risk possibly related to the C677T polymorphism of the gene for methylene-tetrahydofolate reductase appeared to be less well supported when 26,000 cases are analyzed (90).

Data from prospective studies with folate (and vitamin B_6 and B_{12}) supplementation have not yet provided consistent support for homocysteine as a significant risk factor for heart disease in the general population. The Homocysteine Lowering Trialists' Collaboration has attempted to estimate by meta-analysis the size of the reduction in homocysteine levels due to different doses of folic acid with or without the other vitamins, all in randomized controlled trials. One meta-analysis showed ~25% reduction in homocysteine with doses of folic acid ranging from $0.5 \geq 3$ mg per day (91). A second meta-analysis that included additional studies showed that 0.8 mg of folate could lower homocysteine by ~23%, with only a 7% increased effect on addition of vitamin B_{12}, and no change after addition of vitamin B_6 (92). For recurrent cardiovascular events it was estimated that the risk increases for each 5 μmol/L increase in serum homocysteine concentration.

The Trialists' Collaboration is currently following 12 randomized trials that involve 52,000 participants, 32,000 with vascular disease in unfortified populations, and 14,000 with vascular disease and 6,000 with renal disease in fortified populations (93). Thus, an answer is likely to come from these studies. Some of these randomized studies have reported initial results, and none shows a difference in outcome. Patients with prior vascular disease or diabetes and treated with 2.5 mg of folic acid, 50 mg of vitamin B_6, and 1 mg of vitamin B_{12} showed no difference in major cardiovascular disease (94). Another trial of secondary prevention of myocardial infarction using all three vitamins including 0.8 mg folic acid showed a possible harmful effect on the rate of acute myocardial infarction (95). Both studies showed ~25% reduction in plasma homocysteine concentrations. A similar negative result has been shown with prevention of ischemic stroke (96). Thus, the strength of association of homocysteine with risk of vascular disease is probably weaker than suggested by the epidemiologic data, and may not exist at all (97).

The studies thus far continue to be consistent with the recommendations of the American Heart Association (AHA) to screen for hyperhomocysteinemia only in those patients at high risk (e.g., premature arteriosclerosis, renal failure) (98). The AHA and the Canadian Task Force on Preventive Health Care recommend a well-balanced diet without supplemental vitamins. Any change in these recommendations should await the results of studies that confirm a role of folate and/or other vitamins in altering the risk of cardiovascular disease in high-risk populations (99).

Cognitive Decline. Low levels of folate and cobalamin are seen in aged patients with cognitive decline. The low vitamin status is likely secondary to decreased intake. Many poorly controlled trials have suggested a role for folate supplementation in improving cognition, but the severity of cognitive decline is not correlated with the degree of folate deficiency (100). Although folic acid (0.75 mg per day) lowers serum homocysteine levels, a systematic review of double-blind, placebo-controlled intervention trials revealed that no benefit was seen in measures of cognition or mood in older, healthy women or in patients with mild to moderate cognitive decline (101). Epidemiologic studies continue to record that high homocysteine and low B vitamin levels predict cognitive decline, but whether this

is merely an indicator of another process or a causative link will need to be determined by further studies (102). There is more skepticism of an association with cognition than previously thought, similar to the skepticism of an association with cardiovascular disease.

Depression. An association between folate and serotonin metabolism has been suggested, in that folate-mediated methylation of homocysteine produces S-adenosyl-methionine, a metabolite that alters serotonin metabolism. This suggestion has led to randomized controlled trials of folate in treatment of depression. Analysis of two such trials provided a suggestion that an active form of folate in large doses (15 or 50 mg of methyltetrahydrofolate) might be useful as adjunctive therapy with other antidepressant drugs (103). In addition there is an association between depression and low folate levels (104). It seems indicated to treat patients with folate deficiency and depression and to await more studies to see whether there is a benefit on the depressive symptoms. What is not clear is whether it is currently indicated to treat patients with depression who have a normal red cell folate level.

Cancer. The Nurses Health Study found that the risk for the development of colon cancer was lower in women who had used vitamin supplements containing folate for more than 15 years than in women who had used such preparations for shorter periods (105). This association has been repeated in the Swedish Mammography Cohort (106). Moreover, in the large (519,978 patients) cohort that is the European Prospective Investigation of Cancer and Nutrition (EPIC) from 10 countries, folate in food may be protective of colorectal cancer, but there is no effect of added supplements (107). Folate supplements have been shown to decrease mucosal proliferation (108) and to reverse DNA hypomethylation (109) in high risk groups of patients with recurrent colonic adenomas. However, supplemental folate has not yet been shown prospectively to have a protective effect on the rate of colorectal cancer or adenoma formation. Epidemiologic studies also provide some support for a modulating role of folate in breast and pancreatic cancer; however, the findings are only suggestive, despite the prospective nature of some of the studies (107).

Treatment

Medication. The form of folacin used therapeutically is the unreduced pteroylglutamic acid. Tablets of 0.1, 0.4, 0.8, and 1.0 mg are available, and quantities of 0.2 to 1.0 mg are included in some multivitamin preparations; 200 to 500 μg per day is needed to treat most deficiency states. Oral replacement is preferred, except in severe malabsorption, in which parenteral [intramuscular (IM), intravenous (IV), or subcutaneous (SC)] folate (5 mg per mL) can be used. At the concentrations used for total parenteral nutrition, folate is stable if the pH of the solution is above 5.0. Leucovorin calcium (5-CHOH-tetrahydrofolic acid) is available as solutions (3 mg per ampule or 10 mg per mL in 5-mL vials). This compound is used only after methotrexate therapy to avoid toxicity. In the large doses offered, it is not meant as vitamin replacement therapy for deficiency states, especially because the large doses can mask vitamin B_{12} deficiency.

Fortification. The U.S. Food and Drug Administration (FDA) specified in 1996 that certain grain products (especially most enriched breads, flours, cornmeal, rice, noodles, and macaroni) be fortified with 0.14 mg of folic acid per pound of product. The FDA estimated that this practice would raise the folate intake of women of childbearing age by 100 μg per day yet avoid exceeding the UL of 1,000 μg per day in nontarget populations (110). This UL was selected so as not to mask vitamin B_{12} deficiency and allow neurologic progression. Considerable debate regarding all aspects of the fortification program continues, including the dose added, the effect on nontarget populations, and the risk for masking pernicious anemia. The use of a higher level of cereal-based folate supplementation (499 to 665 μg per day) than that recommended by the FDA (127 μg per day) produced a greater rise in serum folate and a significant fall (11%) in serum homocysteine levels; these findings suggest that more folate should be added to foods (111). However, in a study of a cohort before and after folate fortification was approved, the percentage of subjects with low serum levels of folate fell from 22% to 1.7%, and the percentage of those with high serum homocysteine levels fell from 18.7% to 9.8% (112). The ability of folate to lower serum homocysteine may be related to the intake of other vitamins (e.g., >500 mg of vitamin

C per day) that can interfere with vitamin B_{12} metabolism (113). The UL of 1,000 μg per day has been challenged on the grounds that all but eight cases of masked neurologic progression in vitamin B_{12} deficiency occurred in patients taking more than 5 mg of folate per day (59). This concern does not affect most patients on supplemental folic acid. Since folate supplementation of grain in the United States began, there has not been an increase in low vitamin B_{12} levels seen in a large VA center (114). In addition, analysis of >60,000 blood samples showed no correlation between vitamin B_{12} deficiency [the presence of low cobalamin levels and macrocytosis (elevated MCV)] and whether the serum folate was low or high (115).

Toxicity

Folic acid and phenytoin compete for intestinal transport and possibly uptake in the brain. Thus, very large doses of folate (>100 times the RDA) may precipitate convulsions in patients treated with phenytoin (116). A few cases of hypersensitivity have been documented at doses of 1 to 10 mg. Fever, urticaria, pruritus, and respiratory distress have been reported (117).

Cobalamin (Vitamin B_{12})

Dietary Reference Intake

The total body content of cobalamin is approximately 2 to 2.5 mg, most of which is in liver. Estimates of half-life vary from 480 to 1,284 days. Thus, daily losses of cobalamin average about 1.3 μg. Because absorption is about 70% efficient at low levels of intake, the RDA for adults of ~2 μg per day was formerly considered sufficient to maintain the body pool. In response to findings that 10% to 30% of people more than 51 years old may have protein-bound vitamin B_{12} malabsorption, the new DRI for this age group has been set at 2.4 μg per day (3). Malabsorption in the elderly is probably a consequence of reduced secretion of pepsin and gastric acid, perhaps related to *Helicobacter pylori* infection. Because intrinsic factor is present, these people can absorb free (synthetic) vitamin B_{12}. Thus, it is recommended that the vitamin be ingested mostly in the form of a dietary supplement to ensure that intake is adequate (118). Table 6-21 gives the DRIs for adults and children.

Food Sources

The term *cobalamin* refers to cobalt-containing corrinoids with biologic activity in humans. The average diet in the United States provides 5 to 15 μg per day. Cobalamin is produced by bacteria and enters animal tissues during the ingestion of contaminated foods or after production in the rumen. Microorganisms in the colon synthesize cobalamin, but

TABLE 6-21. Dietary Reference Intakes for Cobalamin

Life stage group	Cobalamin (μg/day)	Life stage group	Cobalamin (μg/day)
Infants		**Adolescents and adults**	
0–6 months	0.4[a]	(M/F) 14–>70 years	2.4
7–12 months	0.5[a]	**Pregnancy**	
Children		≤18–50 years	2.6
1–3 years	0.9	**Lactation**	
4–8 years	1.2	≤18–50 years	2.8
9–13 years	1.8		

[a] Estimate based on adequate intake (AI). All others based on recommended dietary allowance (RDA). Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline.* Washington, DC: National Academies Press, 1998.

the vitamin is not absorbed at that site. Thus, cobalamin deficiency develops in strict vegetarians. Most of the cobalamin in normal feces arises from bacterial synthesis in the colon and does not represent unabsorbed vitamin, so that fecal excretion is unrelated to dietary intake. The usual dietary sources are seafood, meat and meat products, fish, eggs, and to a lesser extent milk and milk products. The vitamin is now added to many grain products, including cereals, breads, pasta, and enriched rice. Most cooking methods do not destroy cobalamin. Boiling meat can lead to losses of up to 30% into the water. However, during drying, the cobalamin in some food is converted to inactive analogues (119). Evidence that ingesting megadoses of vitamin C (500 to 1,000 mg) destroys some of the cobalamin in food is conflicting. It is not clear how frequently, if ever, cobalamin deficiency occurs in persons who take megadoses of vitamin C. Table 6-22 lists selected foods containing cobalamin.

Assessment

Intake or Absorption. No reliable method is available to assess intake of cobalamin, but the Schilling test accurately reflects absorption. Free cobalamin does not occur in plasma or elsewhere until all binding proteins are saturated, after which free cobalamin is filtered through the glomerulus. A parenteral injection of 1,000 μg of unlabeled cyanocobalamin is given to saturate binding proteins in tissue and serum. Any serum to be drawn for assessment of body stores must be obtained beforehand. An oral dose of $[^{57}Co]B_{12}$ linked to intrinsic factor is then given. Excretion of the labeled cobalamin in urine for 24 hours should exceed 8% of the administered dose if absorption is normal. In cases of possible bacterial overgrowth, absorption can be tested after the administration of 1 g of tetracycline per day.

A value >8% and <10% is an indeterminate result and accounts for about 25% of test results (120). Problems with the test involve the collection of urine and intertest variability (as much as 30%–50%). When urine collection is incomplete or renal disease is present, a low rate of cobalamin excretion is unreliable. It is a mistake to attach too much importance to an arbitrary normal limit of 10% excretion. Stimulation of urinary excretion by twofold or more with the addition of intrinsic factor is suggestive of intrinsic factor deficiency, even if the excretion without intrinsic factor is in the 8% to 10% range.

TABLE 6-22. Approximate Cobalamin Content of Selected Foods

Food	Portion	Cobalamin (μg)	Percentage of RDI (6μg)
Beef, ground	3 oz	2.4	>40
Liver, beef	3 oz	95	>100
Liver, chicken	1 each	1.87	25–39
Oysters, raw	1 cup	40–48	>100
Crab	1 cup	9.9	>100
Salmon	3 oz	4.93	>40
Egg	1 each	0.59	5–12
Lamb chop	3 oz	1.58	25–39
Pork, center loin chop	4 oz	0.62	5–12
Chicken, light meat, roasted	3 oz	0.291	1–5
Cheese	1 oz	0.2–0.45	5–12
Milk, whole/skim	1 cup	0.871/0.93	10–24
Yogurt, whole/low-fat, plain	1 cup	0.84/0.9	10–24
Soy products/meat substitutes[a]	1 patty/link	1.49–1.72	~25
Cereals (Total/Bran flakes)[a]	1 cup	7.0/2.49	50–100

RDI, recommended dietary intake.
Data from Hands ES. *Food finder,* 2nd ed. Salem, OR: ESHA Research, 1990.
[a] Amounts refer to fortified products. Check label to make certain the product is fortified. Soy milk by itself contains no cobalamin.

In 30% to 40% of cases, low serum cobalamin levels cannot be explained by the decreased absorption of free vitamin B_{12}. The multiple causes of a "falsely" normal Schilling test result include the following: (a) erroneous value; (b) dietary insufficiency of cobalamin; (c) metabolic disorder of cobalamin metabolism, such as an inborn error; (d) malabsorption of cobalamin that has been corrected by the use of antibiotics; (e) "falsely" low serum cobalamin level, which occurs much less often than formerly assumed (see section on body stores); and (f) malabsorption of food-bound cobalamin. The absorption of cobalamin in food requires the liberation of free cobalamin by gastric proteases. Therefore, the Schilling test result may not always correlate with physiologic alterations in cobalamin absorption, especially when gastric physiology is altered.

When serum levels of cobalamin are low, three patterns of absorption can be seen (121). Decreased dietary intake is associated with low absorption rates of free and protein-bound vitamin B_{12}. In gastric disease, absorption of the free form is normal, but the absorption of bound vitamin B_{12} is decreased. In intestinal disease, absorption of both forms is decreased. It is unlikely that cobalamin deficiency develops in gastric disease without at least a partial defect in the production of intrinsic factor. With the availability of more sensitive and convenient assessment of body stores, there is very little need to perform Schilling tests. When dealing with a population at risk for developing cobalamin deficiency, the first step is to assess body stores, and if low, assume that the mechanism whereby deficiency develops is consistent with that seen in the population at risk.

Body Stores

Serum vitamin B_{12} (cobalamin). This parameter usually correlates with body stores. Unlike the folacins, cobalamin is not more concentrated in blood cells than in serum. Thus, hemolysis is not a major factor in producing false results. Transcobalamin II (TCII), the serum carrier protein that delivers cobalamin to tissues, accounts for 30% to 40% of total serum cobalamin (122). The rest is bound to haptocorrin. Therefore, in TCII deficiency, serum levels of cobalamin can be normal, but the vitamin is not delivered to tissues and body stores are low. However, it is clear that marginally low levels (140 to 200, or even up to 350 pg/mL) can be associated with neurologic defects.

Radioisotope dilution assays are based on the principle that endogenous serum cobalamin competes with radioactive cobalamin for binding to a limited amount of cobalamin-binding protein (17). These assays are now simple and reliable. Some commercial kits make it possible to measure cobalamin and folate simultaneously. Heparinized samples cannot be used because heparin interferes with the assay. A number of studies have found that the results of the radioisotope dilution assay compare well with those of the older microbiologic assay.

A serum cobalamin level of less than 140 pg/mL is always associated with low body stores if dilution, protein deficiency, folate deficiency, or altered cobalamin binding protein levels are not present (Table 6-23). Cobalamin deficiency should be suspected in patients with levels of 140 to 200 pg/mL. Such patients should undergo further testing (methylmalonic acid, homocysteine levels), or the results should be correlated with abnormal hematologic or neurologic findings. Evidence of cobalamin deficiency will not be found in all patients with marginal serum cobalamin levels. However, in doubtful cases, a therapeutic trial with cobalamin replacement is safe, and reversal of the abnormal findings is diagnostic. Thirty percent of patients with folate deficiency have low serum cobalamin levels, although the reason is not clear. Protein deficiency lowers the amount of total serum cobalamin without having as much effect on delivery of cobalamin to tissues because about 10% to 30% of the cobalamin-binding protein in serum is TCI. Up to 75% of strict vegetarians have low serum cobalamin levels without evidence of deficiency. Signs of anemia are likely to develop in patients with continued inadequate dietary intake. In patients with HIV infection, cobalamin deficiency may create cognitive changes when clinical acquired immunodeficiency syndrome (AIDS) is not present. Pregnant women have low cobalamin levels secondary to dilution and redistribution of the binding proteins. Transcobalamin I (haptocorrin) deficiency is uncommon, but can present with low cobalamin levels, because at least half of the serum cobalamin is carried on this protein. The condition may be more common than has been suspected (123).

TABLE 6-23. Guidelines for Interpretation of Serum Cobalamin Levels

Range	WHO	Lindenbaum et al. (68)	Comments
Deficient	<110 pmol/L <150 pg/mL		
Low	110–147 pmol/L 150–200 pg/mL		Falsely low: folate deficiency, pregnancy, oral contraceptives, multiple myeloma, haptocorrin deficiency
Acceptable	≥147 pmol/L ≥201 pg/mL	≥258 pmol/L ≥350 pg/mL	Falsely normal: myeloproliferative disorders (PV, CML), liver disease, TCII deficiency, intestinal bacterial over-growth, treatment with cobalamin

PV, polycythemia vera; CML, chronic myelogenous leukemia; TCII, transcobalamin II; WHO, World Health Organization.
Adapted from Sauberlich HE. *Laboratory tests for the assessment of nutritional status,* 2nd ed. Boca Raton, FL: CRC Press, 1999; Lewis CJ, Crane NT, Wilson DB, et al. Estimated folate intakes: data updated to reflect food fortification, increased bioavailability, and dietary supplement use. *Am J Clin Nutr* 1999;70:198; Lindenbaum J, Rosenberg IH, Wilson PW, et al. Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr* 1994;60:2.

For elderly patients, a cutoff of 200 pg/mL may be too low to detect all cases of deficiency. A level of 258 pmol/L (350 pg/mL) has been suggested for patients older than 67 years because serum methylmalonic acid was found to be markedly elevated in 11% of patients with cobalamin levels below that threshold (124). Between 8% and 20% of elderly patients and a smaller percentage of others present with a serum cobalamin level below 180 pg/mL, yet they do not exhibit anemia, macrocytosis, clinical deterioration, or a red blood cell response to cobalamin treatment, and their Schilling test result for cobalamin absorption is normal. These patients need to be further evaluated in all cases because subclinical cobalamin deficiency may be present and lead to neurologic damage. Workup should include (a) a careful neurologic examination and (b) measurement of serum metabolites.

Concentrations above 1,000 pg/mL are seen in acute liver disease because of release from the hepatocytes and in leukocytosis because white blood cells produce haptocorrin, which increases the total cobalamin-binding capacity. These disorders also can raise the levels of serum cobalamin in patients with cobalamin deficiency to normal values. A high level (up to 10x ULN) can be seen in patients with acute or chronic myelogenous leukemia, and in hypereosinophilic syndrome, as haptocorrin is secreted from the abnormal white cells (125). Less striking elevations can be seen in patients with polycythemia vera, myelofibrosis, and chronic myelomonocytic leukemia. More commonly, a high level is due to parenteral injection of the vitamin. Lymphoproliferative diseases almost never present with elevated serum cobalamin.

Serum methylmalonic acid and total homocysteine. Levels of these metabolites increase when the two cobalamin-dependent enzymes, methylmalonyl CoA mutase (methylmalonic acid increased) and methionine synthetase (homocysteine increased), are impaired. Other metabolites that can be assayed include cystathionine (produced from homocysteine by a vitamin B_6-dependent enzyme) and 2-methyl citric acid, a methyl acceptor metabolite derived from methionine via *S*-adenosyl methionine. These metabolites can be used to differentiate the effects of vitamin B_6 deficiency (increased homocysteine, decreased D-cystathionine) and folate deficiency (increased homocysteine, decreased 2-methyl citric acid) from those of cobalamin deficiency alone (increased homocysteine, increased methylmalonic acid) (Table 6-20). A reference value is not available, because many factors influence the concentration in serum, including age, gender, and test method. The range of

normal serum values is 70 to 270 nmol per L (126). The cutoff value for methylmalonic acid to diagnose vitamin B_{12} deficiency is 376 nmol per L. The level of serum methylmalonic acid that should detect all cases of vitamin B_{12} deficiency is <638 nmol per L, to correspond with the cutoff of serum cobalamin (350 pg per ml or 258 pmol per L) that detects nearly all cases of cobalamin deficiency (124). Causes of elevated serum methylmalonic acid besides cobalamin deficiency include renal insufficiency (GFR <20), hypovolemia, and inherited metabolic defects.

"Normal" values for homocysteine are 2.2 to 13.2 μmol per L (127). Levels of homocysteine in "typical" Western populations are ~12 μmol per L (91). There is still uncertainty whether this level of homocysteine carries a risk for chronic disease. The significance of serum homocysteine levels for chronic disease risk is discussed in this chapter in the section on folate.

Holo-TCII. The measurement of holo-TCII has been suggested to be the most sensitive method to detect cobalamin deficiency and to detect deficiency earlier than other tests (128) (Table 6-24). The half-life of holo-TCII is only 6 minutes, so levels are low within a week of cessation of oral cobalamin intake. Holo-TCII (i e., cobalamin bound to TCII) is measured by separating TCII from haptocorrin–cobalamin in serum by a monoclonal antibody capture method (HoloTC RIA, Axis-Shield) (129). Because TCII delivers cobalamin to all tissues, a fall in the TCII–cobalamin complex (i.e., holo-TCII) may detect early stages of deficiency, even when serum cobalamin levels are normal. Holo-TCII levels, in parallel with red cell folate and total serum cobalamin levels, are inversely related to serum homocysteine concentrations (128). Values below 35 pmol/L (<46 pg per mL) are considered deficient, with borderline low values ranging from 35 to 44 pmol/mL (46 to 60 pg per mL). The new assays are more accurate than the original ones, and reference values are available from laboratories in both the United Kingdom (128) and the United States (129). Values are different in men and women and also vary with age. Measurement of holoTC explained more of the observed variance in methymalonic acid and homocysteine levels than did total vitamin B_{12}, but ROC curve analysis showed that serum vitamin B_{12} and holoTC were essentially equivalent in their ability to diagnose deficiency (129). Because holoTC may become abnormal at an earlier time, it may be used together with serum vitamin B_{12} as a screening test for deficiency. However, it is not clear if the prediction is correct that holoTC would be more sensitive and provide an early signal than existing tests, and the role of holoTC in diagnosing cobalamin deficiency is not yet established.

TABLE 6-24. Laboratory Tests in Sequential Stages of Cobalamin Deficiency

	Stage of cobalamin deficiency				
Parameter	**None**	**I**	**II**	**III**	**IV**
CBL balance	Normal	Negative balance	Depletion of stores (early)	Tissue damage (late)	Tissue damage (late)
Serum holo-TCII	>60 pg/mL	Low	Low	Low	Low
Serum CBL	>201 pg/mL	>201 pg/mL	>201 pg/mL	Low	Low
Serum MMA	<376 nmol/L	<376 nmol/L	<376 nmol/L	High	High
Serum Hcy	<15 μmol/L	<15 μmol/L	<15 μmol/L	High	High
RBC folate	>160 pg/mL	>160 pg/mL	>160 pg/mL	>140 pg/mL	>100 pg/mL
Neurologic	None	None	None	Sometimes	Frequent symptoms
MCV	Normal	Normal	Normal	Normal	High
Hemoglobin	Normal	Normal	Normal	Normal	Low

CBL, cobalamin; TCII, transcobalamin II; MMA, methylmalonic acid; Hcy, homocysteine; RBC, red blood cell; MCV, mean corpuscular volume.
Adapted from Herbert VD. *Round table series 66.* London: Royal Society of Medicine Press, 1999.

Screening. Because abnormal serum parameters of cobalamin metabolism precede manifestations of tissue damage, screening populations who are at risk for deficiency is recommended. Persons at risk include strict vegetarians; those older than 65 years (especially if institutionalized or with a history of decreased food intake); patients with unexplained neurologic/psychiatric symptoms; those with anemia, *H. pylori* infection (or taking proton pump inhibitors on a long-term basis), thyroid or autoimmune disease, HIV disease, Crohn disease, chronic pancreatitis, multiple sclerosis, or malabsorption of any cause; and persons who have undergone gastric or small-bowel surgery. Serum holo-TCII measurements are available routinely now, and they can be used initially or in conjunction with serum cobalamin levels. If serum cobalamin is used alone, values below 350 pg per mL (Lindenbaum criteria, Table 6-23) should be investigated further if cobalamin deficiency is suspected clinically. Tests to confirm deficiency include measurements of serum methylmalonic acid, homocysteine, and serum holo-TCII, depending on availability and cost. When a serum cobalamin level below 350 pg/mL (268 pmol/mL) is used, an elevated methylmalonic acid concentration has a diagnostic sensitivity of 0.4 and a specificity of 0.98, certainly enough to recommend the measurement of methylmalonic acid to detect deficiency (126). If anemia is present, the status of folate, iron, and copper must also be considered.

Physiology

Conversion to Coenzymes. The stable cyanocobalamin must be converted to active coenzymes in the body. Adenosyl cobalamin is the form of 70% of the vitamin stored in liver, whereas methyl cobalamin is the major form in plasma (60% to 80%). Cobalamin forms the coenzyme for two enzymes, methylmalonyl CoA mutase, and 5-methyltetrahydrofolate-homocysteine methyl-transferase (methionine synthetase). Methionine synthetase links cobalamin to folate metabolism by transferring the methyl group from methylfolate to regenerating tetrahydrofolate. Therefore, in cobalamin deficiency, the movement of plasma methyltetrahydrofolate into cells is decreased. Serum folate levels are normal or high, whereas red cell folate levels are low (130).

Cobalamin Absorption. Cobalamin is bound to enzymes in food and must first be liberated by gastric proteases. The free vitamin is then bound to haptocorrin (nonintrinsic factor-binding protein) in the stomach; haptocorrin has a tenfold greater affinity for cobalamin than does intrinsic factor. In the upper small bowel, pancreatic enzymes hydrolyze haptocorrin to produce free cobalamin (131). Intrinsic factor is not protease-sensitive and now binds cobalamin. The intrinsic factor–cobalamin complex attaches to its specific receptor, cubilin, in the ileal mucosa and is taken up by the cell via receptor-mediated endocytosis (69). Cubilin is attached to the membrane by binding to the product of the amnionless gene. This complex mediates the uptake of intrinsic factor. Megalin, a 600 kD member of the low-density lipoprotein receptor family, participates in the uptake of intrinsic factor-cobalamin complexes in the renal tubule, a function not yet demonstrated in the intestine. In the kidney the cubilin-amnionless complex also mediates the uptake of albumin, apolipoprotein A-I, and transferring (69, 132). Thus, patients with a defect in amnionless (many Imerslund-Grasbeck patients) also have proteinuria. In the absence of ileal receptors, only about 1% of the vitamin is absorbed passively. Cathepsin L degrades intrinsic factor within lysosomes, liberating cobalamin to bind to transcobalamin (TCII) in another compartment of the enterocyte, from which it is released and carried to tissues where it is needed. The crystal structure of transcobalamin has been discovered, consisting of two domains with the cobalamin buried inside the domain interface (133). In the liver, cobalamin is bound again to haptocorrin and excreted in the bile. In the intestine, the biliary haptocorrin–cobalamin complex is digested and absorbed in the same manner as the dietary vitamin. The enterohepatic circulation delivers approximately 5 to 10 μg of cobalamin per day to the intestine, an amount nearly equal to daily dietary intake. Potential daily losses without malabsorption are 1 to 2 μg. With malabsorption, estimated daily losses can approach 10 μg. Therefore, depletion of the 4 to 5 mg of body stores occurs slowly in dietary deficiency but much more rapidly in malabsorption.

Deficiency

Deficiency occurs in a variety of clinical situations (Table 6-25) (134). Symptoms are insidious and develop during 2 to 3 years. Weakness, fatigue, and dyspnea are related to anemia. However, fatigue is a very nonspecific symptom, and cobalamin supplementation is widely overused for this indication. Sore tongue, paresthesias, anorexia, loss of taste, and dyspepsia are seen, along with diarrhea, hair loss, impotence, irritability, and memory disturbances. Numbness and tingling due to peripheral neuropathy are noted first in the lower limbs, but deficiency can be associated with myelopathy or myeloneuropathy as well (19). Some patients present with a psychiatric illness, often depression. Macrocytosis is a feature in many cases. This anemia must be differentiated from the macrocytosis of alcoholism and hypothyroidism, or that seen in patients with IBD who are treated with 6-mercaptopurine or azathioprine.

Dietary deficiency occurs exclusively in persons on a strict vegetarian diet. Cheese, milk, and eggs have low levels of cobalamin but can provide the needed amounts when they are major sources of calories. Increased utilization can occasionally lead to low serum cobalamin levels, as in bone marrow cells in multiple myeloma (135). Patients taking metformin have decreased cobalamin absorption and low serum cobalamin and holoTCII levels, thought due to the effect of the drug on a calcium-dependent ileal membrane system (136). HIV-infected patients can have low serum levels of vitamin B_{12} without clinical AIDS. The clinical significance is uncertain; not all patients with decreased cobalamin absorption improve when intrinsic factor is replaced. The mechanisms of these changes require clarification. Deficiency can develop during the prolonged use of proton pump inhibitors, but this is usually confined to patients with Zollinger–Ellison syndrome and sustained drug-induced achlorhydria, which does not occur with the usual doses of proton pump inhibitors.

Multiple Sclerosis. Patients with multiple sclerosis can have low serum cobalamin levels and high homocysteine levels (137). The problem is complicated by the fact that the presentation of the two conditions can be confused. The neuropathology of cobalamin deficiency involves the myelin sheath and white matter. MRI imaging of the brain and spinal cord can show, in some cases, a pattern of white matter degeneration similar to multiple sclerosis,

TABLE 6-25. Patient Populations at Increased Risk for Cobalamin Deficiency

Disorder	Prevalence	Pathophysiology
Decreased intake	High	Elderly, strict vegans, alcoholism
Pernicious anemia	Near 100%	Autoimmune gastritis, lack of IF
Helicobacter pylori gastritis	Variable	Chronic gastritis, some ↓ in IF
Age >65 years	~10%	Atrophic gastritis, malabsorption of food-bound CBL
Crohn disease	↑With resection	Ileal disease or resection, loss of IF receptor
HIV disease	~15%	↓ Acid/IF secretion, ↓ ileal absorption
Gastric surgery	High	Loss of parietal cells producing IF
Bacterial overgrowth	Variable	Organisms compete for CBL in bowel
Chronic pancreatitis	Low	Lack of pancreatic enzymes to transfer CBL to IF
Malabsorption	Variable	Loss of IF-CBL receptor, if ileum involved
Zollinger–Ellison syndrome	Moderate	Prolonged inhibition of gastric (and IF) secretion
Hyperhomocysteinemia	Moderate	↓ Activity of methionine synthase; r/o folate, B_6 deficiency
Dementia	Moderate	↓Myelin formation

IF, intrinsic factor; CBL, cobalamin.

including a hyerintensity on the T2 image in the cord and periventricular white matter (138). It has been proposed that subclinical cobalamin deficiency aggravates underlying multiple sclerosis, but this association remains to be confirmed.

Dementia and Neuropsychiatric Presentations. The neurologic manifestations of cobalamin deficiency occur in about 75% of patients (139) (Table 6-26). Moreover, they often develop in the absence of anemia and can be the major presentation in elderly patients. Both folate and cobalamin have been linked to psychiatric disease, especially depression, but direct causal relationships are still uncertain (140). The association of these symptoms in the elderly with cobalamin deficiency is variable, and in one cross-sectional study, no correlation with cognitive impairment or general health was found (141). The clinical presentation of cobalamin deficiency in the elderly may differ from that seen in Alzheimer disease, in that the deficit was confined to cognitive tasks and was reversible with supplements (142). Involuntary myoclonus-like muscular contractions reversed with cobalamin have been reported (143). Myelopathy, neuropathy, and cognitive decline all may suggest cobalamin deficiency (144).

Hyperhomocysteinemia. This metabolite is regulated by folate, vitamin B_6, and cobalamin. Serum concentrations are also related to age, sex, renal function, drug ingestion, genetic polymorphism, and other factors as yet unknown. The variable rates of prevalence and the still uncertain upper limit of normal values may be associated with the need to use freshly separated plasma so as to avoid homocysteine synthesis by red blood cells in vitro. The implications of this finding in regard to cardiovascular disease are still unclear (see section on folate). Even when folate and cobalamin levels are found to be below average, it is not clear whether this represents a deficiency state and whether supplemental vitamins will either correct the plasma abnormality or prevent any clinical disorders, particularly cardiovascular disease (145). The fact that an increase in cardiovascular disease has not been

TABLE 6-26. Neuropsychiatric Presentations of Cobalamin Deficiency

Clinical syndrome	% of cases	Symptoms	Signs	Localization
Myeloneuropathy	54%	Paresthesias, numbness, weakness, incontinence	↓ Vibration, touch, position, ↓ reflexes	Peripheral/autonomic nerves
Peripheral neuropathy	9%	Gait ataxia	Romberg sign, ↑ reflexes, Babinski sign, spasticity	Spinal cord
Neuropsychiatric & dementia	38%	Aphasia, hemiparesis, impaired visual fields	Lateralized signs, optic atrophy	CNS (r/o stroke)
Cognitive dysfunction	34%	↓ Memory, concentration, depression, confusion, ↓ processing speed	Abnormal symptom scales	CNS (r/o Alzheimer)

Prevalence of neurologic syndromes adapted from Aaron S, Sudhir K, Vijayan J, et al. Clinical and laboratory features and response to treatment in patients presenting with vitamin B12 deficiency-related neurological syndromes. *Neurol India* 2005;53:55.

detected in pernicious anemia, the most common cause of cobalamin deficiency, raises a question about the nature of the association with hyperhomocysteinemia.

Treatment

Dietary deficiency responds to as little as 1 to 3 μg per day taken orally. Malabsorption requires additional supplementation (150 to 300 μg per month) because the enterohepatic circulation is interrupted. A single injection of 100 μg produces a complete remission of symptoms in most cases. An increased sense of well-being is noted within 24 hours, painful tongue improves in 48 hours, and reticulocytosis begins in 5 to 7 days. Serum folate falls rapidly. Neurologic findings may take 6 months to reverse. Monthly injections of 100 to 200 μg sustain the remission, although 1,000 μg is often used. Patients with rare inborn errors of metabolism, such as vitamin B_{12}-responsive methylmalonic acidemia, require treatment with large amounts of the vitamin because they are resistant to normal levels of cobalamin.

Elderly subjects are advised to meet daily needs by taking synthetic cobalamin in enriched foods or supplements (3). The amount of cobalamin found in most multivitamins (≤6 μg) is not sufficient to treat cobalamin deficiency, which is more prevalent in the elderly. Healthy people under age 50 consuming a diet that contains animal products do not require cobalamin supplements. Some healthy people over the age of 50 may require supplements, but it is not clear how many. Thus, it seems reasonable to screen this population, but the best approach to population screening and the best dose to prevent deficiency are still uncertain. If elevated levels of methylmalonic acid or holoTCII are found, treatment with cobalamin in deficiency doses can normalize them.

No studies have tested whether Alzheimer-type dementia responds to cobalamin. Because these patients are elderly, they should be screened and treated if deficiency is present. Some data support the use of cobalamin to treat painful uremic neuropathy (146). Elevated homocysteine levels are seen in patients with stroke, and in a study of 628 Japanese patients with poststroke hemiplegia, combined therapy with folate and methylcobalamin reduced the risk of fractures by ~80% without improving bone mass or reducing falls (147). The effect was so striking that it needs repeating, but this may not be easy to do in countries with folate supplementation. Cobalamin injections have been used for years to treat fatigue, but evidence of its efficacy has not been found in controlled trials.

Parenteral cobalamin is supplied in solutions of 1,000, 100, and 30 μg/mL. Oral cobalamin can be used for treatment in most patients with an adequate gastrointestinal tract, although the response is slightly slower than when an injectable vitamin is used (148, 149). A systematic review revealed two randomized controlled trials of oral versus parenteral cobalamin treatment for cobalamin deficiency, and concluded that 2 mg per day initially and then weekly or monthly for life were as effective as parenteral vitamin in patients with an intact intestine (150). Nasal cobalamin is available (Nascobal, 500 μg per 0.1 mL) for maintenance use once a week. It appears to be well tolerated and can even be used more frequently for the initial treatment of mild deficiencies (151).

Toxicity

Cobalamin causes no toxic effects, so no UL has been suggested (3).

Vitamin C (Ascorbic Acid)

Requirement

A daily intake of 10 mg of ascorbic acid cures clinical signs of scurvy but does not maintain body stores. When the daily intake is above 200 mg, most of the ingested vitamin is excreted. Between these extremes, body stores vary with intake. Age and sex have only minor effects on the vitamin C requirement. The requirement is compounded by the fact that vitamin C has a chemoprotective effect in many disorders, at doses far in excess of those necessary to prevent scurvy. These include colon cancer, heart disease, and cataracts. A well-designed study has now identified the vitamin C intake and tissue saturation levels that allow maximal protective effects of the vitamin (152). With the ingestion of 60 mg of vitamin C per day (the previous RDA), wide fluctuations in plasma vitamin C were associated with small changes in the amount consumed. The first intake dose at which plasma levels were beyond the first sigmoid part of the saturation curve was 200 mg per day.

Saturation did not occur until intake levels were at 1,000 mg per day. These data fit with the estimated vitamin C content of diets (~225 mg per day) that appears to be of chemoprotective value (153). The DRI values represent a compromise between the old RDA value of 60 mg per day and the value needed for chemoprevention (Table 6-27). This compromise also takes into account dietary availability, bioavailability, urinary excretion, potential adverse effects, and biochemical and molecular function in relation to vitamin concentration.

Needs are increased at some life stages. Premature infants have low body pools. Newborn infants ingest about 35 mg from breast milk, and the DRI for them is set to at least equal that source. During pregnancy, about 10 mg of vitamin is added to the fetus each day, which must be added to the DRI for pregnant women. The vitamin C concentration in human milk is about 30 mg per L for a volume of 750 mL (first 6 months), which creates an additional need of 22 mg per day.

Food Sources

Ascorbic acid is widely distributed in foods in high concentrations, especially in green vegetables and citrus fruits. However, the content is quite variable from one food to another and within each type, even for foods from the same region and source, depending on species and degree of ripeness (154). Table 6-28 lists the ascorbic acid content of some common foods. Grain products do not contain ascorbic acid unless they have been enriched. Nuts and sweets contain little or no ascorbic acid. The DRI for adult men (90 mg) can be achieved with one and one-half glasses of freshly squeezed orange juice, or three-fourths cup of raw broccoli. Agencies that suggest vitamin C for chemoprevention of chronic disease (U.S. Department of Agriculture, National Cancer Institute) suggest consumption of five servings of fruits/vegetables each day (200 to 280 mg per day). However, in the third National Health and Nutrition Examination Survey (NHANES III), vitamin C intake for adults was only 70 to 80 mg per day (155). Furthermore, ascorbic acid is heat-labile and easily destroyed by oxidation. Prolonged exposure to oxygen, iron, or copper destroys the vitamin. In addition, like other water-soluble vitamins, ascorbic acid can be lost in cooking water. Often, only 50% of the content of the raw food survives processing and cooking.

Assessment

Intake or Absorption. In general, plasma or serum ascorbate levels reflect intake. Low levels do not necessarily indicate scurvy, but scurvy is invariably associated with low

TABLE 6-27. Dietary Reference Intakes for Vitamin C

Life stage group	Vitamin C (mg/day)	Life stage group	Vitamin C (mg/day)
Infants		**Females**	
0–6 months	40[a]	9–13 years	45
7–12 months	50[a]	14–18 years	65
		19–>70 years	75
Children			
1–3 years	15	**Pregnancy**	
4–9 years	25	≤18 years	80
		19–50 years	85
Males			
9–13 years	45	**Lactation**	
14–18 years	75	≤18 years	115
19–>70 years	90	19–50 years	120

[a] Evidence sufficient to suggest a DRI based only on adequate intake (AI). All others based on recommended dietary allowance (RDA).
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for vitamin C, vitamin E, selenium, and beta-carotene and other carotenoids.* Washington, DC: National Academies Press, 2000.

TABLE 6-28. Ascorbic Acid Content of Foods

Food	Serving	Ascorbic acid per portion (mg)	Percentage of RDI (60 mg)
Fruits			
Banana	One (9 in)	10	10–24
Cantaloupe	1 cup	68	>100
Orange	Whole (2 1/2 in)	70	>100
Grapefruit	Half, red	47	>40
Strawberries	1 cup	85	>100
Pear	One Bartlett	7	10–24
Apple	One (2.75 in)	8	10–24
Fruit juices			
Orange, fresh	1 cup	124	>100
Orange, frozen	1 cup	97	>100
Grapefruit, canned	1 cup	72	>100
Pineapple, frozen	1 cup	30	>40
Grape drink[a]	1 cup	250	>100
Vegetables			
Green beans, fresh uncooked	1 cup	18	25–39
Spinach, cooked from fresh	1 cup	40	>40
Cabbage, cooked	1 cup	36	>40
Broccoli, cooked from fresh	1 cup	116	>100
Peas, frozen	1/2 cup	8	10–24
fresh, cooked	1 cup	23	25–39
Potato, baked	1 each	26	>40
Lettuce, iceberg	1 cup	2.2	1–5
Tomato, fresh	1 each (2.2 in)	22	25–39
Green pepper, fresh	1/2 cup	44	>40
cooked	1/2 cup	50	>40
Dairy products			
Milk, cow's, whole	1 cup	2.3	1–5
Milk, human	1 cup	7–12	10–24
Cheese	1 oz	0	0
Egg	1 each	0	0
Meats			
Beef liver, fried	3 oz	19	25–39
Bacon, lunch meat	2 pieces	10	10–24
Fish	3 oz	4	5–12

RDI, recommended dietary intake.
[a] Vitamin C is fortified in some drinks; check label.
Data from Hands ES. *Food finder,* 2nd ed. Salem, OR: ESHA Research, 1990.

levels. Plasma levels may not always reflect intake. Levels of ascorbate may be reduced in patients with chronic inflammatory diseases, cigarette smokers, persons experiencing acute emotional or environmental stress, and women taking oral contraceptives. The nutritional meaning of these changes is obscure. This test is readily available, and its value is that a normal result rules out scurvy. Vitamin C is stable in plasma when collected in metaphosphoric acid. The method of choice for plasma or blood vitamin C measurement is HPLC, according to the recommendations of the World Health Organization (WHO) (17). Levels <23 μmol per L indicate deficient intake or absorption (Table 6-29). Seasonal changes occur, with the highest levels seen in summer, when large amounts of fresh fruits and vegetables are consumed. Levels are very high in the first 3 days of life. When intake is

TABLE 6-29. Guidelines for Interpreting Vitamin C Status

Test	Deficient (high risk)	Low (moderate risk)	Acceptable (low risk)
Serum ascorbic acid (μmol/L)	<11	11–23	>23
Leukocyte ascorbate (μmol/L)	<150	<200	300–600

From second National Health and Nutrition Examination Survey, Canada Nutrition Survey, and adapted from Sauberlich HE. *Laboratory tests for the assessment of nutritional status,* 2nd ed. Boca Raton, FL: CRC Press, 1999.

decreased, deficiency develops within 3 to 5 months. Severe infections and acute illness can lower serum levels in the absence of deficiency. Levels should be measured in patients at risk, including those with a poor diet (elderly, alcohol or drug abusers, patients with chronic disease or cancer), patients on dialysis, and smokers.

Body Stores. Ascorbate concentrations in leukocytes are more closely related to body stores than concentrations in plasma. Red cell levels of ascorbate do not fall with depleted stores. Separation of cells on a Ficoll density gradient followed by HPLC analysis has made accurate measurement possible in blood samples of 2 mL or less. Both ascorbic acid and the oxidized form, dehydroascorbate, can be measured. Because a fivefold variation in vitamin C content (μg per 10^8 cells) is seen between mononuclear cells (higher) and polymorphonuclear cells (lower) (17), vitamin C levels vary with differing degrees of leukocytosis. Because the diagnosis of scurvy must be made quickly, a test must be rapid and readily available to be of any use at all. For these reasons, when an assessment is obtained, plasma ascorbate is preferred, even though it does not measure tissue stores. Guidelines for the interpretation of the results of these tests are listed in Table 6-29.

Physiology

Absorption. The absorption of ascorbic acid is carrier-mediated, active, and sodium-dependent. Two sodium-dependent vitamin C cotransporters have been cloned, SVCT1 and SVCT2 (156). SVCT1 is found in kidney, intestine, and liver; SVCT2 is in choroid plexus and pigmented epithelium of the retina. Efflux across the basolateral membrane is mediated by an unknown sodium-independent mechanism. Neither cotransporter recognizes oxidized ascorbic acid (dehydroascorbate). This metabolite crosses the blood–brain barrier via the GLUT1 glucose transporter, and ascorbic acid is regenerated in the brain and thus trapped in that tissue. Ascorbic acid efflux occurs by exocytosis and by volume-sensitive pathways, triggered by glutamate.

The efficiency of ascorbic acid absorption decreases with a daily intake above 180 mg. In such cases, 55% to 90% of the ingested vitamin appears in the urine. The stool contains the rest, with the proportion increasing as the oral dose increases. When excessive ascorbate is ingested, osmotic diarrhea ensues. Plasma concentrations are tightly controlled, so the concentration needed for antitumor activity in vitro (>100 μmol per L) cannot be achieved in humans by oral dosing (157). This may explain the negative results of studies trying to link vitamin C intake or plasma levels to cancer prevention. Ascorbic acid is catabolized to oxalate and accounts for 20% to 30% of urinary oxalate under normal conditions. Ingestion of >4 g per day increases urine oxalate excretion. Large doses of vitamin C increase oxalate excretion to 60 to 100 mg per day. The range of molar conversion varies from 2.5% to 3.0%. Average stores are about 900 mg, and the mean daily excretion of dietary vitamin C is 2.7%. At higher doses, the vitamin is uricosuric.

Metabolic Functions. Metabolic functions of ascorbic acid are not completely understood (158). It is important in the hydroxylation of proline and lysine and affects collagen formation. It enhances the hydroxylation of lysine to hydroxylysine, and of proline to

hydroxyproline. The collagen matrix produced under stimulation by ascorbic acid may potentiate differentiation. Ascorbic acid influences tyrosine metabolism when large amounts of tyrosine are ingested. It is involved in the formation of norepinephrine from dopamine and in converting tryptophan to 5-hydrotryptophan and subsequently to serotonin. Vitamin C also aids in the synthesis of carnitine and adrenal hormones, and enhances microsomal drug metabolism, wound healing, and leukocyte functions. Ascorbic acid is an excellent antioxidant, scavenging free radicals. The half-life in the body is 10 to 20 days. By its reducing power, the vitamin enhances the absorption of inorganic iron and the transfer of iron from transferrin to ferritin, and it may function as an antioxidant for vitamins A and E. The formylation of tetrahydrofolinic acid is enhanced by vitamin C.

Deficiency

Scurvy is manifested by weakness, irritability, bleeding gums, gingivitis, joint pains, and loosening of teeth. Musculoskeletal problems dominate the clinical picture, including arthralgia, myalgia, hemarthrosis, and hematomas in the muscle (159). Trabecular and cortical loss of bone mass is common. Interference with neurotransmitter synthesis may explain the fatigue, weakness, and vasomotor instability associated with scurvy. Hemorrhaging occurs in the skin, especially the perifollicular regions, conjunctivae, nose, and gastrointestinal and genitourinary tracts. Anemia and hyperkeratosis of hair follicles are common. The condition can present as leukocytoclastic vasculitis (160). Infants are subject to weight loss and subperiosteal hemorrhage. Cessation of the growth of long bones is a prominent feature of infantile scurvy. Scurvy is a rare disorder in the United States because of the wide availability of fresh fruits and vegetables and the common supplementation of packaged foods with vitamin C. When scurvy occurs, it is usually in alcoholics. Because the assessment of vitamin C stores is difficult, information is lacking about other possible deficiency syndromes. Despite many claims to the contrary, no deficiency state for vitamin C other than scurvy has been documented.

Therapy

Scurvy. Scurvy responds to as little as 10 mg of vitamin C per day. A dose of 60 to 100 mg per day is recommended for replenishing body stores. Tablets are available in doses of 25, 50, 100, 250, 500, 1,000, and 1,500 mg. It is available as a syrup at a dose of 500 mg per 5 mL. Parenteral preparations offer 500 mg per mL.

Low Serum Levels of Vitamin C. Persons at risk include the elderly (older than 65 years), smokers (especially men), diabetics, and oral contraceptive users. They should be encouraged to increase their vitamin C intake, most likely via a supplement, because 5 to 10 servings of fruits/vegetables are needed to fulfill their increased requirement.

Prevention of Chronic Disease. In addition to its antiscorbutic role, many potential benefits of vitamin C have been suggested, so that vitamin C supplements are now more widely used than any other supplement in the United States. Evidence exists for a role of vitamin C in the prevention of cataracts, diabetes, hypertension, coronary heart disease, cancer, asthma, and the common cold (22, 158). Vitamin C concentration in cells is high and falls rapidly during stress and infection, leading to the concept that ascorbate plays a role in immune responses (161). The data on the prevention of rhinovirus infection are still equivocal (22), but a systematic review of vitamin C prophylaxis for the common cold found no benefit in the general population at doses up to 8 g per day (162). However, in 6 trials involving marathon runners, skiers, and soldiers on sub-Arctic exercise, there was a 50% reduction in colds. Similarly, the evidence for a role in relieving asthma or allergy is equivocal (163).

The role of vitamin C as an antioxidant has been extensively examined in humans, often in combination with other potential antioxidants, especially vitamin E, but no change in markers of oxidation or clinical benefit have been found in general (164) (see also the section on vitamin E in this chapter). Evidence in small numbers of subjects suggests a possible role for vitamin C in enhancing immune function, but none in exercise-induced oxidative stress (22). Many epidemiologic studies show an inverse correlation between vitamin C levels and coronary artery disease and also between vitamin C levels and hypertension (165, 166), but prospective trials have not been performed. An epidemiologic study in

83,639 male physicians showed no correlation of vitamin C (or E) use with changes in cardiovascular mortality over 5 years (167). On the other hand another study of 85,118 women showed a 28% reduced risk in those who took vitamin C supplements, but not in those with the highest intake of dietary vitamin C (168). Another large study showed an inverse association between cardiovascular mortality and vitamin C plasma levels and vitamin C intake (mostly due to supplements) (169). The same correlations and lack of prospective interventional studies have been noted for cataracts (22) and gastric, esophageal, oral, and pharyngeal cancers (170). It is reasonable to suggest an increased dietary vitamin C intake for these patients, but it is premature to recommend supplements. If supplements were given, there are no data on the necessary dose, whether vitamin C alone would be effective, whether primary or secondary prevention would be affected, or which population might respond the best (171).

Iron Absorption. The addition of ascorbate to inorganic iron preparations enhances absorption. The effectiveness of ascorbate in improving ferrous sulfate absorption is greater when used with meals that contain inhibitors of iron absorption, requiring a molar ratio of ascorbate:iron of 4:1, or ~10 mg per mg of iron (172),

Industrial Uses. Industrial uses of ascorbic acid include prevention of food spoilage, maintenance of the red color of canned meat, prevention of rancidity of fats, and stabilization of milk.

Toxicity

Earlier reports of adverse effects with supplemental vitamin C have largely not been substantiated in normal healthy populations (173). However, a UL for adults has been set at 2,000 mg per day (3) (Appendix B). Although the urinary excretion of oxalate increases with high doses of the vitamin, no relationship with kidney stones has been found in normal persons. Likewise, the inorganic iron-enhancing feature of the vitamin does not affect serum ferritin. High doses of vitamin C do not appear to destroy cobalamin. Nonetheless, it would be well to remember that this lack of toxicity applies only to normal populations, and that high doses of supplemental vitamin C have not been shown to be beneficial. Moderation of intake can be suggested for any patients considered at risk for iron overload or renal oxalate stones.

The pH of chewable vitamin C tablets (500 mg) is less than 2.0. Because vitamin C acidifies the urine, it can decrease the excretion of acidic drugs such as aspirin and increase the excretion of basic drugs such as tricyclic antidepressants. Large doses (>500 mg) also can interfere with the laboratory measurement of levels of serum bilirubin, glucose, lactic dehydrogenase, and transaminases, and with tests to detect fecal occult blood. Such doses can cause false-negative determinations of urine glucose with glucose oxidase and false-positive determinations with copper reduction or Benedict's solution.

Biotin

Requirement

Biotin is synthesized by many microorganisms, and it is felt that colonic flora contribute to the available biotin in humans. Thus, estimation of the requirement is difficult. It has been suggested that a biotin intake of 60 μg per 1,000 kcal prevents deficiency. The estimated safe dietary intake ranges from 30 to 100 μg per day in adults because data on the availability in foods and the intestinal contribution are incomplete. The DRIs for biotin are 5 to 12 μg per day in infants and children, 20 to 25 μg per day in adolescents, and 30 μg per day in adults (3).

Food Sources

The average diet in the United States contains 100 to 300 μg of biotin. It is present in free and bound forms. In egg yolks, biotin is bound by the protein avidin. Biotin is liberated in the intestine by enzymatic hydrolysis. The vitamin is heat labile, but much of it is retained in processed foods. Rich sources (600 to 2,000 μg per 100 g) include yeast extracts, liver and other organ meats, fish, soybeans, dairy products, and egg yolks (174). Poor sources (<10 μg per 100 g) include muscle meats, dairy products, grains, fruits, and vegetables. Many of the values in foods are likely to be inaccurate, as the results show marked variability compared to a sensitive avidin-binding assay (174).

Assessment

Biotin is measured with *Lactobacillus plantarium* as the assay organism. Values for plasma and whole blood in the literature are variable (17). Normal whole blood levels are 244 ± 61 pmol per L. Mean urinary excretion is 35 ± 14 nmol per 24 h (17). Values well below these have been reported in biotin deficiency (175). Expression of mRNA for biotin-related genes may be relatively sensitive indicators of marginal biotin deficiency (176). These genes include methylcrotonyl-CoA carboxylase chains A and B, propionyl-CoA carboxylase isoforms A and B, holocarboxylase synthetase, biotinidase, and 2 potential biotin transporters, sodium-dependent multivitamin transporter (SMVT) and solute carrier family 19 member 3 (SLC19A3).

Physiology

Biotin is a cofactor for carboxylating enzymes. Biotin accepts carbon dioxide to form an intermediate compound and then transfers carbon dioxide to the substrate. It is thus essential as an intermediary in the metabolism of carbohydrate, protein, and fat. Biotin is absorbed by the small intestine and probably colon by the sodium-dependent multivitamin transporter (SMVT) that also transports pantothenic acid (177). An electrogenic sodium–biotin cotransport system has been identified. Colonic and small-bowel absorption explains the rarity of human deficiency states. Fecal synthesis by bacteria is prominent but can be inhibited by broad-spectrum antibiotics.

Deficiency

Dietary Biotin Deficiency. Dietary biotin deficiency is rare in humans (178). High levels of phenylpyruvate, seen in phenylketonuria, inhibit pyruvate carboxylase and lead to a functional biotin deficiency. In experimental deficiency, a maculopapular dermatitis (along with lingual atrophy) and pallor are noted after many weeks. Lassitude, muscle pain, paresthesias, and anorexia with nausea occur. In some children with seborrheic dermatitis, biotin levels are low. Ingestion of large amounts of raw egg has produced a deficiency as a result of an excess of avidin, which binds biotin. Biotin deficiency as a complication of long-term total parenteral nutrition can produce alopecia and dermatitis (179). Dermatitis and alopecia are also seen in deficiencies of essential fatty acids and zinc. Biotin deficiency produces a scaly dermatitis, whereas in zinc deficiency, the dermatitis is wetter. A correlation between marginal biotin status and teratogenicity has been reported during pregnancy (180).

Biotin-Responsive Carboxylase Deficiencies. These types of deficiencies have been rarely reported. Affected children present with an erythematous rash, alopecia, and keratoconjunctivitis. It is not clear that the syndrome is caused by biotin deficiency, but at least one case has responded to biotin supplements of 10 mg per day (181). Single cases of biotin deficiency have been reported due to deficiency in 3-methylcrotonyl-CoA carboxylase (182) and to a defect in cellular transport of biotin (183).

Biotinidase Deficiency. Biotinidase deficiency is an autosomal recessive disorder in which biotin cannot be cleaved from peptides and recycled. Patients may become biotin-deficient during early childhood, with seizures, rash, alopecia, ataxia, hearing loss, delayed development, coma, and death. A simple screening test is available for blood in neonates, and the symptoms are reversed by pharmacologic doses (10 mg) of biotin provided they are given early in the course (184).

Therapy

The addition of 200 to 1,000 μg of biotin daily reverses the symptoms of deficiency. The vitamin is available in multivitamin preparations and as 1-, 5-, and 10-mg tablets.

Toxicity

No toxic effects have been reported, and no UL has been established.

Pantothenic Acid (Vitamin B_5)

Requirement

When consuming 5 to 7 mg of pantothenic acid daily, normal subjects excrete 2 to 7 mg per day in the urine and 1 to 2 mg per day in the stool. The data are insufficient to base the DRIs for pantothenic acid on RDAs. The AI-based recommendations are 4 mg for

adolescents 9 to 13 years old and 5 mg per day for older adolescents and adults (3). The AI for children is 1.7 to 3 mg per day. During pregnancy and lactation, deficiency has not been reported, but increments of 1 and 2 mg per day are suggested, respectively.

Food Sources

Animals and some microbes cannot synthesize pantothenate, and are dependent on exogenous vitamin. Pantothenic acid is widely distributed in foods (the term pantothenate is derived from the Greek "pantothen" meaning "from all sides"), especially in animal tissues, whole-grain cereals, and legumes. Cow's milk contains 3.5 mg per L. An egg contains 1 mg, and liver contains about 8 mg per 100 g. Beef and pork contain about 0.3 to 0.6 mg per 100 g; vegetables and fruits contain less vitamin. Microflora may produce some vitamin, although this has not been clearly demonstrated in humans. Some vitamin is lost during the heating and processing of foods.

Assessment

Urinary excretion correlates with intake, and excretion of more than 1.0 mg per day is probably normal. No good method exists to determine body stores of pantothenic acid.

Physiology

Pantothenate is available in the intestine from the diet and from bacteria. It is transported in the small and large intestine by the SMVT system shared with biotin and lipoate (177). Pantothenic acid is the "backbone" of CoA, which is needed to activate acetate for its many functions in the synthesis of fatty acids, cholesterol, and sterols and in acetylation reactions. In addition, it is a key participant in the formation of citric acid, which enters the Krebs cycle. The rate limiting step in CoA synthesis is pantothenate kinase, and is controlled by the end-products of the pathway (185). This is the enzyme that when mutated causes a neurodegenerative disease.

Deficiency

Because of the wide availability of pantothenate in foods, a syndrome of spontaneous human deficiency is not clearly recognized. Experimental deficiency induced by an antagonist, ω-methylpantothenic acid, leads to tenderness of the heels and feet, fatigue, paresthesias, weakness, sleep disturbances, irascibility, and leg cramps. The "burning feet" syndrome seen in malnourished persons responds to pantothenic acid and may represent a specific deficiency. The disease formerly known as Hallervorden-Spatz syndrome and now known as neurodegeneration with brain iron accumulation (NBIA) is due to mutations in the PANK2 gene, one of 4 genes encoding pantothenate kinase (186). Thus, it is clear that severe pantothenate deficiency can cause disease in humans.

Treatment

If deficiency is suspected, it is treated by the oral administration of 10 mg per day. The vitamin has been used to treat paralytic ileus, with 50 to 100 mg per day given parenterally. No evidence for its effectiveness has been noted. Tablets of 25 and 500 mg are available as calcium pantothenate. Pantothenic acid has been studied for its effects on hypercholesterolemia, exercise performance, and arthritis, but data are too fragmentary for any conclusions to be made (22). The vitamin is marketed as an "antistress" treatment, but no evidence supports this claim.

Toxicity

Daily administration of as little as 10 to 20 mg of the calcium salt has been reported to produce diarrhea. Ordinarily, larger doses are required before this complication is seen. As a result, no UL has been established.

Coenzyme Q

Requirement

Coenzyme Q is a fat-soluble, vitamin-like quinone, known otherwise as ubiquinone and vitamin Q_{10}. It is associated with a number of deficiency syndromes in humans, and so it is included in the vitamin section, even though it can be synthesized de novo by mammalian cells. No exogenous requirement is known for coenzyme Q.

Food Sources

Coenzyme Q_{10} was isolated first from beef mitochondria, and is found in all tissues, but more concentrated in those with high energy turnover, such as heart, brain, liver, muscle, and kidney (187). Humans get about 3 to 5 mg per day from the diet in addition to their endogenous synthesis (188).

Assessment

Heparinized blood must be collected on ice and frozen until analyzed by high-performance liquid chromatography (189). Total coenzyme Q is the sum of ubiquinone and ubiquinol. Reference mean values (95% CI) for adults are 1.04 μmol per L (0.5–1.77 μmol per L), and for older children 0.88 μmol per L (0.37–1.54 μmol per L). Because coenzyme Q is carried on lipoproteins, concentration is referenced to LDL. For adults total CoQ/LDL is 0.33 (0.17–0.53); for older children it is 0.37 μmol per μmol (0.21–0.58). Levels tend to decrease after the age of 40.

Physiology

Coenzyme Q is a vital factor in transfer of electrons in the mitochondrial respiratory chain, the final product of which is ATP. Coenzyme Q increases ATP levels, prevents lipid peroxidation, and stabilizes calcium channels to prevent calcium overload (187). Levels appear to decrease as congestive heart failure (CHF) worsens in animals and in humans. Coenzyme Q_{10} supplements have protected animals from perfusion-reperfusion injury.

Deficiency

Deficiency of coenzyme Q (CoQ_{10}) was established by recognition of a rare autosomal recessive disorder with 5 major phenotypes: an encephalomyopathic form (exercise intolerance, myopathy, myoglobinuria, seizures, ataxia); a multisystem infantile form (encephalopathy, cardiomyopathy, ataxia, optic nerve atrophy, deafness, nephritic syndrome); a cerebellar form (ataxia, cerebellar atrophy); Leigh syndrome (growth retardation, ataxia, deafness); and isolated myopathy (190,191).

A state of relative deficiency of coenzyme Q has been proposed for a number of conditions. One randomized controlled trial of 1,200 mg per day showed less functional decline in patients with Parkinson disease (187,188). Some mitochondrial encephalomyopathies tend to respond but maximum effect can take 6 months or more, blurring the relationship between dosing and improvement (192). A number of randomized controlled trials found several parameters of CHF improved, but the data are not clearly supportive. The Agency for Healthcare Research and Quality (AHRQ) report of studies with >60 participants followed for 6 months concluded that the value of coenzyme Q supplements is still unresolved (www.ahrq.gov/clinic/epcsums/antioxsum.htm). One placebo controlled study using 3 × 100 mg per day for 3 months showed an effect on prevention of migraine (193).

Treatment

Most commercial sources of coenzyme Q are produced in Japan from fermentation of yeast strains. They are available in many forms, but absorption is erratic, and maximum serum concentrations are not reached for several weeks (188). One form, UbiQGel, was granted orphan status by the FDA for treatment of mitochondrial cytopathies. Doses range from 150 mg per day up to 3,000 mg per day after titration. Claims for treatment of CHF for coenzyme Q10 have been allowed in Japan for 3 decades. Doses for CHF have usually been 50 to 200 mg per day. Doses available range usually from 100 to 300 mg per soft gel, which is the usual form. A full list of brands is available at www.consumerlab.org/results/CoQ10.asp (187).

Toxicity

Despite one report of warfarin interaction, that issue has not been confirmed. Several studies showed coenzyme Q10 depletion following statin treatment, particularly at higher doses. Depletion tends to occur more in the elderly and those with heart failure (patients possibly with lower pretreatment levels), and the laboratory evidence of depletion can be prevented by supplementation with doses up to 200 to 300 mg per day (194). The American College of Cardiology feels that the value of coenzyme Q10 supplements with statin use has not been established, and that more studies are needed (195).

FAT-SOLUBLE VITAMINS

The functions, symptoms of deficiency, and common food sources of the fat-soluble vitamins are summarized in Table 6-2.

Vitamin A

Requirement

Dietary Reference Intakes. The estimated average requirement on which the current RDAs are based is intended to ensure adequate stores of vitamin A (196). The term *vitamin A* refers to retinoids with the biologic activity of retinol, and also includes retinal, the aldehyde, and retinoic acid. The infant AI is derived from the average retinol content of human milk (485 μg per L). If 780 mL of milk is ingested, breast-feeding supplies about 385 μg of retinol. Because of the large body stores in the liver and the lack of functional criteria for vitamin A status in infants, a precise daily requirement for infants is not known. The allowance for adults is based on many experimental nutritional studies and amounts to 900 μg of retinol per day for men and 700 μg for women. The allowance for children and adolescents is extrapolated to fall between the values for infants and those for adults. The allowance is increased only slightly in pregnancy, based on the small fetal hepatic content. The increase during lactation is based on the vitamin A content of milk.

The determination of dietary vitamin A is complex, and the determination of β-carotene is even more so. Dietary provitamins (of which carotene is the major one) are used much less efficiently than retinol or its esters. No reproducible biologic activities in humans are available to use in establishing the AI. Epidemiologic studies show a correlation between low (but within normal range) serum levels and a variety of chronic diseases, but intervention trials have not produced positive results (197). In addition, some carotenoids (e.g., lutein and zeaxanthin) are preferentially accumulated in the retina and other ocular tissues (198), whereas others lack provitamin A activity but exhibit other biologic activities (e.g., lycopene) (199). Although many observational studies suggest that higher blood levels of β-carotenes and other active carotenoids are associated with a lower risk for several chronic diseases, evidence is not currently convincing that a certain percentage of dietary vitamin A must be derived from provitamin A carotenoids as part of the RDA for vitamin A. However, recommendations to increase the consumption of fruits and vegetables rich in carotenoids for their health-promoting benefits are supported strongly by the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (4). The DRIs for vitamin A are included in Table 6-30.

Retinol Equivalents. Most often, vitamin A activity in foods is expressed in international units; 1 IU is the equivalent of 0.3 μg of all-*trans*-retinol or of 0.6 μg of β-carotene. Since 1969, the RDAs have been expressed as retinol equivalents (REs). This change was considered desirable because of the poorer utilization of dietary provitamins in comparison with retinol. The Committee currently uses retinol activity equivalents (RAEs) to measure dietary provitamin A carotenoids, mainly β-carotene, α-carotene, and β-cryptoxanthin (196). The RAE values of these nutrients have been set at 12, 24, and 24 μg, respectively. The RAE has been estimated as one half the vitamin A activity in comparison with the RE. This change in equivalence was made because of the observation that β-carotene activity in oil is twice that of dietary β-carotene. As a result of the change, more darkly colored, carotene-rich fruits and vegetables are needed to meet the vitamin A requirement; the change also means that vitamin A intake was overestimated in the past. When the RAE is used, approximately 26% and 34% of vitamin A consumed by men and women, respectively, is derived from provitamin A carotenoids. Ripe or cooked colored fruits and yellow tubers contain more readily converted carotenoids than do equal weights of dark green, leafy vegetables. By the 2001 definition:

1 REA = 1 μg of all-*trans*-retinol
= 12 μg of all-*trans*-β-carotene
= 24 μg of other provitamin A carotenoids
= 10.8 IU of activity from β-carotene

TABLE 6-30. Recommended Daily Dietary Intakes of Vitamin A

Life stage group	Vitamin A (μg/day)	Life stage group	Vitamin A (μg/day)
Infants[a]		**Females**	
0–6 months	400	9–13 years	600
7–12 months	500	14–18 years	700
		19–>70 years	700
Children			
1–3 years	300	**Pregnancy**	
4–8 years	400	14–18 years	750
		19–50 years	770
Males			
9–13 years	600	**Lactation**	
14–18 years	900	14–18 years	1200
19–>70 years	900	19–50 years	1300

[a] Estimate based on adequate intake (AI). All others based on recommended daily allowance (RDA). Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington, DC: National Academies Press, 2001.

The previously accepted 6:1 equivalence of β-carotene to vitamin A has been questioned, also because of the inefficient bioconversion of plant carotenoids (200). Until 10 years ago, the provitamin A content of foods was measured by extinction at 450 nm of a nonpolar organic extract. However, this measurement included carotenoids with no vitamin A activity. Food content is now measured with HPLC, which correctly identifies the provitamin A content. The equivalence from the older measurements may vary from 1:2 in orange fruits to 1:26 in green plants. β-Carotene in red palm oil has an equivalence of 1:2 to 1:3. Thus, with vegetarian diets and in areas where intake from animal sources is poor, a conversion of 21 μg of β-carotene per microgram of retinol has been proposed, which reduces retinol intake to well below the RDA (107). In many regions in Africa, South America, and Asia, supplementation with preformed vitamin A should be considered.

Food Sources

Synthesis is limited to plants and microorganisms. Median daily intake in the United States is about 624 RE. Vitamin A as retinyl esters is found only in animal foods, whereas provitamin or vitamin A precursors are found in the vegetable kingdom. Knowledge of the content of retinol or β-carotene in many foods is incomplete. Grains and flours are not sources of vitamin A unless egg, milk, or fruit is added to baked goods. More than 600 carotenoids are found in food among the 5 to 10,000 bioactive plant compounds, only about 50 of which have provitamin A activity and 40 of which are part of the usual diet in the United States. Only about 20 carotenoids are found in human blood and tissues, the most abundant of which (in the United States) are β-carotene, lycopene, α-carotene, lutein, and zeaxanthin. Table 6-31 lists the vitamin A content and RE values of selected foods. Enriched foods account for much of the vitamin A intake, including ready to eat cereals (0.7–2.5 mg per 100 g), instant powdered breakfast foods (3–6 mg per 100 g), and margarines (0.8 mg per 100 g) (201). Liver content varies from 4 to 20 mg per 100 g, and carotenoids in carrots, sweet potatoes, pumpkin, kale, spinach, collards, and squash contain ~5 to 10 RE per 100 g. Losses of vitamin A during cooking are small. Many food lists are still given in IUs. When IUs are given for vegetable sources, the total must be divided by 6 to estimate the REs because of poor absorption and conversion to retinol. The Committee on Dietary Allowances of the Food and Nutrition Board recommends that food tables list retinol and provitamin carotenoids separately so that the total REs (μg) can be calculated.

In many countries, including the United States, dairy products and margarines are supplemented with retinyl esters, which are the main dietary source (202). Factors that affect bioavailability include fiber intake (203), cholesterol-lowering drugs (204), and fat-free

TABLE 6-31. Approximate Vitamin A Content of Selected Foods

Food	Portion	RE		Percentage of RDI (1,000 RE)
		As retinol	As pro-vitamins	
Grains				
Corn bread	1 muffin	16	16	1–5
Wheat bread	1 slice	0	0	0
Meats				
Salmon	3 oz	43		1–5
Liver, beef	3 oz	9,119		>100
Chicken, roasted	1 cup	22		1–5
Shrimp	1 oz	6		>1
Tuna, fresh broiled	3 oz	642		>40
Tuna, canned, water	4 oz	62		5–12
Fruits and vegetables				
Apple	2.75 in		7	1–5
Orange	2.6 in		27	<1
Strawberries	1 cup		5	>40
Cantaloupe	1 cup		516	>40
Watermelon	1 cup		59	5–12
Green beans, fresh	1 cup		83	5–12
Spinach, cooked, fresh	1 cup		1,750	>100
Corn, cooked, fresh	1/2 cup		18	1–5
Potatoes, white	8.75 in		0	0
Potatoes, sweet	1 each		2,450	>100
Carrots, cooked	1/2 cup		1,292	>100
Tomatoes	1 each		139	10–24
Dried apricots	16 halves		676	>40
Dried prunes	7 halves		187	10–24
Dairy				
Milk				
Whole	1 cup	76		5–12
Skim, enriched	1 cup	149		10–24
Eggs, large	1 each	97		5–12
Butter	1 tbs	106		5–12
Ice cream	1 cup	133		10–24

RE, retinol equivalents; RDI, recommended dietary intake.
Data from Hands ES. *Food finder,* 2nd ed. Salem, OR: ESHA Research, 1990.

foods. Human milk contains 400 to 600 RE per L. A linear decline in levels is seen during the first 6 weeks after childbirth. Esters (85% of the total) are split by milk lipase, which is activated by bile salts (205). Richer sources among animal foods are liver and enriched dairy products. Many factors affect the absorption of vitamin A and carotenoids, and therefore, their bioavailability. These factors are generally more significant for carotenoids. In general, pigmented vegetables and fruits, especially the yellow ones, contain large amounts of β-carotene. Dried fruits are concentrated sources. Table 6-32 provides an estimate of carotenoid sources in foods.

Assessment

Intake or Absorption. Carotene is not stored in the body. Thus, persons with only preformed vitamin A in their diet will have vitamin A in their serum without carotene. The intake of both carotene and vitamin A is reflected in the serum levels. Total and individual carotenoids are easily determined by HPLC methods; when this test is performed, it is important to determine whether carotene has been ingested recently. When intake is persistently

TABLE 6-32. Relative Content of Carotenoids in Food Sources

Food	β-Carotene	α-Carotene	Lutein/zeaxanthin	Lycopene
Apricots	4+	—	—	1+
Beet greens	1+	tr	—	—
Broccoli, cooked	1+	—	1+	—
Carrot, cooked	3+	2+	—	—
Corn	tr	—	—	1+
Mango	1+	tr	—	—
Spinach, raw	2+	—	3+	—
Tomato juice, canned	1+	—	—	1+

1+, 8–25 mg/3.5 oz; 2+, 25–60 mg/3.5 oz; 3+, 60–110 mg/3.5 oz; 4+, >110 mg/3.5 oz; tr, trace. Adapted from Sauberlich HE. *Laboratory tests for the assessment of nutritional status,* 2nd ed. Boca Raton, FL: CRC Press, 1999. Other good sources of β-carotene include red palm oil, herbs and greens, peaches, sweet potatoes, pumpkin, squash, and tomato ketchup; of α-carotene, pumpkin and banana; of lutein, beets, egg yolk, and kiwi fruit of zeazanthin, egg yolk and potato; and of lycopene, watermelon.

low, the serum vitamin A level falls. This result reflects both low intake and marginal body stores. With continued low intake, serum levels fall further and more accurately reflect decreased body stores. Low carotene levels are meaningful only if carotene is being ingested in the diet. Furthermore, low levels do not distinguish low intake from poor absorption. Therefore, spot vitamin A and carotene levels by themselves are poor screening tests for malabsorption.

Body Stores. The stellate (Ito) cells contain stores of vitamin A as esters, which are hydrolyzed and taken up by hepatocytes or parenchymal cells when needed. These stores turn over at a rate of 0.5% per day in adults. The storage efficiency of dietary vitamin A is about 50% in the repleted state. The liver produces retinol-binding protein, which is secreted into the serum and metabolized by the kidney. Serum/plasma retinol concentrations, serum retinol-binding protein levels, and the relative dose–response assay are used to assess vitamin A status (17).

Retinol. Retinol can be measured by fluorometric, spectrophotometric, or HPLC methods, and retinol measurement is the most commonly used method to determine vitamin A status. The WHO recommends HPLC methods for population surveys. The vitamin is stable in serum or plasma for up to 2 years. Breast milk retinol has been proposed as a good population measure of vitamin A status, as the samples do not have to be processed in the field (206). However, the secretion of vitamin A in chylomicrons is not highly regulated, and thus milk concentrations of vitamin A reflect the mother's current vitamin A status. Serum vitamin A levels reflect body stores, but only when the level is very low is the interpretation clear (Table 6-33). Serum vitamin A levels increase somewhat with age but usually do not exceed 65 μg per dL. Samples should be obtained in the fasting state to avoid the fluctuations that follow meals. Retinol levels can decline with fever, physical exercise, and prolonged exposure to the sun. Occasionally, the serum level of vitamin A may be normal in the face of depleted hepatic stores. This situation may be seen in alcoholic liver disease—either fatty liver or alcoholic hepatitis. The therapeutic implications of such a discrepancy are not clear because an adequate serum level would imply adequate tissue delivery.

Low levels of vitamin A can be unrelated to decreased intake or absorption, as in chronic infection and liver disease. In severe liver disease, the vitamin A level falls because retinol-binding protein is not produced. However, carotene is not converted to vitamin A, and carotene levels tend to rise. The serum retinol concentration usually decreases transiently

TABLE 6-33. Guidelines in Interpreting Serum Vitamin A and Carotene Levels

Interpretation	Vitamin A		Carotene	
	(μg/dL)	(μmol/L)	(μg/dL)	(μmol/L)
Normal	>20	>0.7	>40	>1.4
Normal, not ingesting vegetables	>20	>0.7	<40	<1.4
Low intake, marginal stores	10–19	0.35–0.66	20–39	0.7–1.34
Deficient stores	<10	<0.35	Variable	
Severe liver disease	<20	<0.7	>40	>1.4
Excess vitamin A ingestion	>65	>2.28	>40	>1.4
Excess carotene ingestion (also, hypothyroidism, hyperlipidemia, anorexia nervosa, hypercholesterolemia of diabetes)	>20	>0.7	>300	>10.5

Adapted from Sauberlich HE. *Laboratory tests for the assessment of nutritional status,* 2nd ed. Boca Raton, FL: CRC Press, 1999.

because of a diminished release of retinol-binding protein during an acute-phase response to trauma or inflammation (207).

This finding complicates the use of serum retinol as an indicator of vitamin A stores. It is unclear whether the fall in serum retinol occurs only in patients who have a marginally sufficient vitamin A status and whether they require therapy. Levels of vitamin A can be elevated (>100 μg per dL) in patients on hemodialysis because of impaired conversion of retinol to retinoic acid in the kidney. Elevated carotene levels with low vitamin A levels are sometimes seen in anorexia nervosa. Pregnancy and the use of oral contraceptives raise vitamin A levels by increasing serum retinol-binding protein. Because retinol-binding protein is catabolized in kidney, vitamin A levels rise in renal disease.

Retinol-binding protein and transthyretin (prealbumin). Retinol-binding protein circulates as a 1:1 molar complex; filtration and loss from the kidney are prevented by prealbumin. The normal concentrations in plasma are 40 to 50 μg per mL (1.9–2.4 μmol per L) for retinol-binding protein and 200 to 300 μg per mL for prealbumin. Radial immunodiffusion assay kits are commercially available. Retinol and retinol-binding protein levels are lowered in diabetes, zinc deficiency, and protein–calorie malnutrition, and in response to trauma and infection. Levels of both parameters are elevated in women taking oral contraceptive pills. Liver disease lowers the levels of retinol-binding protein and transthyretin, whereas renal disease raises them. In these situations, the serum levels of vitamin A do not correlate with body stores.

Relative dose–response assay. This test is based on the fact that when vitamin A stores are low, aporetinol-binding protein accumulates in the liver (206). Thus, the test measures the changes in retinol concentration in serum following the administration of a small oral dose (450 to 1,000 μg) of retinol. An increase of more than 20% implies low hepatic stores of retinol. Because the test depends on hepatic synthesis of the binding protein, a false-negative result can be obtained in the presence of liver disease, protein malnutrition, infection, inflammation, or trauma.

Functional assays. The conjunctival impression cytology assay provides an early measure of histologic ocular changes. Examination for night blindness also can be sensitive in establishing vitamin A deficiency (208). The clinical demonstration of night blindness also provides evidence of inadequate body stores. Impaired dark adaptation is an early sign of vitamin A deficiency in patients with cirrhosis. However, this finding is not specific, resulting also from zinc and protein deficiency.

Physiology

Absorption. Vitamin A is usually ingested as the ester or as carotene and is hydrolyzed by pancreatic retinol ester hydrolase and brush border phospholipase B before absorption[201]. Pancreatic retinol ester hydrolase does not require bile salts as a cofactor for activity. The retinol transporter has not yet been identified. Carotenes in food are bound to macromolecules and are more poorly absorbed than either dietary or synthetic vitamin A. Factors that influence vitamin A or carotenoid release from food and its inclusion in lipid droplets in the intestinal lumen include heating (increased), ingestion of lipid-rich foods (increased), and lipid malabsorption or ingestion of lipid drugs or additives (decreased). Such compounds include mineral oil, cholestyramine (which causes fat malabsorption), and olestra. In addition, some carotenoids are more lipophilic (carotenes, lycopene) than others (lutein, zeaxanthin), affecting their relative rates of absorption. Lycopene is absorbed more slowly in cigarette smokers.

Metabolism of Retinol and Carotene. Inside the enterocyte, retinol is converted back to a retinyl ester by the action of acyl CoA:retinol acyltransferase or lecithin CoA:retinol acyltransferase and is incorporated into chylomicrons (209). Carotene is either hydrolyzed in the enterocyte to two retinol molecules or absorbed intact. In the former case, it is handled like dietary retinol; in the latter, it is transported intact in the lymphatics. About 10% of the carotene cleaved in the gut is converted to retinoic acid, a metabolite that supports cell growth but does not function in the visual cycle or in reproduction. Most absorbed retinol arrives at the liver in chylomicron remnants, and uptake is mediated by LDL receptors on hepatocytes. Retinol is released bound to retinol-binding protein and taken up by stellate (Ito) cells. The retinyl esters are stored in lipid droplets in Ito cells in the liver (~80% of liver content) or are converted to retinol for transport to the tissues. Absorbed carotene is also converted to retinol in the liver. A small percentage (~10%) of hepatic retinol is converted to retinoic acid via the aldehyde retinal.

Enterohepatic Circulation of Retinoic Acid. Retinoic acid is conjugated with glucuronide and excreted in the bile to be reabsorbed by the intestine via the portal vein. This enterohepatic circulation retains retinoic acid, which is not helpful for visual functions. The concentration of vitamin A metabolites in bile is low when liver stores are low, but the excretion rate increases proportionally as hepatic reserves enlarge (210). However, in malabsorptive states, those metabolites are lost from the body. Because body stores of retinol are converted in part to retinoic acid, this loss can lead to a further depletion of the body pool of retinol, but the significance of the loss is unknown. In vitamin A deficiency, little of the incoming vitamin is deposited in the liver but is delivered to depleted tissues.

Function of Retinol. Retinol maintains normal epithelia by aiding in glycoprotein synthesis. It (but not retinoic acid) also forms an essential part of the visual cycle and is required for normal reproductive function. Vitamin A is felt to play a role in cell growth. It suppresses malignant transformation of cell lines, prevents chemical induction of some animal tumors in vivo, and has been reported to induce regression of basal cell carcinomas. Vitamin A plays a major role in cell differentiation and morphogenesis. Thus, it is important in reproduction, bone development, skin integrity, and immunity. Retinoic acid, transported to the nucleus, interacts with one or more retinoic acid receptors, which are members of the superfamily of secosteroid receptors. The effect of retinoic acid is not limited to embryonic tissues, but the precise mechanism by which it mediates differentiation is not known.

Function of Carotenoids. Carotenoids mediate many functions, including antioxidation, intercellular communication, immune response, neoplastic transformation, and modification of detoxifying enzymes (211). These effects can be mediated by the parent carotenoid or by retinoid metabolites and are influenced by other carotenoids and metabolic products. Thus, it is not possible to estimate the overall effect of carotenoids in humans, and no reproducible effect has been identified other than their provitamin A activity.

The evidence that carotenes are antioxidants is crucial to their use in nondeficiency states, but in fact, it is not clear that they are general antioxidants. They are good scavengers

of singlet oxygen, but they are neither generalized reducing agents (like vitamin C) nor universal antioxidants (like vitamin E). β-Carotene differs greatly in potency from system to system in comparison with vitamin E (211). Moreover, its antioxidant properties are unpredictable in humans. Although β-carotene has been approved as an antioxidant in foods and supplements, the FDA has noted that no direct scientific evidence exists for such activity in humans and has based its decision to allow the antioxidant label on the antioxidant properties of β-carotene demonstrated *in vitro*.

Deficiency

The only unequivocal clinical signs of deficiency in humans occur in the eye. These changes have been classified in five stages, listed in order of increasing severity:

X0—Effect on the retina: poor dark adaptation.
X1—Effect on the conjunctiva: xerosis (dryness) detected by dullness of the conjunctiva in bright light; frequent presence of Bitot spots, an accumulation of foamy white debris and fatty material near the limits of the eye, especially laterally.
X2—Effect on the cornea: xerosis along with superficial erosion.
X3—Effect on the cornea: irreversible corneal ulceration.
X4—Effect on the cornea: scarring and softening.

In the United States, only night blindness is usually encountered, most frequently in chronic alcoholics. Persons with malabsorptive states are the other major group at risk for vitamin A deficiency. When zinc deficiency is also present, the effect on visual adaptation may be magnified.

Therapy

When vitamin A is used for therapy, it is provided entirely in the form of retinol, and its biologic potency is expressed in IUs. In this use, therefore, 1 IU and 1 RE are identical. Because of continued frequent use, the doses are listed here in IUs.

Deficiency. Deficiency states respond to daily doses of vitamin A from 5,000 to 30,000 IU. The higher doses should be used when severe malabsorption is the cause of the deficiency. A dose of 5,000 IU three times weekly has been effective in treating vitamin A deficiency in extremely low-birth-weight infants, and in slightly decreasing the risk for lung disease (212). Loading doses of vitamin A supplements recommended for patients with severe malnutrition (on day 1), measles (days 1 and 2), and xerophthalmia (days 1, 2, and 14) are the following: young infants (0 to 5 months) 50,000 IU, older infants (6 to 11 months) 100,000 IU, and children (>12 months) 200,000 IU (213). These schedules are also recommended by the WHO as single doses for prevention of disease in high-risk populations. Vitamin A is available in liquid form (5,000 IU per 0.1 mL); an emulsifier solubilizes the vitamin but probably does not enhance absorption when bile acids are deficient in the intestinal lumen. The vitamin is also available as capsules of 5,000 to 50,000 IU and in injectable forms (50,000 IU per mL).

Therapeutic doses of vitamin A are available as retinol, whereas the RDA of 5,000 IU (1,000 μg RE) per day assumes an intake that is half retinol and half β-carotene. Thus, 5,000 IU of retinol, the "standard" replacement dose, is in fact excessive. This is one of the reasons why vitamin A toxicity develops in some persons when it is taken in large doses.

Vitamin A Derivatives. 13-*cis*-Retinoic acid and eretrinate, an aromatic analogue, have been used to treat severe acne, rosacea, fulminant psoriasis, and Darier disease. Eretrinate has been reported to decrease bronchial metaplasia in heavy smokers, but serum levels of vitamin A are normal in patients with cancer. All-*trans*-retinoic acid (ATRA) is effective in the treatment of acute promyelocytic leukemia by causing blast cells to differentiate (214). ATRA combined with anthracycline-based chemotherapy achieves a 90–95% response rate, and 5-year survival approaches 75%. However, no other differentiating agents have been useful in other forms of leukemias.

Prevention of Chronic Disease. Because of their antioxidant properties *in vitro*, carotenoids have been implicated in many chronic diseases often linked with vitamins E and C, the other vitamin antioxidants (22,197,211). This topic is also discussed under Vitamin E (see the section in this chapter), and in Chapter 15.

Epidemiologic studies showed an inverse association between intake of total vitamin A (retinol plus carotenes) and the risk of certain cancers (197). Moreover, laboratory studies in animals showed that β-carotene was protective against cancers and was antiproliferative in cell culture studies. The World Cancer Research Fund evaluation in 1997 by a panel of experts concluded that carotenoid intake was indeed effective against lung cancer. However, more recent reviews, especially that of the National Research Council's Dietary Reference Intake Panel on Antioxidants concluded that the data were insufficient to make a recommendation regarding the relationship of any carotenoid to any chronic disease, including lung and prostate cancer, and age-related macular degeneration (196). A review of carotenoid intake and lung cancer in seven cohort studies in North America and Europe reached the same conclusion that there was no evidence for an association (215). No relationship was found between intake of β-carotene and cancers of the gastrointestinal tract, even when combined with vitamin A, C, or E (216). Greater intake of fruit and vegetables appears protective against chronic cardiovascular disease, but there are no convincing data implicating individual components of these foods. None of the main dietary carotenoids (lycopene, β-carotene, α-carotene, β-cryptoxanthin, lutein, and zeaxanthin have been found to have consistent associations as risk factors for cardiovascular disease (217).

Prevention of Infection. Vitamin A has been used to treat children severely ill with measles (218) and at doses of 8,333 IU per day to prevent mortality from infection in children less than 3 years old in areas where deficiency is endemic (219). Current evidence suggests that two doses of vitamin A reduced mortality and pneumonia-specific mortality in children under the age of two years, but no benefit was found when a single dose was used (218).

Toxicity

Amount of Intake. Because vitamin A is readily stored in the body, toxic levels can accumulate if intake is excessive. At levels of daily intake above 4,000 IU per kg (especially >500,000 IU per d), toxic symptoms can develop (220). These levels can easily be achieved by the use of supplements that offer the vitamin in capsules of 50,000 IU. Unfortunately, these higher doses of vitamin A can be obtained without a prescription. Toxicity is correlated with serum levels >1,000 μg per dL, with intake of 18,000 IU per day for 1 to 3 months in infants less than 6 months old, and with intake of 1 million IU for 3 days, 50,000 IU per day for more than 18 months, or 500,000 IU per day for 2 months in adults. UL values have been set for adults at 3,000 μg of retinol per day (~10,000 IU) (196) (Appendix B).

Manifestations. In children with acute hypervitaminosis A (>10 times the RDA), vomiting and bulging fontanelles are noted. In older children, growth failure, pseudotumor cerebri, sixth nerve paresis, and optic atrophy develop. At all ages, nonspecific findings such as irritability, skin dryness, desquamation of the skin over the palms and soles, myalgia, arthralgia, abdominal pain, and hypoplastic anemia may be present. Hepatosplenomegaly also occurs. In chronic hypervitaminosis, cortical thickening of bones of the hands and feet develops, with tenderness and weakness. Premature closure of the epiphyses has been observed.

In adults, early symptoms of overdose include nausea, vomiting, anorexia, malaise, cracking of skin and lips, headache, and irritability. Long-term use of vitamin A by the elderly can lead to increased plasma levels of retinol and biochemical evidence of liver damage (17). Hepatic fibrosis has been associated with excessive ingestion of vitamin A in a few cases. In adults receiving 50,000 to 100,000 IU per day, nausea, vomiting, skin desquamation, fatigue, hair loss, bone pain, and hepatomegaly can occur (221). One case-control study has shown that a high intake of dietary retinol is associated with an increased risk for osteoporosis (222).

Teratogenicity. Doses of 15,000 IU per day ingested between days 14 and 40 of gestation can cause microcephaly, dilated ventricles, and aqueduct stenosis. Spontaneous abortions have been reported with isotretinoin. Microphthalmos and atresia of the external auditory meatus have been reported. The risk of a malformation in the newborn was 1 in 57 for mothers who ingested more than 10,000 IU of preformed vitamin A as a supplement

during pregnancy (223). However, mothers ingesting supplemental vitamin A in current multivitamin preparations (up to 6,000 IU per day) were not found to be at increased risk for delivering infants with birth defects. Thus, it is probably safe for mothers to ingest an amount of vitamin A not in excess of the RDA (800 RE, or 2,640 IU of vitamin A as retinol). Because folate supplementation, needed to prevent neural tube defects, is most readily available in multivitamin preparations, it is important that mothers not shun both supplements for fear of excessive vitamin A ingestion.

Retinoic Acid Syndrome. Retinoic acid syndrome is the main adverse event resulting from tretinoin therapy for promyelocytic leukemia. It is characterized by elevated and rising leukocyte counts, weight gain, respiratory distress, serous effusions, and cardiac and renal failure (224). The average time of onset is 7 to 12 days, but it can begin after 1 day of treatment. It can be reversed or controlled with dexamethasone.

Osteoporosis. Four large prospective observational studies have been reported from the United States and Scandinavia, regions with a high prevalence of osteoporosis (220). These studies found an association between preformed vitamin A intake and hip fracture or osteoporosis, with doses as low as 1,500 RE per day, much lower than the tolerable upper intake level of 3,000 RE. These reports do contradict earlier studies. The UK-based Expert Group on Vitamins and Minerals concluded that the effect is a graded one and for that reason did not establish a safe upper level for intake (www.food.gov.uk/multimedia/pdfs/vitamin2003.pdf).

Vitamin D

Requirement

Types of Vitamin D. Vitamin D_2 is produced during ultraviolet (UV) irradiation of ergosterol, a plant sterol. Vitamin D_3, cholecalciferol, is formed from 7-dehydrocholesterol in the skin by the action of UV light. About 100 IU is produced per day from endogenous sources in persons living in temperate zones. The maximum amount of previtamin converted to vitamin D_3 is increased by an elevated skin temperature and is limited to 15% to 20% daily regardless of the amount of light. This limitation is a consequence of photoisomerization to other compounds. 7-Dehydrocholesterol in membranes after sunlight is converted to the 5,6-*cis*,*cis* (cZc) conformer of previtamin D_3 that is rapidly converted to vitamin D_3, and cannot rotate to the more stable 5,6-trans,cis (tZc) form (225). Other photoproducts include lumisterol, tachysterol, suprasterols, and toxisterols. Thus, the skin cannot generate toxic levels of D_3 after sunlight. Sunscreens (protection 15) can reduce production of D_3 by >95%. If tanning occurs, then vitamin D is being produced. When melanin is abundant in skin, 10 to 50 times more sunlight is needed to equal the amounts of vitamin D produced in skin without melanin pigment. Because more than 90% of circulating 25-hydroxycholecalciferol (25-hydroxyvitamin D_3) in the plasma is derived from vitamin D_3 and thus is endogenously produced, the daily requirement has not been established. Moreover, intake becomes important in persons with normal absorption only when exposure to sunlight is limited. Estimated allowances were previously given in IUs but now are usually expressed as micrograms of cholecalciferol (10 μg of cholecalciferol = 400 IU of vitamin D).

Dietary Reference Intake. Vitamin D in a dose of 2.5 μg (100 IU) prevents rickets, but 10 μg (400 IU) was recommended previously as the RDA for growing children. This recommendation represented in part the underdeveloped 25-hydroxylase activity in the liver of newborns. After the age of 24 years, 5 μg (200 IU) was considered adequate. After a careful review of the literature in 1997, the Institute of Medicine concluded that it is not possible to determine an RDA for vitamin D, but suggested an AI of 5 μg for infants, older children, and young adults (2) (Table 6-34). This AI recommendation was based on the literature and assumed some exposure to sunlight. In some elderly patients (>70 years), calcium intake and exposure to the sun may be decreased, and they may convert less of the dietary previtamin to the active form and produce less active metabolites of vitamin D in response to calcium depletion. Vitamin D deficiency is more prevalent in persons over the age of 50 than in younger adults. Thus, the recommended AI of vitamin D for adults older

TABLE 6-34. Dietary Reference Intakes of Vitamin D[a]

Life stage group	Vitamin D (μg/day)	Life stage group	Vitamin D (μg/day)
Infants/children		**Females**	
0–8 years	5	9–50 years	5
		51–70 years	10
Males		>70 years	15
9–50 years	5		
51–70 years	10	**Pregnancy/lactation**	
>70 years	15	≤18–50 years	5

[a] All values based on adequate intake (AI).
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride.* Washington DC: National Academies Press, 1997.

than 50 years is now set at twice that of younger adults, and for adults older than 70 years, it is three times greater (15 μg or 600 IU per day). A UL for infants 0 to 12 months of age has been set at 25 μg per day (1,000 IU), and for older children and adults it has been set at 50 μg per day (2,000 IU).

Some estimates of vitamin D requirements in the absence of the skin supply exceed 15 μg per day, so that concern has been expressed that the current recommendation is not high enough for patients not exposed to sunlight (226). Moreover, oral vitamin D is inactivated by the liver, unlike that supplied by skin, which makes vitamin D supplements more problematic in patients with chronic liver disease. The DRI of 5 μg is considered adequate for all healthy children and adults exposed to some sunlight, but at least 15 μg should be supplied daily to people not exposed to sunlight.

Many experts feel that the recommendations of the Institute of Medicine are too low, in part because the standard method of defining a "normal" distribution of 25-hydroxyvitamin D levels is not sufficient, and in part because the use of biomarkers has confirmed that normal bone function requires higher circulating vitamin levels (227). Factors that need to be considered include race, lifestyle habits, sunscreen usage, age, latitude, calcium absorption, bone mineral density, and parathyroid hormone levels. By using all these factors the levels of 25-hydroxyvitamin D that must be maintained to avoid deficiency have been estimated at ,≤80 nmol per L or 32 μg per L (227). To reach these levels in otherwise healthy subjects without exposure to sunlight requires 1,000 IU per day (225). At this level of 25-hydroxyvitamin D, the serum PTH level is lowered into the normal range. Even in those countries that require vitamin D fortification, vitamin D intake is still too low, due to low milk consumption, vegetarian diets, no use of supplements, or lack of sufficient exposure to sunlight (228). African Americans are especially at risk for developing vitamin D deficiency. Elderly persons (>65 years old) have a fourfold decreased capacity to produce cutaneous vitamin D, and are less responsive to the hormonal effects of 1,25 di-hydroxyvitamin D_3 (229). The efficiency of calcium absorption increases at 25-hydroxyvitamin D concentrations up to 80 to 90 ng per mL, providing further reason to provide more vitamin D to elderly patients, and to estimate a level.

One concern raised by the Food and Nutrition Board in setting DRIs was not to exceed the tolerable upper intake level (UL), set at 2,000 IU (50 μg) per day. The exposure to vitamin D should be judged by the amount that an adult can make by full skin exposure to summer light, estimated at up to 250 μg per day (230). Recent evaluations deriving the "no observed adverse event level" (NOAEL) from the European Commission (www.europa.eu.int/comm/food/fs/sc/scf/out157_en.pdf) and the UK's Expert Group on Vitamins and Minerals (230) have set the NOAEL at 25 μg (1,000 IU) per day, and the UL at 50 μg per day, respectively. Some experts still feel that these ULs are not sufficient to allow supplementation of the elderly and those not exposed to sunlight in order to maintain 25-hydroxyvitamin D levels >30 μg per mL. This is certainly the view of the

Vitamin D Council, a tax-exempt nonprofit group. Their newsletter provides information, both published and unpublished (www.vitamindcouncil.com). The newsletter is supportive of changing the DRI and the UL for vitamin D, and its board consists of many of the leading vitamin D scientists. The positions advocated by the Council, and based on vitamin D needs in the absence of sunlight, are not yet universally accepted, but many other experts now advocate that 1,000 IU per day may not be enough to maintain 25-hydroxyvitamin D levels >25 mg per mL when the need is increased, e.g., during pregnancy and lactation (231). The desire to increase these recommendations is linked to the association between vitamin D deficiency and a variety of chronic diseases, including cancer and cardiovascular disease (225).

Food Sources

Endogenous production is the most important source. The usual dietary intake in the United States is 1.25 to 1.75 μg per d (U.S. Department of Agriculture, *National Food Consumption Survey,* 1977–1978). The major natural food sources are fatty fish (e.g., mackerel, salmon), fish liver and oils, egg yolk, and beef liver. Fortified foods now provide the major dietary source. Milk and breakfast cereals are the major fortified foods in the United States, whereas in Canada milk and margarine are fortified (232). Fortification occurs in countries in Northern Europe as well, but the level of fortification is under evaluation, as 25-hydroxyvitamin D levels are low during the long winters above the 51.9° latitude (Ireland, Denmark, Finland) (233). In countries without staple food fortification, vitamin D levels are too low (234).

The reason for the high vitamin D content of fish liver is not apparent. It has been speculated that fish liver contains a nonphotochemical system for making vitamin D, but no real evidence for such a system has been found. Table 6-35 lists the major dietary sources of vitamin D. The content in cow's milk varies with the seasons from 4 IU per quart in winter to 40 IU per quart in summer, unless supplements are added. The mean concentration of vitamin D in human milk is 0.5 μg per L and is proportional to maternal intake. This is well below the level needed to prevent rickets, yet rickets occurs only when milk is not given and sunshine is not provided. Thus, vitamin D in milk may be more biologically available than that from other dietary sources.

In NHANES III (1988–1994), 5% to 7% of men more than 20 years of age had 25-hydroxyvitamin D serum concentrations of 15 ng per mL or less, whereas 12% to 15% of women had these levels (235). However, almost no adults had a vitamin level above 50 ng per mL. Thus, relatively older persons in the United States have a marginal vitamin D status and are at risk for complications related to vitamin D deficiency. In fact, postmenopausal women presenting with hip fractures have evidence of vitamin D insufficiency

TABLE 6-35. Foods Sources of Vitamin D

Food	Portion	Vitamin D content (IU)
Milk, whole or non-fat	1 cup	100
Butter	1 tsp	1.4
Cheese, cottage	1 cup	5
Egg yolk	1 each	23
Egg white	1 each	0
Cereals (e.g., corn flakes, raisin bran)	1 cup	40–50
Beef liver	3 oz	11.9
Oysters, raw	4 each	2.9
Canned sardines	1 oz	85
Canned salmon	1 oz	142
Lunch meats	1 piece	8–12
Margarine	1 tsp	15–20
Cod liver	1 tsp	400

Data from Hands ES. *Food finder,* 2nd ed. Salem, OR: ESHA Research, 1990.

(lower 25-hydroxyvitamin D levels) in comparison with women undergoing elective hip replacement (236).

Assessment

Assessment of vitamin D status may include measurement of serum 25-hydroxyvitamin D (body stores), serum 1,25-dihydroxyvitamin D (renal metabolism), or serum levels of total and ionized calcium, inorganic phosphate, and alkaline phosphatase (late-stage tissue damage) (17).

25-Hydroxyvitamin D (25OHD). The 25-hydroxyvitamin D level is low when body stores, intake, or endogenous production is low, and measurement of this level is a satisfactory (but not sensitive) method for assessing deficiency of the vitamin D body pool. The available methods include HPLC, competitive protein binding, and radioimmunoassay. HPLC methods are good for determining both vitamin D metabolites in a single serum sample. Commercial radioimmunoassay kits are also available that are equally sensitive and practical, but they measure only one metabolite at a time. The cutoff values for vitamin D deficiency based on Gaussian distribution of population levels are below 30 nmol per L (Table 6-36). Competitive protein binding assays give values that are 20% to 30% higher than for RIA (237). When measurements for 25-hydroxyvitamin D were compared using either RIA, HPLC, or chemiluminescent protein binding assays, the variability of results produced problems with making the diagnosis of vitamin D deficiency, even when the same method was used (238).

Because assay variation confounds the diagnosis of vitamin D deficiency, there is a great need for standardization (238), and concerns have been raised about the inability of some 25OHD assays to measure $25OHD_2$, when ergocalciferol is the supplement used. The international Vitamin D Quality Assessment Scheme (DEQAS) has been established since 1989 (www.deqas.org), and there are now >100 participating laboratories in 18 countries (239). This group has compared values for $25OHD_2$ obtained from the DiaSorin RIA, the IDS RIA, the IDS EIA, the competitive protein-binding assay, HPLC, and the Nichols automated chemiluminescence assay. Most commercial methods were found to give results close to the standard value, but results were highly operator dependent. Moreover the Nichols method consistently produces higher values than the other methods. In the United States many commercial supplements have converted to the use of the $25OHD_3$ form, making this source of variation somewhat less critical.

More than 90% of plasma 25-hydroxyvitamin D is derived from cholecalciferol produced by the skin. However, the production of this vitamin is not closely regulated—levels rise or fall as its precursor is made available. The mitochondrial 25-hydroxylase is not regulated by vitamin D, unlike the microsomal enzyme, which is regulated by its substrate.

TABLE 6-36. Suggested Guidelines for Evaluating Vitamin D Status

Test	Deficient	Low	Acceptable	High
25-Hydroxyvitamin D				
(nmol/L)	≤12	<25	≥30	>200
(ng/mL)	≤4.8	<10	≥12	>80
1,25-Dihydroxyvitamin D				
(pmolL)			48–100	
(pg/mL)			20–42	
24-hour urinary calcium (mg/kg)	**<2**		**>2**	
Bone density (SD from mean)	**>2.5**	**>2**	**1–1.5**	

Data derived in part from Sauberlich HE. *Laboratory tests for the assessment of nutritional status,* 2nd ed. Boca Raton, FL: CRC Press, 1999. Estimates by some experts, based on the vitamin D level necessary to prevent secondary hyperparathyroidism, put the acceptable range as >80 nmol/L or >32 ng/mL (227).

Concentration in plasma is 5 to 10 times greater than in other tissues, except for adipose tissue. 25-hydroxyvitamin D in plasma is bound to a protein that binds all metabolites and is less than 5% saturated. Finally, the plasma half-life of 25-hydroxyvitamin D is long (24 hours). Thus, the level reflects recent intake or exposure to sunlight, so that the sensitivity of this measurement in the assessment of vitamin D deficiency is limited.

The binding capacity of the plasma for excess 25-hydroxyvitamin D is very great, and levels rise as intake increases. Moreover, levels remain elevated for some time. Therefore, 25-hydroxyvitamin D levels reflect vitamin D intake or production only in a general way but do correlate with body stores until they become depleted. Levels of 25-hydroxyvitamin D are low in states of dietary deficiency, decreased absorption, deficiency of UV light, prematurity, and severe liver disease, and when drugs are ingested that alter its metabolism (e.g., anticonvulsants). Levels are low when plasma binding-capacity is decreased. Levels are high in growing children, conditions associated with hyperparathyroidism, sarcoidosis, and certain forms of idiopathic hypercalciuria (240). Factors other than intake affect plasma levels of 25-hydroxyvitamin D. The amount of UV irradiation reaching the skin is dependent upon the intensity of sunlight, thickness of the ozone layer, and pigmentation of the skin. Thus, the 25-hydroxyvitamin D levels rise in summer and fall in winter. Pregnancy, ovulation, and the use of oral contraceptives increase the plasma level of vitamin D-binding protein. Because this protein is normally unsaturated, the capacity of the plasma to retain vitamin D metabolites is increased, not necessarily the steady-state levels of the metabolites. Despite these confounding factors, the 25-hydroxyvitamin D concentration is the best available test for determining vitamin D status. The level is almost always low when deficiency is present. The 25-hydroxyvitamin D level is an accurate parameter of vitamin D intoxication (levels above 150 ng per mL or 375 nmol per L) because the level rises progressively as intake is increased.

1,25-Dihydroxyvitamin D_3. The production of this vitamin is regulated, but not by vitamin D stores unless they are extremely low. The metabolite is assayed by HPLC or by radioimmunoassay with use of a nuclear receptor. The normal concentration of 20 to 42 pg per mL (48 to 100 pmol per L) cannot be increased by feeding 1,25-dihydroxyvitamin D_3. Normal ranges differ with the age and calcium intake of the population studied. Fluctuations occur during the ovulation cycle and also diurnally. Levels are higher during periods of growth and decline during growth retardation. The serum concentration responds to calcium and phosphate levels and is part of the endocrine system of vitamin D metabolism. The production rate and concentration of this vitamin are altered rapidly and inversely by high (3 g per day) and low (0.5 g per day) intakes of phosphorus (241). The plasma half-life is 4 to 6 hours, hence the rapid functional changes. The level of this form of vitamin D correlates with certain functions of vitamin D but not with intake, absorption, or body stores until deficiency is apparent. Values of 25-hydroxyvitamin D_3 fall in the winter and are lower in patients over 60 years of age.

Various conditions are associated with abnormal values. 1,25-Dihydroxyvitamin D_3 levels are low in profound vitamin D deficiency, and in chronic renal disease (if serum phosphorus levels are high and renal enzyme activity is decreased despite elevated parathyroid hormone levels), hypoparathyroidism, vitamin D-resistant rickets type I, and osteolytic states not related to parathyroid hormone (cancer, hyperthyroidism, and possibly osteoporosis of the elderly). However, 1,25-dihydroxyvitamin D_3 levels do not always reflect total body stores. In primary biliary cirrhosis, this metabolite is not excreted in bile, so that synthesis is decreased and plasma levels are normal, yet malabsorption of vitamin D and osteopenia develop (242). Primary hyperparathyroidism, vitamin D-resistant rickets type II, and pregnancy are conditions in which 1,25-dihydroxyvitamin D_3 levels are elevated. In hypervitaminosis D, the 25-hydroxyvitamin D_3 level is markedly elevated, but the 1,25-dihydroxyvitamin D_3 level is altered only slightly.

Twenty-Four-Hour Urinary Calcium Excretion. Because of problems with the interpretation or availability of vitamin D metabolite levels, the state of vitamin D repletion is often assessed by functional measurements. This is best accomplished in patients with a normal intestine by measuring the 24-hour urinary calcium excretion as an estimate of calcium absorption. At steady state, urinary calcium excretion equals net intestinal absorption. If no intestinal disease is present and the serum parathyroid hormone level is normal,

calcium absorption depends in large part on the active vitamin D metabolites. Patients should be kept on a constant calcium intake of 800 to 1,200 mg per day for 4 to 5 days before a 24-hour urine sample is collected. Normal urinary calcium levels range from 100 to 300 mg (about 2 to 4 mg per kg of body weight).

Serum Alkaline Phosphatase. Serum alkaline phosphatase levels become elevated in osteomalacia secondary to vitamin D deficiency. However, the increase develops late in deficiency states, and elevations of phosphatase occur for a large number of other reasons. Thus, the usefulness of this test is limited. It is clear that the value of serum calcium, phosphate, and alkaline phosphatase are not reliable in detecting vitamin D deficiency, even when 25OHD levels were sufficiently low to elicit a response of elevated PTH levels (243).

Bone Densitometry. Single-photon absorptiometry of the forearm and os calcis is rapid (15 minutes) and relatively inexpensive. However, in patients under the age of 60 years, it does not assess risk for vertebral fracture. Computed tomography and dual-photon absorptiometry of the spine are better predictors of vertebral fracture (see section on assessment of calcium deficiency in Chapter 7). For patients at risk for vitamin D deficiency, these screening tests are very useful. Their role in screening postmenopausal women for osteoporosis is much less clear. 25-Hydroxyvitamin D_3 levels vary directly with vertebral bone density in some studies of postmenopausal women (244). Thus, vitamin D deficiency may be more common than appreciated in this group of patients.

Functional Indicators of Vitamin D Sufficiency. There is a need for reliable functional endpoints to establish an estimated average requirement (EAR) (245). This is because of the many reasons why normally distributed $25OHD_3$ levels in healthy subjects do not provide enough correlation with function, as noted above. Table 6-37 outlines the potential candidates that are being evaluated as functional indicators for vitamin D sufficiency. These indicators might have importance not only for population estimates but also for demonstration in patients of the functional status of vitamin D, a concept that has proven difficult to document.

Physiology

Calcium and Phosphate Absorption. Calcium and phosphate absorption is increased by 1,25-dihydroxyvitamin D_3 to maintain blood levels of calcium and phosphorus (246,247). Bone mineralization results because the plasma is supersaturated with both minerals. In addition, the vitamin mobilizes calcium (and phosphate) from bone and increases the renal reabsorption of calcium. A decline in calcium concentration leads to reduction of calcium binding to the calcium-sensing G-protein coupled transporter system found in the parathyroid gland (248). All these effects result in increased serum levels of calcium and phosphate and normal mineralization. Evidence for an independent effect of the vitamin

TABLE 6-37. Potential Candidates as Functional Indicators for Vitamin D Sufficiency

Indicator	Vitamin D effect on function	Measure of insufficiency
PTH	Active transport of calcium	↑PTH, ↓ with vitamin D
Ca++ absorption	Optimizes absorption	% of calcium absorption
Fracture risk	↓ serum PTH, bone turnover	↑ fracture risk vs. control
Muscle strength	↑active PO4 transport, ↓ PTH	Muscle strength tests
Bone turnover	↓ turnover and serum PTH	↑bone resorption, ↓ turnover
Immunoregulatory	Maturation of antigen presentation	↑T cell proliferation, ↓ killer cells
Cell proliferation	↓ proliferation	More cells in G1 vs. G2
Metabolic	β-cell function, GTT	Glucose clearance rates

Adapted from Whiting SJ, Calvo MS. Dietary recommendations for vitamin D: a critical need for functional end points to establish an estimated average requirement. *J Nutr* 2005;135:304.

(especially 25-hydroxyvitamin D) on bone mineralization is limited. 1,25-Dihydroxyvitamin D produced in the kidney under regulation by PTH plays an important role in mobilizing calcium from bone to maintain serum calcium and phosphorus levels within a normal range. PTH also binds to receptors on the osteoblast, stimulating increased bone turnover and calcium/phosphorus mobilization (249). Both PTH and 1,25-dihydroxyvitamin D_3 enhance distal tubular calcium reabsorption, retaining most of the 7 g of calcium filtered each day.

Other Functions. Vitamin D improves muscle function and corrects decreased phosphate concentrations in muscle in deficiency states. Some vitamin D metabolites, especially 25-hydroxyvitamin D, may have a direct effect on bone to improve calcium deposition. Insertion of a 24-hydroxyl group into 1,25-Dihydroxyvitamin D reduces the affinity of the vitamin for the nuclear vitamin D receptor and thus its classic activity. Other hydroxylations (C23 and C26) may lead to various selective activities on growth and differentiation via effects on the nuclear receptor.

Vitamin D has been implicated in many general cellular functions, such as cell proliferation and myocardial function. 1,25 dihydroxyvitamin D_3 downregulates hyperproliferative cell growth (225). Cancer cells have 1-hydroxylase activity, and low exposure to sunlight is associated with increased mortality from breast cancer. Vitamin D also induces 24-hydroxylase activity, which acts on 1,25-Dihydroxyvitamin D_3 to form the inert metabolite calcitroic acid.

1,25-Dihydroxyvitamin D_3 is produced from the 1-hydroxylated intermediate (made in the liver) by action of 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1), an enzyme that is present in many extra-renal sites (250). These sites include osteoblasts, colonocytes and other epithelial cells, macrophages, synovial cells, keratinocytes, pancreatic islets, and vascular endothelial cells. In these extra-renal sites regulation is not tightly linked to 1,25-dihydroxyvitamin D_3 levels as it is in the kidney. Thus, the possibility exists for intracellular deficiency of the active 1,25-dihyroxyvitamin D_3, predisposing to multiple chronic diseases. Thus, patients with chronic renal or cardiac disease, cancer, diabetes, musculoskeletal disorders, or infectious, inflammatory, or autoimmune diseases in theory could be relatively deficient in vitamin D. See the section on vitamin D deficiency below for possible functions of vitamin D in specific disorders.

Metabolism. Vitamin D from the skin is bound to a plasma-binding protein, so that its uptake by the liver is limited. Dietary vitamin D is absorbed by incorporation into mixed micelles and enters very-low-density lipoproteins or chylomicrons, which are taken up by the liver. Thus, hepatic uptake is not limited by the plasma binding-protein, and toxic levels of metabolites can be reached after oral ingestion. The liver adds a 25-hydroxyl group, whereas the kidney adds hydroxyl groups at positions 1 and 24. Adipose tissue is the major storage site of vitamin D metabolites. Both 1,25-dihydroxyvitamin D_3 and other polar metabolites of vitamin D are excreted in bile and participate in an enterohepatic circulation, although the quantitative importance of this in humans is not clear. In deficiency of either calcium or phosphorus, the formation of 1,25-dihydroxyvitamin D_3 is increased. Parathyroid hormone, calcitonin, estrogens, prolactin, and growth hormone enhance the formation of active dihydroxyvitamin D. Many of these factors also regulate (reciprocally) the formation of 1,25-dihydroxyvitamin D_3, but some other metabolites are also functional. The production of 24,25-dihydroxyvitamin D_3 in the kidney is not closely regulated. The biologic importance of this metabolite is not established, but it may alleviate bone disease in uremic patients.

Deficiency

Several syndromes result from vitamin D deficiency, all related to decreased body stores of calcium or phosphorus.

Rickets. Rickets, the major deficiency syndrome, is caused by poor bone mineralization. The newborn infant is at high risk because the vitamin D content of unfortified milk (<1 μg per L) is low and 25-hydroxylase activity in the liver is not fully developed. The incidence seems to be increasing in children, most of whom do not ingest the recommended intake of vitamin D. Reasons for increased incidence in children in North America include dark pigmented skin, little exposure to sunlight, limited vitamin D supplementation, and breast

feeding as the only source of nutrition (237). A minimum of 200 IU of vitamin D per day has been recommended throughout childhood and adolescence to prevent rickets.

In rickets, or childhood osteomalacia, the calcification of newly formed bone and epiphyseal cartilage is decreased. Decreased amounts of calcium are deposited in the collagen elaborated by cartilage cells. Wide osteoid seams are found most often in the long bones because they grow the fastest. Craniotabes, chest deformity, bending of long bones, enlarged epiphyses of long bones, greenstick fractures, swollen wrists, muscle weakness, seizures, tetany, inability to initiate walking, and decreased growth are all noted. Serum calcium levels may be normal or low. The tetany associated with vitamin D deficiency results from hypocalcemia. Muscle weakness is probably caused by a decrease in muscle phosphate.

Adult Osteomalacia. Vitamin D deficiency (defined as 25-hydroxyvitamin D levels <15 ng per mL (<37.5 nmol/) affected 42% of African American women and only 4.2% of white women aged 15 to 49 years, in the NHANES-3 database (251). In adults, the endochondral growth of long bones has ceased; consequently, decreased calcification of cartilage is not a factor. Osteoblast-mediated mineralization is affected by vitamin D deficiency, but changes occur over a longer period of time, and the clinical presentation is not as fulminant as in children. Subclinical bone disease occurs with normal blood calcium levels. By the time bone disease has become severe, hypocalcemia and hypophosphatemia are often present. Skeletal pain and muscle weakness occur anywhere in the body, but the long bones are less affected than are bones in the shoulders, hips, and spine. Adult osteomalacia is associated with aging, renal disease (lack of 1-α-hydroxylase), severe hepatic disease (decreased 25-hydroxylase activity), and intestinal resection and celiac disease (decreased absorption); it is also seen after gastric surgery (possibly because of decreased uptake), in IBD (multifactorial), pancreatic insufficiency/cystic fibrosis (malabsorption due to steatorrhea with calcium-fatty acid complex formation), and after use of anticonvulsant medication (which may cause inactive metabolites to form) (252). Vitamin D-resistant rickets is the cause of osteomalacia in a few patients. The contribution of an interrupted enterohepatic circulation to vitamin D deficiency in malabsorption is probably small. Fewer than one-third of highly polar metabolites are excreted in bile, and virtually no 25-hydroxyvitamin D_3. It has been suggested that a loss of bile salts alters the hepatic metabolism of vitamin D and leads to the rapid half-life of the vitamin in malabsorption. During chronic liver disease, vitamin D is malabsorbed, and these patients also may have decreased sunlight exposure and dietary intake. Moreover, production of 25-hydroxyvitamin D may be decreased when hepatic function is severely impaired in cirrhotic patients (253). Supplementation of 1,000 to 2,000 IU (25 to 50 μg) per day is recommended for such patients. Patients with Crohn disease are more likely to have low bone mineral density than those with ulcerative colitis (254). This finding is probably related to many factors, including malabsorption, chronic inflammation, smoking, and chronic steroid use.

Involutional Osteoporosis. This disorder is defined by a low bone mass. Although vitamin D and calcium are the primary nutrients involved, other vitamins (K, C, and B_6) also play a role in bone formation (255). Three etiologic categories of osteoporosis are recognized: early postmenopausal, late postmenopausal (after 70 years of age), and drug-induced. A decline in renal 1-α-hydroxylase activity with age may result in decreased calcium absorption and increased secretion of parathyroid hormone. Chronic vitamin D deficiency may be a factor in osteoporosis in elderly patients in nursing homes. In about 15% of elderly people, dietary intake is poor or outdoor activity is decreased. Vitamin D deficiency develops because of decreased skin production, decreased metabolism of vitamin D to the 1,25-dihydroxylated form, and decreased oral intake (256). Chronic abuse of alcohol is a frequently overlooked cause of osteoporosis in men (257). The cause(s) are probably multifactorial and include vitamin D deficiency. Chronic pancreatitis and small-bowel injury resulting from alcohol abuse may impair calcium and amino acid absorption. Elevated blood levels of cortisol and parathyroid hormone may contribute to bone destruction. Decreased intake of vitamin D, lack of sunlight, and altered vitamin D metabolism (in cirrhotics) are probably important. The hypomagnesemia seen in many alcoholics may play a role. Reversal of important factors in individual patients may retard the otherwise

progressive bone loss. Although some evidence has been found that short-term therapy with low-dose 1,25-dihydroxyvitamin D_3 relieves osteoporosis, improvement is not maintained. This result is consistent with the transient improvement seen in patients with osteoporosis after various forms of therapy.

Therapy

Deficiency. Oral vitamin D maintains vitamin D status less effectively than skin-derived vitamin D; with the latter, release is more constant and the rate of hepatic metabolism to less active isomers slower. Nevertheless, oral supplements are sometimes needed. Dietary deficiency still occurs, especially in hospitalized patients (258). Indications for supplementation include breast-feeding in infancy, fat malabsorption, advanced age, institutionalization (especially if the patient is not exposed to the sun), uremia, and long-term use of corticosteroids. Many forms of vitamin D are available. Some vitamin D products contain tartrazine, which may cause allergic reactions in susceptible persons.

Bone Health. When taken with calcium, vitamin D increases serum 25-hydroxyvitamin D levels, minimizes bone loss observed on bone density testing, and may reduce the incidence of fractures (22). Calcium absorption is only about one-third of normal (10% vs. 33%) when vitamin D is deficient (259). A meta-analysis of four randomized placebo-controlled trials demonstrated that intakes of vitamin D <800 IU per day (20 μg per day) have never been effective in decreasing the incidence of hip or nonvertebral fractures (260). Doses at or above that level produced approximately a 30% decrease in fractures. Another meta-analysis of seven randomized studies showed that vitamin D at doses of 700 to 800 IU per day (along with calcium varying from 500 to 1,200 mg per day) reduced hip and nonvertebral fractures in elderly patients, but that 400 IU was not effective (261). However, this meta-analysis did not contain the results of two trials that reported no benefit of high dose vitamin D_3 (800 IU per day) with calcium (1,000 mg per day) (262,263). A meta-analysis including these studies concluded that there was no effect of vitamin D alone in preventing fractures (264). The differences in these studies may reflect differences in baseline vitamin D insufficiency, differences in fracture rates or falls, or insufficient power, despite the large number of subjects in these studies. Higher 25-hydroxyvitamin D levels were associated with greater reduction in fracture rates (261).

Calcium (1 g) taken along with a lower dose of vitamin D (400 IU per day) resulted in a slight improvement in hip bone density but no change in fracture rate in women (265). However, the women were taking vitamin D supplements in both the placebo and treated groups, and serum 25-hydroxyvitamin D levels were the same in both groups, suggesting that the delivered vitamin D supplement level was >10 μg per day, blunting the possibility to see a difference in the two groups. Another randomized blinded study supports the role of 500 mg of calcium in addition to 200 IU of vitamin D in improving bone density in women over age 45 (266). Calcium (1 g per day) and vitamin D (12.5 μg per day) have prevented loss of bone mass in patients with rheumatoid arthritis and corticosteroid-induced osteoporosis (267). Vitamin D may also be effective when given in combination with other drugs that diminish bone loss (268). In summary, the question of the value of added calcium to vitamin D is still unresolved, but it seems reasonable to add calcium to a sufficient dose of vitamin D (probably 800 IU per day) in elderly patients, based on the available data.

Muscle Function and Falls. Concentrations of 25-hydroxyvitamin D are lower in elderly patients with less handgrip strength, those who had recently fallen, or those who could not climb stairs or participate in outdoor activity (269). Muscle cells express a vitamin D receptor, and the vitamin alters cellular metabolism via interaction with transcription factors and genes to alter calcium and phosphate uptake and cellular differentiation into mature muscle fibers. In addition, muscle cells in culture demonstrate rapid changes in calcium metabolism that cannot be explained by the slower effects on the genes.

Cancer. Epidemiologic studies are not consistent in finding an association between vitamin D and colon cancer risk (22). This may be because both calcium and the vitamin are needed, or because other vitamins and foods differ among the cohort groups. However, the majority of studies have found a protective effect of vitamin D sufficiency and a lower rate of cancer of many organs, including colon (20 of 30 studies), breast (9 of 13 studies),

prostate (13 of 26 studies), and ovary (5 of 7 studies) (270). A study of supplementation with 400 IU of vitamin D and 1,000 mg of calcium for an average of 7 years as part of the Women's Health Initiative found no effect on the incidence of colorectal cancer (271). It is difficult to conclude too much from this study, as the dose of vitamin D was low, and the study was part of three overlapping studies. Nonetheless, it does suggest that the usual doses of supplementation may not be enough to demonstrate an effect on colorectal cancer. It is sensible to maintain adequate levels of vitamin D in adults and in elderly patients without being able to recommend this policy for cancer prevention based on current evidence. The issue then becomes one of determining an "adequate" vitamin D level, whether the current DRI values (Table 6-36), or the higher ones currently suggested by many experts (225,272).

Chronic Nonmalignant Disease. The finding that higher levels of 25-hydroxyvitamin D are needed to suppress PTH levels has led experts to suggest that organs that respond to vitamin D (muscle, gut, kidney, bone, inflammatory cells) may be in a state of relative vitamin D deficiency, and that supplementation might help treat chronic diseases of those organs (273). The data are quite fragmentary at the present time, although the theory is attractive. In patients with end-stage renal disease (ESRD) supplementation with 1α-hydroxyvitamin D_3 (alfacalcidol) with a median dose of 0.5 μg showed a lower risk of cardiovascular death, but not other deaths (274). There are multiple suggestions that vitamin D status might alter immune responsiveness. Toll-like receptor (TLR) activation of human macrophages upregulates expression of the vitamin D receptor, and the 1-hydroxylase gene, inducing expression of the antimicrobial peptide cathelicidin and killing of intracellular *Mycobacterium tuberculosis* (275). TLRs play an important role in innate immunity, a defense mechanism implicated in a number of chronic inflammatory conditions.

A case control study of 40 patients with multiple sclerosis correlated lower serum 25-hydroxyvitamin D_3 levels with relapses of the disease (276). No controlled trials of supplementation have been undertaken to date. A link between vitamin D status and IBD has been suggested, based on animal and epidemiologic data (277). In a trial of men with CHF receiving 2,000 IU (50 μg) per day of vitamin D, no effect was found on survival or left ventricular function (278). However, serum concentrations of TNF α decreased, and levels of IL-10 increased, consistent with an effect on regulation of innate immune function.

Vitamin D Preparations. ***Cholecalciferol (Vitamin D_3).*** Cholecalciferol (Vitamin D_3) is the natural form of the mammalian vitamin. In the past it was not the major source available in supplements in the United States, but now it is the form routinely added to multivitamin and to vitamin D + calcium preparations. This is the most effective form of vitamin D to elevate the serum 25-hydroxyvitamin D_3 level (260,279), as it is about twice as efficient as ergocalciferol (vitamin D_2). The best source of cholecalciferol as a single ingredient is Bio Tech Pharmacal, Inc., an FDA approved source that makes capsules of 1,000, 5,000, and 50,000 IU (Table 6-38). Many health food stores sell capsules from other providers of 1,000 IU. Many more preparations can be expected to contain 1,000 or 2,000 IU of cholecalciferol as the publicity for increasing vitamin D intake increases. 2,000 IU per day will ensure that ~80% of Americans will achieve a vitamin D level of ~35 ng per mL or higher without toxicity (280). For breast-fed children, a safe and inexpensive preparation containing vitamin D is Tri-Vi-Sol. An appropriate mixture of preparations might be one multivitamin containing 400 IU of cholecalciferol and one vitamin D supplement containing 400 to 1,000 IU of cholecalciferol (225). Taking too many multivitamin tablets would lead to excessive vitamin A being ingested (5,000 IU of all-*trans*-retinol/tablet). Vitamin A antagonizes the actions of vitamin D in some way and the vitamin A content in one serving of liver (10,000 to 20,000 IU) can antagonize the rapid calcium response (nongene mediated) to vitamin D in humans (281). The fastest way to replete a patient with vitamin D deficiency and normal intestinal absorption is to give 50,000 IU of cholecalciferol once a week for up to 8 weeks, checking to ensure that the serum vitamin D level exceeds 35 ng per mL (225).

Vitamin D_2 (ergosterol, ergocalciferol). Vitamin D_2 is available in large doses of 600 or 1,200 μg (25,000 or 50,000 IU per capsule) for daily replacement. These large doses are used for patients with refractory rickets or malabsorption. Although an injectable form in sesame oil contains 500,000 IU per mL, its bioavailability is still questionable. In liquid form, ergosterol is available solubilized with polysorbate 80 or polyethylene glycol at a

TABLE 6-38. Available Forms of Vitamin D and its Metabolites

Compound name	Generic name	Commercial name	Daily dose (μg)
Activated 7-dehydrocholesterol cholecalciferol	Vitamin D		10–50
(5Z,7E,22E)-(3S)-9,10-ergosta-5,7,10(19),22-tetraen-3-ol	Ergocalciferol	Drisdol, Calciferol	5–25
10,19-dihydrotachysterol	Dihydrotachysterol	Hytakerol[b]	125–1,000
$1\alpha,25(OH)_2D_3$	Calcitriol	Rocaltrol[b]	0.5–1.0
$1\alpha,25(OH)_2D$	Calcitriol	Calcijex (IV)[b]	0.5 (IV)
$1\alpha(OH)D_2$	Doxercalciferol	Hectorol[b]	10, 3x/wk
$1\alpha(OH)D_3$	Alfacalcidol	One-alfa, Alpha-D_3[a]	0.25–1.0
$1\alpha,24(OH)_2$-19-nor-D_3	Paricalcitol	Zemplar[b]	2.8–7 qod
$1\alpha,24(OH)_2D_3$	Tacalcitol	Bonalfa[a,c+]	40–80 (topical)
$1\alpha,24S(OH)_2$-22-ene-24-cyclopropyl-D_3	Calcipotriene	Dovonex[c]	40–80 (topical)

[a] Available in Japan (Onealfa, Bonalfa), in Denmark (One-alfa), and Israel (Alpha-D_3), but not in the United States.
[b] Indicated for renal osteodystrophy, or for renal osteodystrophy with secondary hyperparathyriodism (Zemplar).
[c] Indicated for plaque psoariasis.

concentration of 200 μg (8,000 IU) per milliliter (Drisdol, Sanofi Winthrop Pharm; Calciferol, Schwarz Pharma). These preparations contain 200 IU (5 μg) per drop, if it is assumed that a milliliter contains 40 drops. The liquid form, which is adequate for most needs, provides the greatest flexibility.

Dihydrotachysterol. Dihydrotachysterol (DHT), a vitamin D_2 derivative that is active without 1-α-hydroxylation, is available in tablets or capsules of 0.125 mg, and in tablets of 0.2 or 0.4 mg and in oral solution (0.2 mg per mL). It is used to treat postoperative tetany; 1 mg is equivalent to 3 mg of vitamin D_2.

1,25-Dihydroxyvitamin D_3 (Calcitriol). 1,25-Dihydroxyvitamin D_3 (Calcitriol) is marketed as 0.25- and 0.5-μg tablets, in oral solution of 1 μg per mL, and in injectable (IV) form (1 or 2 μg per mL). The usual IV dosage is 0.01 to 0.05 μg per kg 3 times per week. This form is indicated for renal osteodystrophy with hypocalcemia. It is most often given to patients undergoing renal dialysis, for whom such frequent IV dosing is possible. This form of vitamin D does not alter serum levels of 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D, so repletion should be monitored by measurement of serum or 24-hour urinary calcium. Daily oral requirements are met by 0.5 to 1.0 μg per day, with indications for renal osteodystrophy, hyperparathyroidism and associated hypocalcemia, and postmenopausal osteoporosis.

No good information exists to estimate dose when malabsorption is present. To avoid toxicity, serum and urinary calcium levels should be followed, although toxicity is unlikely in the presence of malabsorption. Although 1,25-dihydroxyvitamin D_3 is more water-soluble than the parent compound and does not require incorporation into bile acid micelles for solubility, its advantages in the treatment of malabsorption have yet to be demonstrated, and it is more expensive. Its use should be confined mostly to patients who cannot form 1,25-dihydroxyvitamin D_3 (e.g., those with renal failure) when the aim is rapid reversal of hypocalcemia. It is often used to induce the mild hypercalcemia required to offset excess calcium secretion in renal failure. 1,25-Dihydroxyvitamin D_3 is degraded in the gut (282). Thus, the oral drug is not delivered to tissues as efficiently as the IV drug. Parenteral calcitriol is available for IV use. It is used to normalize plasma ionized calcium in some uremic patients. The recommended dose is 1 to 2 μg 2 to 3 times weekly in predialysis patients >3 years of age. Parenteral use suppresses parathyroid hormone levels more effectively than oral dosing. This formulation is not suitable for replacement of vitamin D in deficient patients.

25-Hydroxyvitamin D_3 (calcifediol, Calderol). 25-Hydroxyvitamin D_3 (calcifediol, Calderol) is no longer available, as the product has been discontinued by West Orange, Organon (NJ). The rationale for this decision was likely that maintenance of 25-hydroxyvitamin D levels is achieved as well by providing cholecalciferol that is now more regularly available.

Synthetic analogs. Other analogs (Table 6-38) have been synthesized primarily for the indication of renal osteodystrophy, as the active vitamin, 1,25-dihydroxyvitamin D_3 cannot be made by patients with this condition. Paricalcitol (Zemplar) decreases PTH in patients with ESRD, without an effect on serum calcium or phosphate levels (283,284). Moreover, the drug improved survival from cardiovascular and infectious causes of death. The rationale for improvement in cardiovascular disease, based on cell system and animal in vivo data, includes anti-inflammation, protection against blood vessel injury, inhibition of cardiac hypertrophy, and regulation of the renin-angiotensin system (285). Paricalcitol and doxercalciferol (Hectorol) are available in the United States. Other analogs (tacalcitol, alfacalcidol) are available only in Japan (Table 6-38). The value of these preparations over calcitriol is not clear, although they have been designed to produce less hypercalcemia.

Toxicity

Hypervitaminosis D occurs because the plasma binding capacity for 25-hydroxyvitamin D_3 is relatively unlimited. Although serum 1,25-dihydroxyvitamin D concentrations are regulated by calcium levels, 25-hydroxyvitamin D levels are not. Because 25-hydroxyvitamin D_3 itself has physiologic effects, albeit less potent than those of 1,25-dihydroxyvitamin D, hypercalcemia and hypercalciuria can ensue. Toxicity is caused by excessive oral ingestion rather than UV irradiation because skin production of the active vitamin is limited to 15% to 20% of the provitamin content per day. Total body sun exposure potentially provides up to the equivalent of 250 μg (10,000 IU) of vitamin D per day (286). A UL of 50 μg per day has been recommended for adults (3) (Appendix B).

Acute hypercalcemia causes nausea, anorexia, itching, polyuria, abdominal pain, constipation, bone pain, metallic taste, and dehydration. In chronic cases, nephrocalcinosis, metastatic calcification, renal failure, and kidney stones may develop. Weight loss, irritability, psychosis, pancreatitis, photophobia, hypertension, cardiac arrhythmias, and elevated levels of blood urea nitrogen, cholesterol, aspartate aminotransferase, and alanine aminotransferase have been reported. For treatment, prednisone, diuresis, and a low calcium diet may be required, along with withdrawal of vitamin D. Periodic measurement of 25-hydroxyvitamin D is essential, as levels below 140 nmol per L are not associated with adverse effects (286). The 24-hour urine calcium excretion provides a functional assay because it reflects excessive absorption of calcium. If this method is used to assess vitamin D toxicity, measurement should be frequent, perhaps monthly, during the initiation of therapy if malabsorption is not the cause of deficiency and should be repeated every 3 to 6 months for patients on long-term replacement. The product of serum calcium and phosphate (Ca × P) should not exceed 70 to prevent precipitation of calcium phosphate.

Vitamin E

Requirement

Chemical Forms. It is not possible to determine vitamin E requirements accurately for several reasons: (a) the vitamin is heterogeneous chemically; (b) the requirements depend on the intake of natural oxidants, such as polyunsaturated fatty acids (PUFAs) and selenium; and (c) evidence of vitamin E deficiency develops uncommonly (287). The term *vitamin E* refers to all tocopherols showing biologic activity of D-α-tocopherol. The natural vitamin E produced by plants includes at least 8 different forms (α, β, γ, and δ plus the corresponding tocotrienols). Tocopherols contain a phytyl tail with three places where they could be either L or R isomers. D-α-tocopherol is now called *RRR*-α-tocopherol to designate the orientation of the three chiral centers in the molecule (288). The synthetic form contains eight stereoisomers in equal amounts, and so is called *all-rac*-α-tocopherol acetate (all racemers). It is the form used in food fortification. In mixed diets, the non–α-tocopherols account for about 20% of the total activity, although they are less potent than α-tocopherol. γ-Tocopherol is the major form of vitamin E in the U.S. diet (289). It is a more effective trap for

lipophilic electrophiles than is the α isomer, but it is largely metabolized and does not accumulate. The γ form and its major metabolite inhibit cyclo-oxygenase activity.

One international unit of vitamin E equals 1 mg of DL-α-tocopherol acetate. The natural form of the vitamin, D-α-tocopherol, has a biopotency of 1.36 IU (acetate) and 1.21 IU (succinate). Commercial vitamin E is made from a mixture of many stereoisomeric synthetic forms of α-tocopherol acetate or succinate. The synthetic DL-α-tocopherol succinate has a potency of 1.49 IU. The requirement for vitamin E increases as PUFA intake increases, but dietary fats also contain vitamin E, so that dietary deficiency is unlikely. About 0.4 to 0.8 mg of vitamin is needed for each gram of PUFA, and possibly more than1.5 mg per g in diets containing high numbers of long-chain PUFAs. Variability in requirement can be related both to dietary PUFA intake and to tissue composition depending on prior dietary habits.

Dietary Reference Intake. The RDA was based previously on assumptions of a diet containing no more than 0.1 parts per million of selenium, average amounts of sulfur amino acids, 0.4 mg of vitamin E for each gram of PUFA, and less than 1.5% linoleic acid in 1,800 to 3,000 kcal. Current recommendations take into consideration the possible role of vitamin E as an antioxidant in preventing chronic disease and the increased intake of polyunsaturated fatty acids (PUFAs) in the U.S. diet, in addition to serum vitamin E concentrations from NHANES III. However, these levels were not corrected for serum lipid or cholesterol, which might exaggerate the prevalence of low vitamin E body stores. The new DRIs are set at levels about 50% higher than the RDAs of 1989 (Table 6-39). Cigarette smoke alters human vitamin E requirement by leading to faster formation of a major metabolite (290). The hepatic enzymes involved in this metabolism are not known.

Food Sources

Vitamin E is found in lipids of green leafy plants and in oils or seeds. Animal sources derive most of the vitamin from alfalfa, corn, and soybean foods. The richest sources for humans are salad oils, shortenings, and margarines, especially those derived from soybean, cottonseed, peanut, corn, and safflower oils, and wheat germ and nuts. Some of these oils contain more γ-tocopherol than α-tocopherol. Animal sources containing the highest amounts include eggs, liver, and muscle meats.

Vitamin E Content in Foods. Vitamin E content in foods (Table 6-40) is greatly affected by processing, storage, and preparation, especially if cooking in oil is followed by storage. Freezing does not prevent peroxide formation and the destruction of biologic activity. Many foods (e.g., milk) show a seasonal variation in vitamin E content, which is highest in summer. A 2,000- to 3,000-kcal diet in the United States contains 8 to 11 mg equivalents of tocopherol, just barely sufficient for the average adult. An extensive summary of the food content

TABLE 6-39. Dietary Reference Intakes for Vitamin E[a]

Life stage group	Vitamin E (mg/day)	Life stage group	Vitamin E (mg/day)
Infants[b]		**Adults (M/F)**	
0–6 months	4	9–13 years	11
7–12 months	6	14–>70 years	15
Children		**Pregnancy**	
1–3 years	6	≤18–50 years	15
4–8 years	7	**Lactation**	
		≤18–50 years	19

[a] Values refer to α-tocopherol forms occurring naturally, and to the synthetic isomers with comparable biologic activity that occur in fortified foods and supplements.
[b] Estimate based on adequate intake (AI). Other values based on recommended dietary allowance (RDA).
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for vitamin C, vitamin E, selenium, and beta-carotene and other carotenoids.* Washington, DC: National Academies Press, 2000.

TABLE 6-40. Approximate Vitamin E Content of Selected Foods

Food	α-Tocopherol (mg/100 g)	Non-α-tocopherol (mg/100 g)
Grains		
Bread		
White	0.1	0.13
Whole wheat	0.45	1.75
Oatmeal	2.27	1.7
Meat		
Bacon	0.53	0.06
Beef	0.3	0.3
Beef liver	0.6	1.0
Chicken	0.4	1
Pork chops, fried	0.16	0.44
Salmon	1.35	0.46
Shrimp	0.6	6
Vegetables		
Carrots	0.11	0.1
Celery	0.38	0.19
Onion	0.22	0.12
Peas		
Fresh	0.55	1.2
Frozen	0.23	0.4
Canned	0.02	0.02
Peanuts	7	5
Potatoes, French fried	0.3	1
Fruits		
Apple	0.31	0.2
Banana	0.22	0.2
Orange juice	0.04	0.16
Dairy		
Milk, whole	0.036	0.057
Butter	1	0
Margarine	13	48
Eggs	0.46	1
Fats		
Corn oil	12	53
Olive oil	4	—
Peanut oil	19	14
Safflower oil	34	7
Sesame oil	—	53
Soybean oil	10	85

of vitamin E has been published (291). Nuts are high in fat but are an excellent source of α-tocopherol, as well as monosaturated fatty acid, squalene, and phytosterols (292).

Ratio of Vitamin E to PUFAs. The ratio of vitamin E to PUFAs is lower in vegetable oils than in animal products, and the proportion of non–α-tocopherols is often much greater. Olive oil, however, contains much less vitamin E than other vegetable oils (293). Its ability to retard LDL oxidation is attributed to polyphenol compounds. Fish oils are higher in PUFAs but lower in vitamin E; fortunately, the vitamin is ubiquitous in foods. The tocopherol–linoleic acid ratio in milk is 0.79 mg per g, more than the 0.5 mg per g recommended for newborns. Tocopherol levels are higher in colostrum than in milk.

Intake. Median intake in the United States is less than the RDA, 7.3 and 5.4 mg per day in men and women, respectively (NHANES II), and only about half of the current DRI for adults over the age of 19 years. Data from NHANES 1999–2000 showed that the use of

vitamin E supplements ≥400 IU per day was common (294). Increased use of supplements is occurring more widely in the world, and both men and women appear to take vitamin E supplements (295). NHANES III data show that serum concentrations of vitamin E are below 20 μmol per L (low normal) in 20% of whites and 41% of African Americans (296). The vitamin E–PUFA ratio is more than 0.4 mg per g, which is acceptable. About 20% of intake is derived from fruits and vegetables and 20% from fats and oils. Fortunately, most foods high in vitamin E are also high in PUFAs.

Assessment

No measures are available that reflect recent intake because absorption is poor and the tocopherols are carried as part of the lipoprotein complex. Thus, all available assays correlate with body stores (Table 6-41).

Erythrocyte Hemolysis. Serum tocopherol levels and the erythrocyte hemolysis test correlate well, but the latter is a functional assay. It is based on the ability of hydrogen peroxide to liberate hemoglobin from red cells. In the absence of the natural antioxidant, vitamin E, the reaction proceeds more rapidly. Erythrocyte hemolysis above 10% or a serum α-tocopherol level below 0.5 mg per dL is often associated with vitamin E deficiency. The test result is affected by circulating PUFA levels and is positive only at very low serum levels of vitamin E. Unfortunately, it is not clear that this assay (or serum tocopherol itself) indicates α-tocopherol status in body tissues other than blood, especially the major storage pool in adipose tissue. Thus, the exact usefulness of this test has not yet been determined.

Serum Vitamin E. The vitamin E levels of infants and children are lower than those of adults, in fact below 0.5 μg per mL. Therefore, both serum α-tocopherol levels and the erythrocyte hemolysis test should be performed to see whether both suggest a deficiency state. Earlier methods for assessing vitamin E levels have been largely replaced by HPLC procedures (17). The levels are highly correlated with total lipid, and the ratio of vitamin E to total lipid is considered a better indicator of vitamin E stores. This is because vitamin E is carried in plasma exclusively on lipoproteins. Thus, in hypolipidemic states (e.g., malabsorption), vitamin E levels are characteristically low. Premature infants are at special risk for vitamin E deficiency because their levels fall after birth. The ratio of α-tocopherol to cholesterol is the one most conveniently obtained (297). All the samples must be taken in a fasting state, and total lipids can be the sum of triglyceride and cholesterol because the phospholipid concentrations are much lower.

Tissue Damage in Vitamin E Deficiency. End-organ damage is more common than once thought, but detection requires sophisticated techniques in some instances. Neurologic examination may disclose ataxia or peripheral neuropathy. Examination of the fundus may reveal retinal pigment degeneration, and examination of the visual fields can disclose central scotomata. The electroretinogram shows delayed and reduced potentials. Sensory evoked potentials are delayed in the lower limb.

TABLE 6-41. Guidelines for Interpreting Vitamin E Status

Test	Vitamin E status category		
	Deficient	Low	Acceptable
Plasma α-tocopherol			
μmol/L	<11.6	11.6–16.2	≥16.2
μg/ml	<5.0	5.0–7.0	≥7.0
Erythrocyte hemolysis (%)	>20	10–20	≤10
α-Tocopherol/lipid ratios			
Plasma α-tocopherol/total lipid (μg/mg)			$>0.8 \times 10^{-3}$
Plasma α-tocopherol/cholesterol (μg/mg)			$>2.22 \times 10^{-3}$
Serum/plasma α-tocopherol (μmol/L)			≥11.6

Adapted from Sauberlich HE. *Laboratory tests for the assessment of nutritional status,* 2nd ed. Boca Raton, FL: CRC Press, 1999.

Breath Ethane and Pentane. Ethane and pentane are generated though peroxidation of *n*-3 and *n*-6 fatty acids, respectively. Breath ethane has been used to evaluate vitamin E status in children, in whom it correlates negatively with vitamin E serum levels. This test may be useful to screen children and assess response to therapy (298). High doses of vitamin E decrease breath pentane in heavy smokers. A modification of the method uses purified air, which avoids the problem that ambient air contains considerable amounts of ethane (299). Breath pentane and ethane levels are also elevated in vitamin C deficiency, β-carotene deficiency, and low glutathione levels.

Physiology

Function. Vitamin E is localized in membranes and provides a defense against lipid peroxidation of PUFAs. Selenium in glutathione peroxidase is located in the cytosol and provides another defense system. Other antioxidant defense mechanisms include the enzymes catalase, glucose-6-phosphate dehydrogenase, and glutathione reductase; the plasma proteins ceruloplasmin and transferrin; sulfhydryl-containing amino acids; and zinc, copper, and riboflavin. Vitamin E protects the membranes of intracellular organelles from damage. If all the peroxide formed by superoxide dismutase is not destroyed, then singlet oxygen is formed in the presence of ferric ions. Vitamin E acts to destroy these peroxides, which promote peroxidation of LDL in the subendothelial space. Oxidized LDL in turn can induce cytokine production in endothelial cells, which leads to recruitment of macrophages, proliferation of smooth muscle, vasoconstriction, and platelet aggregation. Vitamin E delays these effects, providing a theoretical basis for a role in preventing cardiovascular disease (300).

Platelet adhesion is impaired by an antioxidant-independent action of vitamin E, although a daily dose of 400 IU is required to show an effect *in vivo*. Fewer platelet pseudopods are produced during vitamin E-induced inhibition of protein kinase C (301), which is likely to be the basis of the effect of the vitamin in ischemic damage and the rationale for conjoint therapy with inhibitors of platelet aggregation.

Absorption. Absorption requires biliary (bile salt micelles) and pancreatic (esterase) secretions. Less than 40% of an oral dose is absorbed, and this amount is decreased by excess unsaturated fatty acids in the lumen. The natural form ingested is D-α-tocopherol acetate, which must be hydrolyzed in the intestine by a bile salt-dependent pancreatic esterase. Only free α-tocopherol is found in the intestinal lymph. In serum, two-thirds of the vitamin is bound to and hydrolyzed on LDL, and the remnants are transferred to HDL (302). Some vitamin is transferred to extrahepatic tissues (adipose and muscle), with the rest taken up by the liver via three receptors, for LDL, for the LDL related protein, and by the scavenger receptor B type 1 (SR-B1). Absorption is inefficient; 70% absorption requires 6 to 7 hours. One study showed that vitamin E bioavailability was greater from fortified cereal than from encapsulated vitamin taken as a supplement (303). No carrier is specific for vitamin E; therefore, its serum level is proportional to the total lipid level. The percentage of vitamin E that is absorbed decreases at doses above 30 mg because the vitamin is passively absorbed. Most is deposited initially in liver as lipoprotein lipase acts on lipoproteins, and vitamin E is then distributed to adipose tissue. The α-tocopherol transfer protein in hepatic and cardiac cytosol transfers the vitamin to mitochondria, but the mechanism of transfer is not known (302). Plasma and tissue α-tocopherol are exchanged rapidly. Excess vitamin E is excreted in bile or metabolized by β- or ω-oxidation by P450-dependent hydroxylases. The vitamin is excreted largely in feces, where it is mostly degraded (304). It is not known whether an enterohepatic circulation exists or whether all fecal vitamin derives from oral sources. Less than 1% is excreted in urine.

Anti oxidant Theory. The theory that a relative deficiency of anti oxidant molecules (especially vitamins A/carotenoids, C, and E) is a factor in production of cancer and other chronic diseases (diabetes, cardiovascular, cataracts, etc.) has driven much of the use of vitamin supplements. Because vitamin E is the vitamin most often associated with this theory, the concept will be discussed here (see sections on vitamins A and C and Chapter 15 for other implications of this theory). The theory has been supported largely by experimental studies in animals, by cell culture data, and in humans by epidemiologic cohort and some longitudinal studies that have shown inverse correlations between chronic disease and vitamin intake and/or serum levels. The strongest evidence links specific foods (fruits, vegetables, whole

grains) to decreased risk of certain cancers (305). These results have led to the current dietary recommendations to prevent cancer (see Table 15-1).

Among the groups of fruits and vegetables found to be associated with a lower incidence of chronic diseases, the cruciferous (i.e., brassica) and green leafy vegetables have shown more effect than for specific nutrients such as antioxidants. The brassica group includes broccoli, cauliflower, kale, brussel sprouts, cabbage, and bok choi. In addition to showing a protective relationship against epithelial cancers in cross-sectional studies, the same protection has now been demonstrated for lymphoma (306). Perhaps one reason for the failure of individual antioxidants is that they might be the wrong component of cruciferous vegetables. Glucosinolates and glucarates are other components that show anticarcinogenic activity. These components activate "phase 1" and "phase 2" enzyme systems that degrade carcinogens and other toxins (307). Another finding that suggests that factors other than antioxidants might be active ingredients is that there is great variation in the antioxidant content of food products (308).

The addition of supplements has not confirmed the anti oxidant theory. There have been many reasons given for these negative results, including the use of monotherapy when multiple factors are involved, the time lag to develop chronic disease, the use of older adults as the populations for these studies, and the use of nutritionally repleted subjects. Nonetheless, it is possible that too much has been expected from the anti oxidant theory, and that vitamin supplementation on an individual patient level has little to recommend it other than ensuring adequate nutritional status, a worthwhile goal in itself. The anti oxidant theory has been questioned for lipoprotein oxidation in cardiovascular disease (309). That the relationship of anti-oxidant to chronic disease is still an unproven theory needs to be kept in mind when reviewing the data (see below) and deciding on intervention with supplements.

Deficiency

Persons at Risk. Persons at risk include newborns and premature infants, food faddists, and patients with fat malabsorption or biliary obstruction. Vitamin E crosses the placenta poorly, and adipose tissue stores are small in the fetus *in utero*. The antioxidant properties of the vitamin cannot explain all manifestations of the uncommon deficiency state. Moreover, in most cases, no symptoms have been noted that respond to vitamin E when serum α-tocopherol levels are low. Low serum concentrations of vitamin E, ranging from 0.5% to 24%, were found in a variety of populations, but these were not correlated with serum lipid content, and the significance in regard to risk for disease is uncertain (310).

Deficiency as Part of Medical Conditions. In some muscular dystrophies, the pathologic features are similar to those of experimental vitamin E deficiency in animals, but no relationship of human dystrophies to the vitamin is known. Hemolytic anemia can occur in the premature infant with low body stores, especially if supplementation with linoleic acid and iron is given. Edema, tachypnea, and restlessness are noted. In adult malabsorption syndromes, especially in association with biliary obstruction, α-tocopherol levels decline, and red cell hemolysis and creatinuria have been reported. When serum levels are very low, a ceroid pigment has been found in smooth and skeletal muscle. In short-bowel syndrome and abetalipoproteinemia, unsteady gait, tremor, weakness, ophthalmoplegia, pigmentary retinopathy, and proprioceptive impairment have been noted (19). It is rare for vitamin E deficiency to present as an isolated neuropathy. Patients with hereditary abetalipoproteinemia also can present with myopathy and cerebellar dysfunction. In cystic fibrosis, changes in posterior column axons and nuclei and sensory nuclei of the fifth cranial nerve in the medulla have been observed, but without clinical neurologic defects. A progressive neurologic syndrome associated with low serum vitamin E concentrations has been described in children with cholestatic liver disease. The syndrome includes areflexia, gait disturbance, decreased proprioceptive and vibratory sensation, and paresis of gaze (311). Lipofuscin pigment accumulates in neurons but has no obvious harmful effect.

Isolated Vitamin E Deficiency. A genetic defect in hepatic α-tocopherol transfer protein that prevents vitamin E from reaching tissues results in ataxia and peripheral neuropathy (312).

Cardiovascular Disease. Patients with these conditions have been noted to have serum levels of vitamin E lower than those of control groups. In nearly all such studies, the serum tocopherol levels were not corrected for lipid content. There are theoretical reasons for a

response to antioxidants, and many studies have examined the effect of supplemental vitamin E (sometimes given together with β-carotene). Table 6-42 lists some of the prospective, double-blinded, randomized studies that have been performed. The results are more negative than positive for heart disease, whether given alone or combined with β-carotene or other antioxidant vitamins (313,314). The American Heart Association consensus statement on vitamin E does not consider that vitamin E can yet be recommended for routine use (315). The Health Professionals Follow-up Study of Males showed no correlations between vitamin E, vitamin C, or β-carotene intake and the risk for stroke (316). The failure of vitamin E in these trials could be due to the fact that supplementation with α-tocopherol decreases serum levels of γ-tocopherol, a potent anti-inflammatory compound (317).

Cancer Prevention. The SU.VI.MAX study found a benefit in cancer incidence and mortality in men only, perhaps due to the low serum baseline levels of β-carotene, but vitamin E was combined with other antioxidant vitamins and minerals (318). The Linxian study in China found a decreased mortality from gastric cancer, but again multiple vitamins or minerals were provided (319). The ATBC study gave only vitamin E and showed no effect on cancer incidence, a finding confirmed by the HOPE-TOO trial (320). After controlling for smoking, no effect on the incidence of lung cancer was found in eight prospective studies using vitamins A, C, and E (321), or in 14 trials of antioxidant vitamin supplements for prevention of gastrointestinal cancer (216). Thus, there is very little evidence to support the role of supplemental α-tocopherol in cancer prevention.

Nonalcoholic Fatty Liver Disease (NAFLD). NAFLD covers a spectrum of disorders ranging from triglyceride accumulation in the liver to inflammation (steatohepatitis) with or without fibrosis or cirrhosis (322). Oxidative stress resulting from an imbalance between pro-oxidant and antoxidant systems is one of the theories for the pathogenesis of NAFLD. Treatment of NAFLD includes weight loss; improvement of insulin resistance (metformin, rosiglitazone, pioglitazone); use of cytoprotective agents such as ursodeoxycholic acid; lipid lowering agents (e.g., clofibrate); and antioxidants (e.g., vitamin E, betaine) (323). A few randomized, prospective trials of vitamin E have been carried out, one with 1,000 IU per day along with vitamin C (324), and one with 800 IU of vitamin E along with a weight-reducing diet and metformin (325). The study with E and C showed improvement in fibrosis but not inflammation scores. The trial with vitamin E alone showed less effect than the use of metformin. More studies will be needed to know whether vitamin E or other antioxidants are useful in patients (either ambulatory or in intensive care units) with NAFLD where mitochondrial dysfunction is felt to be more prevalent (326).

Other Conditions (Alzheimer Disease, Parkinson Disease, Tardive Dyskinesia, Cataract) (327). Because of its antioxidant properties, supplements or intake of vitamin E have been examined in a variety of other conditions (22). Preliminary evidence in small numbers of patients suggests that vitamin E may play a role in immune function, Alzheimer disease, tardive dyskinesia, lung function, diabetes, and exercise performance in highly trained athletes, but the data are contradictory. Vitamin E alone had no benefit on patients with mild cognitive impairment or the rate of progression to Alzheimer disease (328). Although there are no clear answers to the use of vitamin E in Alzheimer disease, current practice often favors its use, because there are few other options (329). Data from large, well-designed studies in Parkinson disease and cataract do not support the use of vitamin E (327). Some data suggest prevention of tardive dyskinesia in the first 6 months of therapy with antipsychotic drugs, but more data are needed to make a firm recommendation. Supplementation with vitamins C and E do not reduce the risk of preeclampsia in nulliparous women (330). A multicenter trial by the Maternal-Fetal Medicine Units Network of NICH is currently underway.

Patients with cholestasis malabsorb vitamin E, but clinical signs of deficiency are usually present only in children whose neural development is immature. Oral vitamin E supplementation with 50 IU per day could normalize serum vitamin E levels, if the serum bilirubin were <4 mg per dL, indicative of less than severe cholestasis (331). Vitamin E 600 IU per day has been provided to 16 patients and 15 controls with chemotherapy-induced peripheral neuropathy, with lower mean neuropathy scores (332). This finding will require confirmation. Vitamin E has been used topically in cosmetics and is safe, but real clinical benefit in atopic dermatitis and protection from sunlight-induced malignancy will require prospective controlled studies (333).

TABLE 6-42. Randomized Double-blinded Controlled Studies of Vitamin E Supplementation to Prevent Cardiovascular Disease and Cancer

	Patients			
Study	**Population**	**No.**	**Intervention (dose of vitamin/day)**	**Outcome**
ASAP (2003)	Men and postmenopausal women, cholesterol ≥193 mg/dL	488	D-α-tocopherol 272 IU + vitamin C 500 mg	Intima-media thickness ↓ only in male smokers
ATBC[1] (1994, 2004)	Finnish M smokers, no MI, 50–69 years	27,271	α-tocopherol 50 mg, β-car 20 mg or both, 5–8 years	No ↓ fatal, nonfatal MI, cancer rates
ATBC[2]	Male smokers, Hx of MI	1,862	″	↑ Deaths on β-carotene
ATBC[3]	Male smokers, angina	1,795	″	No benefit
CHAOS[4] (1996)	Angiogram-positive atherosclerosis	2,002	α-tocopherol 400 or 800 IU, ~2 years	72% ↓ Nonfatal MI, no Δ death
GISSI (1999)	Post-MI adults	11,324	Vitamin E 300 mg (synthetic) + 3-n PUFA	No effect on MI, CVD death, stroke
HATS (2001)	Patients with CVD	160	α-tocopherol 800 IU, + 1 g vitamin C + 25 mg natural β-carotene, + 0.1 mg selenium	Progression of stenosis with antioxidant cocktail
HOPE[7] (2000)	>55 years with CV risk factors	9,541	Natural source E 400 mg, 4.5 years	No Δ in CV outcomes
HPS (2002)	High risk for coronary disease, DM, PVD	20,536	Synthetic vitamin E 600 IU + vitamin C 250 mg + β-carotene 20 mg	No Δ in any CV outcome
IVUS (2002)	After cardiac transplantation	40	α-tocopherol 400 IU + vitamin C 500 mg	No ↑ in intimal index
Linxian (1993)	General population (Chinese)	29,584	Group D, β-carotene 15 mg, vitamin E 33 IU, selenium 0.05 mg	21% ↓ in gastric cancer mortality, 5% ↓ in overall mortality, no ↓ in CV mortality
MICRO-HOPE (2002)	Male and female diabetics	3,654	Natural source vitamin E, 400 IU, 4.5 years	No effect on MI, CVD death, stroke
PPP (2001)	Subjects at risk for CVD	4,495	Synthetic vitamin E 300 mg	No effect on IM, CVD death, stroke
SPACE (2000)	Hemodialysis patients with CVD	196	″ + natural α-tocopherol 800 IU	2.2 fold ↓ in primary endpoint, a composite of MI, ischemic stroke, unstable angina. No ↓ in CVD mortality
SU.VI. MAX	Healthy men and women	12,741	Vitamin E (unspecified) 33 IU, β-carotene 6 mg, selenium 0.1 mg, zinc 20 mg for 7.2 years	No ↓ in CVD mortality or cancer incidence in whole study ↓ cancer incidence and all-cause mortality in men, not women

(*continued*)

TABLE 6-42. Randomized Double-blinded Controlled Studies of Vitamin E Supplementation to Prevent Cardiovascular Disease and Cancer (*Continued*)

	Patients			
Study	**Population**	**No.**	**Intervention (dose of vitamin/day)**	**Outcome**
VEAPS (2002)	Elevated LDL-C	353	dl-α-tocopherol 400 IU	No effect on intima-media thickness or clinical events
WAVE (2002)	Postmenopausal women with CVD	423	Vitamin E 800 IU + vitamin C 500 mg + hormone replacement therapy	↑ all-cause mortality in antioxidant + HRT group

ASAP, Antioxidant Supplementation in Atherosclerosis Prevention study; ATBC, Alpha Tocopherol Beta Carotene cancer prevention study; CHAOS, Cambridge Heart Antioxidant Study; GISSI, Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto miocardico-prevenzione study; HATS, HDL-Atherosclerosis Treatment study; HOPES, Heart Outcomes Prevention Evaluation Study; HPS, Health Protection Study; IVUS, Intravascular Ultrasonography Study; MICRO-HOPE, Microalbuminuria Cardiovascular Renal Outcomes-Heart Outcomes Prevention Evaluation trial; SPACE, Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease; SU.VI.MAX, Supplementation en Vitamines et Mineraux Antioxydants; VEAPS, Vitamin E Atherosclerosis Prevention Study; WAVE, Women's Angiographic Vitamin and Estrogen Study. Individual references are included in Kris-Etherton PM, Lichtenstein AH, Howard BV, et al, for the Nutrition Committee of the American Heart Associatioin Council on Nutrition, Physical Activity, and Metabolism. Antioxidant vitamin supplements and cardiovascular disease. *Circulation* 2004;110:637 and Pham DQ, Plakogiannis R. Vitamin E supplementation in cardiovascular disease and cancer prevention: part 1. *Ann Pharmacotherapy* 2005;39:1870.
MI, myocardial infarction; DM, diabetes mellitus; LDL-C, low density lipoprotein cholesterol; PVD, peripheral vascular disease; PUFA, polyunsaturated fatty acid.

Therapy

The premature infant absorbs vitamin E poorly, and large doses are required orally (30 to 60 mg or 45 to 90 IU). Larger doses may be needed for malabsorption syndromes. Vitamin E is available in tablets or capsules of 100, 200, 400, 500, 800, and 1,000 IU and in aqueous suspension at 50 mg per mL (Aquavit-E, Cypress). The therapeutic use of vitamin E falls into three categories (334).

Correction of Deficiency States. Examples include the hemolytic anemia of premature infants and the malabsorption syndromes of patients with cystic fibrosis, cholestatic liver disease, and hereditary abetalipoproteinemia. Large doses may be needed for a response. Up to 100 to 200 IU per kg per day can be given as a liquid emulsion with breakfast or 2 hours after medication that can interfere with absorption (e.g., cholestyramine, vitamin A, antacids). Parenteral (IM) vitamin E has been used as an investigational drug (Ephynal, Hoffman-LaRoche, Nutley, NJ) at a dose of 1 to 2 IU per kg (335), but is not currently available. A truly water-soluble form, such as D-α-tocopheryl polyethylene glycol 1,000 succinate (336), is available over the counter as Liqui-E (Twin Lab, Hauppauge, NY). This compound forms micelles when given at doses of 25 mg per kg per day. Blood levels of vitamin E may rise with replacement in 2 to 3 weeks unless hypolipidemia persists, as in abetalipoproteinemia. It is not clear what this means in terms of transfer of vitamin E to peripheral tissues. Oral vitamin E emulsion (1,000 to 2,000 IU per day) was reported to reverse a deficiency state when given orally three times a week with 0.7 to 3.0 mmol of desiccated ox bile (337).

Countering Effects of Pro-oxidants. Large doses have been used in conditions in which no deficiency exists but large amounts of oxygen or other oxidants are administered. Examples of such use include the prevention or partial relief of retrolental fibroplasia in premature infants, to whom 100 mg of vitamin has been given per kilogram of body weight per day (338). Large doses of the vitamin have been given to lessen the severity of pulmonary

dysplasia in infants exposed to prolonged oxygen treatment for respiratory distress syndrome and also to prevent the cardiotoxic effects of the chemotherapeutic drug doxorubicin.

Compensation for Pre-existing Defects in the Antioxidant Systems of the Body. Large doses of vitamin E have been used in the absence of defined vitamin E deficiency to treat hemolytic anemia secondary to deficiencies in glutathione synthetase and in glucose-6-phosphate dehydrogenase (339). A decrease in the percentage of sickled cells in sickle cell anemia has been reported with 450 IU per day for 6 to 35 weeks (340). Of all the conditions associated with vitamin E listed in Table 6-40, cardiovascular disease is the most prevalent, and prevention of cardiovascular disease has the most support. Although no routine recommendations can be made for this use of vitamin E, doses between 100 and 400 IU per day might be considered for patients with or at high risk for cardiovascular disease, with the higher doses given to patients with documented disease (341). If vitamin E is used, it must be understood that the optimal dosage, duration of use, and appropriate source of the vitamin (diet or supplements) are not known.

Toxicity

No consistent ill effects are noted after ingestion of up to 2,112 mg (3,200 IU) per day in healthy volunteers or in patients with a variety of disorders (342). Occasionally, muscle weakness, fatigue, headaches, and nausea have been reported with these doses. High doses may impair the absorption of other fat-soluble vitamins by displacing them from the mixed bile acid–fatty acid micelle. At doses of 100 to 1,100 mg per day, vitamin E can block the oxidation of vitamin K to its active form, mimicking the action of warfarin; therefore, high-dose vitamin E may be contraindicated in patients with disorders of bleeding. However, no changes in prothrombin time have been noted in patients taking 800 to 1,200 IU per day while on coumadin therapy (22). Thus, the UL for adults has been set at 1,000 mg per day (3) (Appendix B). Multiple organ toxicity has been reported in premature infants receiving IV vitamin E with polysorbate 80 as an emulsifier.

Some of the studies on vitamin E supplementation have suggested that the vitamin may actually increase mortality or morbidity (315,343). A systematic review of 19 randomized controlled trials showed that vitamin E supplementation either alone or combined with other micronutrients in doses ≥400 IU per day increased the risk for all-cause mortality. Because in many studies (10 of 19 studies) vitamin E was not the only supplement provided, it is not possible to know the effects of vitamin E alone. However, it does suggest that for safety the dose of vitamin E should be kept at <400 IU per day.

Vitamin K

Requirement

Two forms of vitamin K occur naturally—K_1 (phylloquinones) in green plants and K_2 (menaquinones) in bacteria and animals. Menaquinones are classified depending on the length of their side chain. Menadione (vitamin K_3) is a synthetic compound without a side chain that is activated by conversion in the body to MK-4. The most common menaquinone found in food is a short-chain vitamer, MK-4 (344). Colonic bacterial synthesis provides an unknown amount of vitamin K, mostly the longer-chain menaquinones (MK-7 to MK-10) that has been estimated to be about 2 μg per kg of body weight. Because of the bacterial synthesis, dietary requirements are uncertain. The role of intestinal bacteria in providing any vitamin K in humans has been questioned, and its overall contribution to vitamin K status is felt to be fairly small (344). When antibiotics are given to alter intestinal flora, a vitamin K intake of 1 μg per kg per day prevents deficiency and is presumably adequate. Body stores of vitamin K are limited (~1 μg per kg body weight) and turnover time is about 1 to 2 days (345).

The RDAs of 1989 were based on the function of the vitamin for the coagulation proteins, but the requirement may be greater for the nonhepatic vitamin K-dependent proteins, including those in bone (346). Because of the lack of data to estimate an average requirement, an AI is based on representative dietary intake data from healthy persons (196). The lower limit of the AI for vitamin K is set at 120 μg for adult men and 90 μg for adult women (Table 6-43). The RDA for other age groups is based on the need for 1 μg per kg of body weight in infants and children. Because human milk contains low levels of vitamin K (2 μg per L) and intestinal flora are underdeveloped, breast-fed infants receiving no other food source are at risk for deficiency and intracranial hemorrhage. Vitamin K (150 μg per day)

TABLE 6-43. Recommended Dietary Allowances for Vitamin K

Life stage group	Vitamin K (μg/day)	Life stage group	Vitamin K (μg/day)
Infants		**Females**	
0–6 months	2	9–13 years	60
7–12 months	2.5	14–18 years	75
		19–>70 years	90
Children			
1–3 years	30	**Pregnancy, lactation**	
4–8 years	55	14–18 years	75
		19–50 years	90
Males			
9–13 years	60		
14–18 years	75		
19–>70 years	120		

All estimates are based on adequate intake (AI).
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington, DC: National Academies Press, 2001. Available on line at *www.nap.edu/books, Crawler list 0309072794.* Accessed May 30, 2006.

is now included in the recommendations for vitamin provision in the new FDA guidelines for TPN for adults (347).

Food Sources

Phylloquinone concentrations of plant leaves are proportional to their chlorophyll content. Thus, the best dietary sources are green leafy vegetables and broccoli, although whole wheat and green tea are also sources. Although the food content varies widely, the vitamin is associated with chloroplasts, and bioavailability is also variable. Other primary dietary sources are certain plant oils, namely soybean, canola, cottonseed, and olive (348,349). However, other commonly used oils (peanut, corn, safflower, and sesame) have a very low content. Fruits, cereals, dairy products, and meat contain less vitamin K. The average diet in the United States contains 60 to 200 μg per day (346). Dihydrophylloquinone is formed during the hydrogenation of plant oils. Menaquinones, in particular MK-4, are found mostly in meat, fermented products, eggs, and dairy products (350). MK-4 is the major form of vitamin K in human brain. Menadione (synthetic vitamin K_3) is commonly added to chicken feed, and the MK-4 found in chicken products may be formed from this source. No single food item is especially rich in MK-4, but these foods are consumed in large amounts in a Western diet (including fast foods) and probably are important in the overall contribution of vitamin K intake. Some vitamin K in the body is derived from bacteria, but this is poorly absorbed, and diet is the major source. The content of representative foods is listed in Table 6-44. Only a small number of vegetables contribute substantially to dietary phylloquinones. Oral phylloquinone at a dose of 500 μg can overcome therapeutic doses of warfarin, but some reports have suggested that a much lower content in enteral products can cause dietary resistance to warfarin (351). If the dietary intake of green vegetables or high-content oils is reasonably constant, there is no need to be concerned with a dietary cause of unstable warfarin effect. High vitamin K intake can blunt the effect of warfarin, and low vitamin K stores can increase sensitivity to warfarin. Typical servings of vegetables (containing <100 μg of the vitamin) have little effect on the INR, but large intake of vegetables (e.g., 400 g containing 0.7 to 1.5 mg of vitamin K) can alter the INR transiently (352). The 2005 *Dietary Guidelines for Americans* suggests 3 cups per week of dark-green vegetables, which contain ~100 to 570 μg of vitamin K per serving. Thus, it seems that only excessive ingestion of dietary vitamin K will have an effect on the INR (see also Chapter 12, vitamin-K restricted diet).

Assessment

Intake: Plasma Phylloquinone. HPLC methods have made this a straightforward measurement. Normal plasma concentrations range from 1.04 nmol per L ± 0.13 in younger

TABLE 6-44. Vitamin K Content of Selected Foods

Food	Portion	Vitamin K content (μg per serving)
Vegetables		
Broccoli	1/2 cup	88
Brussels sprouts	1/2 cup	225
Cabbage	1/2 cup	73
Collard greens	1/2 cup	374
Nuts, mixed (no peanuts)	1 oz	3.2
Potato, baked with skin	1 medium	1.5
Spinach	1/2 cup	324
Dairy		
Milk, 2%	8 oz	0.5
Meat		
Beef, ground	3 oz	2.0
Chicken breast, roasted	3 oz	<0.01
Chicken breast, home fried	3 oz	3.8
Oils		
Cottonseed, olive	1 oz	15
Corn	1 oz	1.5

From Booth SL, Suttie JW. Dietary intake and adequacy of vitamin K. *J Nutr* 1998;128:785.

adults to 1.45 nmol per L ± 0.22 (150 to 200 pg per mL) in older (70 years) adults (17). The recent dietary intake of vitamin K correlates best with the plasma level and is subject to wide variation. Vitamin K is carried in lipoproteins, so levels should be measured after an overnight fast. Plasma levels are elevated most by dietary vitamin K_1, but levels rise more rapidly after ingestion of MK-4, and the plasma half-life of MK-9 is longer than that of other forms (353). The usual assay of phylloquinone does not directly measure menaquinones (350). However, menaquinones can contribute significantly to body stores. An alternative assessment of vitamin K is to measure urinary vitamin K metabolites, as both K_1 and K_2 are excreted as two side-chain shortened metabolites (353). The clinical value of this determination is still unclear.

Body Stores

Prothrombin time. Because vitamin K stimulates the production of clotting factors II, VII, IX, and X, and of protein Z, protein S, and protein C in the liver, the one-stage prothrombin time is used to assess its presence indirectly. For this test, sources of tissue factor (thromboplastin) and calcium are added in excess. Under these conditions, all the clotting factors tested (II, V, VII, X) are responsive to vitamin K except for factor V. The rate of formation of clot is an indirect measure of the amount of factors II, VII, and X. In practice, factor VII is the usual rate-limiting factor. Factor V has a longer half-life than the vitamin K-dependent proteins and is not rate-limiting in the reaction. Normally, the test sample clots within 1.5 seconds of the control [international normalized ratio (INR) of 1.0 to 1.1]. The prothrombin time does not test vitamin K stores and is abnormal only when deficiency is present, synthesis of clotting factors is impaired by hepatic disease, or clotting factors are consumed in intravascular coagulation. Therefore, the test is nonspecific. It is most helpful when acute serious illness or liver disease is not present. In these situations, the interpretation regarding vitamin K is simple. If parenteral administration of vitamin K (5 to 10 mg) restores the prothrombin time to normal, deficiency in vitamin K becomes evident.

γ-Carboxyglutamic acid (Gla)-modified proteins. Because vitamin K mediates the addition of Gla to proteins, detection of these proteins has been examined to evaluate vitamin K status, particularly as applies to extrahepatic tissues. These assays are still not widely available, and more studies are needed before they can become clinically valuable. The assays used, and their "normal" values in adults, include plasma undercarboxylated prothrombin, protein induced by vitamin K absence (PIVKA)-II (1.58 μg per L), plasma

undercarboxylated osteocalcin, (ucOC, 2 to 3.3 μg per L), plasma carboxylated osteocalcin (cOC, 7 to 10 μg per L), and urine Gla–creatinine ratio (3.16 in women, 3.83 in men) (17). Population studies show a correlation between vitamin K levels and those of ucOC and cOC. The most sensitive measure of vitamin K status for bone may be the ucOC/cOC ratio (353). Matrix Gla-protein (MGP) is not made in the liver or bone, but in chondrocytes and vascular smooth muscle, and may reflect vitamin K status of those tissues.

Physiology

Absorption and Metabolism. Vitamin K absorption requires bile acids and is passive, occurring largely in the small bowel. If coprophagy is prevented, rats on a vitamin K-free diet develop deficiency within a few weeks, so colonic absorption of vitamin K is probably minimal (354). Other fat-soluble vitamins in very large amounts can displace vitamin K from the bile acid micelle and limit absorption. After absorption in the lymphatics, vitamin K_1 is taken up and metabolized in the liver and retained there, but vitamin K_2 appears to accumulate preferentially in extrahepatic locations (355). The vitamin is reduced and converted to the epoxide before the original vitamin is re-formed, all by microsomal enzymes.

Tissue Stores. Unlike other fat-soluble vitamins, vitamin K is not stored in large quantities in adipose tissue, and the total body pool is small. The amount in tissue is low, but the vitamin is found in adrenals, lungs, marrow, kidney, cartilage, vascular smooth muscle, and lymph nodes after it leaves the liver. The storage form differs from the plasma form, which is carried in lipoproteins. Long-chain menaquinones are the predominant hepatic form. Phylloquinones account for only 10% of liver reserves, do not cross the placenta, and are depleted first in cases of deficiency.

Function. Vitamin K acts by carboxylating selected glutamic acid residues of proteins (α-Gla) so that they bind calcium. The Gla reaction is catalyzed by a microsomal enzyme, vitamin K-dependent gamma glutamyl carboxylase (GGCX), and requires four substrates: reduced vitamin K, oxygen, carbon dioxide, and the Gla-containing peptide. A microsomal electron transport system is coupled with carbon dioxide fixation during the reaction. This vitamin K cycle oxidizes vitamin K hydroquinone to vitamin K-2,3-epoxide in a process that provides the energy for carboxylation of glutamic acid residues (355). The epoxide is converted back to reduced vitamin K by the warfarin-sensitive vitamin K epoxide reductase (VKOR), acting either alone or with some other enzyme as yet unidentified (356). The endoplasmic reticulum chaperone protein calumenin appears to regulate the activity of the vitamin K-dependent carboxylation system. Vitamin K_2 may also play an independent regulatory role, as it regulates transcription of bone-specific genes by a different mechanism from that involved in the carboxylation of Gla residues (353).

Warfarin blocks the reduction of the epoxide to the quinone and the subsequent hydroxylation to the hydroquinone. The coagulation function of hepatic proteins is proportional to the degree of carboxylation. Variability in the VKOR gene and/or variation in the intake of dietary vitamin K may account for some of the variable effects of warfarin. Vitamin K-dependent procoagulants include prothrombin and factors VII, IX, and X. Vitamin K-dependent anticoagulants include proteins C and S. The half-life of activated protein C is quite short, and the pool of circulating protein C is depleted very quickly when severe septicemia occurs. It is not clear whether providing parenteral vitamin K to septic patients can restore protein C levels. Osteocalcin (bone Gla protein) is important in the extracellular matrix of bone, and matrix Gla proteins in the extracellular matrix of other tissues. Other vitamin K-dependent proteins of unknown function include protein Z, nephrocalcin, plaque Gla protein, Gas-6, PRGP-1, and PRGP-2 (354).

Deficiency

To avoid deficiency, a person must have adequate intraluminal vitamin K, a normal concentration of bile acids, and a normal small bowel, colon, and liver. Deficiency is manifested by easy bruising and clotting abnormalities. Subjects at risk for deficiency include newborn infants, whose intestinal flora is not established; others are patients with malabsorption resulting from loss of intestine or bile acid insufficiency, patients with liver disease, and persons receiving no oral intake while on broad-spectrum antibiotics.

Hemorrhagic Disease of the Newborn. Hemorrhagic disease of the newborn occurs because the placenta transports lipids poorly so body stores are low, the intestine is sterile in the first days of life, turnover of the vitamin is rapid, and human milk is a poor source of vitamin K. Premature infants are at highest risk. Thus, the fall in prothrombin time at birth could lead to bleeding, particularly intracranially. It was routine to give 1 mg of vitamin K by injection routinely (357). It became clear that the problem was seen only in infants fed entirely by breast milk, and the condition was renamed "vitamin K deficiency bleeding." It is not very common now, and occurs only in the first few weeks of life. Late bleeding (after week 2 of life) occurs only about 1 in every 6,000 breast fed infants. Bottle fed babies have almost no risk, because formula feeds are fortified with vitamins. Oral supplementation of newborns is effective, so that injectable vitamin K need not always be indicated (357).

Drug Interference. Drugs interfere with vitamin K metabolism as well as with production in the intestine. Warfarin inhibits vitamin K epoxide formation, hydantoins antagonize vitamin K in some way, certain antibiotics (e.g., moxalactam, cefamandole) decrease peptide carboxylation, salicylates inhibit vitamin K reductase, and the diuretic ticrynafen inhibits part of the microsomal electron transport system.

Bone and Vascular Health. Epidemiologic studies suggest that vitamin K deficiency can cause reductions in bone mineral density, and a few intervention studies suggest further that supplementation with vitamin K can increase bone density and reduce fracture rates (344,353). In postmenopausal women, bone calcification is decreased but arterial calcification is increased. Population studies have suggested an inverse relationship between dietary intake of menaquinones and aortic calcification and cardiovascular death, but no prospective interventional studies have been reported. Two dose-response studies show that the amount of vitamin K needed for maximal γ-carboxylation of osteocalcin is much higher than what is needed to maintain synthesis of hepatic clotting factors, and is probably greater than can be provided by the diet (344). Some data suggest that vitamin K supplements should also contain calcium and vitamin D to have optimal bone effects. A purely dietary deficiency of vitamin K is rare, but expert opinion has begun to question the adequacy of the DRI recommendations for vitamin K intake, due to the possible need for larger intake for bone health and possibly for cardiovascular disease. Vitamin K is essential for the biosynthesis of some bone proteins, and hip fractures (but not bone density) are associated with intakes of <109 μg per day (358). Vitamin K in the form of MK-4 was administered to postmenopausal Japanese women for 2 years and increased bone mass (359), but the link between vitamin K deficiency, if it occurs, and hip fracture in elderly women is not clear (360). Two studies of warfarin use and the risk for fractures reached opposite conclusions, one showing no increase (361) and one showing no overall increase but more rib and vertebral fractures (362). The overall dataset provides some support for the hypothesis that vitamin K might be useful for osteoporosis, but use of the vitamin is not well accepted. Most of the prospective studies and use come from Japan where MK-4 supplements (menaquinone) are commonly prescribed. However, Canadian guidelines do not recommend vitamin K for osteoporosis (363). Vitamin K status is lower in patients with Crohn disease than in healthy controls, and the rate of bone resorption was higher, suggesting a protective role of the vitamin in reducing bone turnover (364). Perhaps the most compelling data that links vitamin K with bone health is the observation of low osteocalcin and bone mineral density in an infant with inherited deficiency of vitamin K-dependent coagulation factors, and the return to normal of the bone parameters following vitamin K supplementation (365).

Therapy

The only synthetic forms of vitamin K available for human consumption are K_1 and MK-4. Both forms are well absorbed, so that parenteral administration is not necessary in most cases. K_1 is the analog used in virtually all the food supplements and multivitamin preparations in Western nations, but MK-4 is becoming available in health food stores. There are no data providing comparisons for efficacy of the two forms, but present formulations permit much larger doses of MK-4 (45 to 90 mg per day). The bioavailability of vitamin K is probably greater from supplements than from natural sources (353). Vitamin K is available in solutions of 2 mg per mL in 0.5 mL ampules or prefilled syringes for parenteral use. Injection should be SC or IM when possible. For anticoagulant-induced or other deficiency of prothrombin in adults, use 2.5 to 10 mg initially or up to 25 mg. If the prothrombin time has not shortened satisfactorily within 6 to 8 hours, repeat the dose. Use blood

replacement when it is hemodynamically necessary. For hemorrhagic disease of the newborn, prophylactic therapy consists of a single IM dose of 0.5 to 1 mg within 1 hour of birth or 1 to 5 mg to the mother 12 to 24 hours before delivery. Hemolytic anemia and hepatotoxicity have been reported with high doses. Long-term use should be limited to patients with malabsorption. Vitamin K_1 is not a component of many multivitamin preparations, but can be prescribed individually as 5 mg tablets of phytonadione (Mephyton).

Toxicity

More than 500 times the RDA can be given without toxicity. Thus, no UL has been recommended (103). Large amounts of vitamin K given during pregnancy or to the newborn (>10 mg) can produce jaundice in the infant. It has been suggested that phylloquinone in infant formulas not exceed 20 μg per 100 kcal (10). Hydantoin antagonizes vitamin K and can produce hemorrhagic disease in the newborn when taken by the mother during pregnancy. IV use in adults has occasionally produced anaphylaxis, even when given at low dose and by slow dilute infusion (366). It is unclear whether this reaction is related to the drug itself or to the solubilizing vehicle, but should be a reminder that IV vitamin K should be used only when absolutely necessary. The newer formulations of the vitamin are well absorbed orally (357).

EFFECT OF DRUGS ON ASSESSMENT OF VITAMIN STATUS

Many drugs can alter the results of tests used to assess vitamin status. These are listed in Table 6-45. Many of the drugs listed alter only the laboratory assessment of nutrient status, and a clear clinical deficiency state is not always described. Therefore, unless treatment is prolonged, replacement therapy is usually not required.

TABLE 6-45. Drugs that Affect Vitamin Utilization and Plasma Concentrations

Drug class	Drug	Vitamin affected	Mechanism
Antibacterial	Isoniazid	Niacin, B_6	Competition with active coenzyme
	PAS	B_{12}	↓ Absorption
	Neomycin	B_{12}, K	↓ Absorption (bile salt sequestration)
	Pyrimethamine	Folate	Inhibits folate reductase
	Tetracycline	C	↑ Excretion
	Trimethoprim	Folate	Inhibits folate reductase
	Broad-spectrum	K	↓ Endogenous production
Anticoagulant	Warfarin	K	Blocks Gla formation
Anticonvulsant	Phenytoin	Folate	↓ Absorption
		D	↓ Hepatic metabolism to 1,25-$(OH)_2$D
		K	Induction of hepatic inactivating enzyme
Antihypertensive	Hydralazine	B_6	Competition with active coenzyme
Anti-inflammatory	Aspirin	C	↑ Excretion (competes with binding)
	Sulfasalazine	Folate	↓ Absorption
	Colchicine	B_{12}	↓ Absorption (intestinal damage)
	Phenylbutazone	Niacin, K	Displacement from albumin binding
Antineoplastic	Methotrexate	Folate	Inhibits folate reductase
Bile salt sequestrants	Cholestyramine	A, B_{12}, folate	↓ Absorption (binding of water-soluble, luminal sequestration of fat-soluble)
	Cholestipol	A, D, K	
Chelating	Penicillamine	B_6	↑ Urinary excretion (adduct formed)
Hormones	Birth control pills	B_1, B_2	↑ Function
		B_6	↓ Plasma binding
		Folate	↓ Absorption, ↑ plasma binding
		B_{12}	↓ Plasma binding

Gla, Carboxy-glutamic acid; PAS, *para*-aminosalicylate.

References

1. National Research Council. *Recommended dietary allowances,* 10th ed. Washington, DC: National Academies Press, 1989.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington DC: National Academies Press, 1997.
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academies Press, 1998.
4. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for vitamin C, vitamin E, selenium, and beta-carotene and other carotenoids*. Washington, DC: National Academies Press, 2000.
5. Haymes EM. Trace minerals and exercise. In: Wolinsky I, Hickson JF Jr, eds. *Nutrition in exercise and sport,* 2nd ed. Boca Raton, FL: CRC Press, 1994:224.
6. Russell RM. New views on the RDAs for older adults. *J Am Diet Assoc.* 1997;97:515.
7. Haller J. The vitamin status and its adequacy in the elderly: an international overview. *Int J Vitam Nutr Res.* 1999;69:160.
8. Selhub J, Bagley LC, Miller C, et al. B vitamins, homocysteine, and neurocognitive function in the elderly. *Am J Clin Nutr.* 2000;71:614S.
9. Lyle BJ, Mares-Perlman JA, Klein BEK, et al. Serum carotenoids and tocopherols and incidence of age-related nuclear cataracts. *Am J Clin Nutr.* 1999;69:272.
10. US Preventive Services Task Force. Routine vitamin supplementation to prevent cancer and cardiovascular disease: recommendations and rationale. *Ann Intern Med.* 2003;139:51.
11. Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention in adults: scientific review. *JAMA.* 2002;287:3116.
12. de Jong N, Chin AP, de Groot LC, et al. Nutrient-dense foods and exercise in frail elderly: effects on B vitamins, homocysteine, methylmalonic acid, and neuropsychological functioning. *Am J Clin Nutr.* 2001; 73:338.
13. Lukaski HC. Vitamin and mineral status: effects on physical performance. *Nutrition*. 2004;20:632.
14. Vieth R. The role of vitamin D in the prevention of osteoporosis. *Ann Med.* 2005;37:278.
15. Fawzi WW, Msamanga GI, Spiegelman D, et al. A randomized trial of multivitamin supplements and HIV disease progression and mortality. *N Engl J Med.* 2004;351:23.
16. Irlam JH, Visser ME, Rollins N, Siegfried N. Micronutrient supplementation in children and adults with HIV infection. *Cochrane Database Syst Rev.* 2005;(4):CD003650.
17. Sauberlich HE. *Laboratory tests for the assessment of nutritional status,* 2nd ed. Boca Raton, FL: CRC Press, 1999.
18. Ganapathy V, Smith SB, Prasad PD. SLC19: the folate/thiamine transporter family. *Pflugers Arch-Eur J Physiol.* 2004;447:641.
19. Kumar N. Nutritional neuropathies. *Neurol Clin*. 2007;25:209.
20. Oriot D, Wood C, Gottesman R, et al. Severe lactic acidosis related to acute thiamine deficiency. *JPEN J Parenter Enteral Nutr.* 1991;15:105.
21. Frank T, Bitsch R, Maiwald J, Stein G. High thiamine phosphate concentrations in erythrocytes can be achieved in dialysis patients by oral administration of benfotiamine. *Eur J Clin Pharmacol.* 2000;56:251.
22. Ames BN, Elson-Schwab I, Silver EA. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased Km): relevance to genetic disease and polymorphisms. *Am J Clin Nutr.* 2002;75:616.
23. Fragakis AS. *The professional's guide to popular dietary supplements*, 2nd ed. Hoboken NJ: John Wiley & Sons, Inc, 2002.
24. Alhadeff L, Gueltieri CT, Lipton M. Toxic effects of water-soluble vitamins. *Nutr Rev.* 1984;42:33.
25. Beecher GR. Overview of dietary flavonoids: nomenclature, occurrence, and intake. *J Nutr.* 2003;133:3248S.
26. McCormick D. Riboflavin. In: Shils M, Shike M, Ross AC, et al., eds. *Modern nutrition in health and disease,* 10th ed. Philadelphia: Lippincott Williams & Wilkins, 2006:434.
27. Powers HJ. Riboflavin (vitamin B-2) and health. *Am J Clin Nutr.* 2003;77:1352.
28. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. *Neurology.* 1998;50:466.
29. Denu JM. The Sir2 family of protein deacetylases. *Curr Opin Chem Biol.* 2005;9:431.
30. Muzaffar S, Shukla N, Jeremy JY. Nicotinamide adenine dinucleotide phosphate oxidase: a promiscuous therapeutic target for cardiovascular drugs? *Trends Cardiovasc Med.* 2005;15:278.
31. Pike NB. Flushing out the role of GPR109A (HM74A) in the clinical efficacy of nicotinic acid. *J Clin Invest.* 2005;115:3400.
32. Bourgeois C, Cervantes-Laurean D, Moss J. Niacin. In: Shils ME, Shike M, Ross CA, et al., eds. *Modern nutrition in health and disease,* 10th ed. Philadelphia: Lippincott Williams & Wilkins, 2006:442.
33. Meyers CD, Kamanna VS, Kashyap ML. Niacin therapy in atherosclerosis. *Curr Opin Lipidology.* 2004;15:659.
34. Shepherd J, Betteridge J, Van Gaal L. Nicotinic acid in the management of dyslipidaemia associated with diabetes and metabolic syndrome: a position paper developed by a European Consensus Panel. *Curr Med Res Opin.* 2005;21:665.

35. Crino A, Schiaffini R, Ciampalini P, et al. A two year observational study of nicotinamide and intensive insulin therapy in patients with recent onset type 1 diabetes mellitus. *J Pediatr Endocrinol Metab*. 2005;18:749.
36. Cosmetic Ingredient Review Expert Panel. Final report of the safety assessment of niacinamide and niacin. *Int J Toxicol*. 2005;24 Suppl 5:1.
37. Jungnickel PW, Maloney PA, van der Tuin EL, et al. Effect of two aspirin pretreatment regimens on niacin-induced cutaneous reactions. *J Gen Intern Med*. 1997;12:591.
38. Rizkallah GS, Mertens MK, Brown ML. Should liver enzymes be checked in a patient taking niacin? *J Fam Pract*. 2005;54:265.
39. McCormack PL, Keating GM. Prolonged-release nicotinic acid: a review of its use in the treatment of dyslipidemia. *Drugs*. 2005;65:2719.
40. Bailey AL, Maisey S, Southon S, et al. Relationships between micronutrient intake and biochemical indicators of nutrient adequacy in a "free-living" elderly U.K. population. *Br J Nutr*. 1997;77:225.
41. de Groot CP, van den Broek T, van Staveren W. Energy intake and micronutrient intake in elderly Europeans: seeking the minimum requirement in the SENECA study. *Age Ageing*. 1999;28:469.
42. Stabler SP, Allen RH, Fried LP, et al. Racial differences in prevalence of cobalamin and folate deficiency in disabled elderly women. *Am J Clin Nutr*. 1999;70:911.
43. Whyte M, Mahuren JD, Vrabel LA, et al. Markedly increased circulating pyridoxal-5′-phosphate levels in hypophosphatasia. Alkaline phosphatase acts in vitamin B_6 metabolism. *J Clin Invest*. 1985;76:752.
44. Said HM, Ortiz A, Ma TY. A carrier-mediated mechanism for pyridoxine uptake by human intestinal epithelial Caco-2 cells: regulation by a PKA-mediated pathway. *Am J Physiol Cell Physiol*. 2003;285:C1219.
45. Mills PB, Surtees RA, Champion MP, et al. Neonatal epileptic encephalopathy caused by mutations in the PNPO gene encoding pyridox(am)ine-5'-phosphate oxidase. *Hum Mol Genet*. 2005;60:1413.
46. Selhub J, Jacques PF, Wilson PW, et al. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *JAMA*. 1993;270:2693.
47. Anonymous. Vitamin B6 (pyridoxine; pyridoxal-5'-phosphate). *Altern Med Rev*. 2001;6:87.
48. Lheureux P, Penaloza A, Gris M. Pyridoxine in clinical toxicology: a review. *Eur J Emerg Med*. 2005; 12:78.
49. Lerner V, Bergman J, Statsendko N, Miodownik C. Vitamin B6 treatment in acute neuroleptic-induced akathisia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2004;65:1550.
50. Eichinger S. Are B vitamins a risk factor for venous thromboembolism? Yes. *J Thromb Haemost*. 2006;4:307.
51. Bender DA. Non-nutritional uses of vitamin B_6. *Br J Nutr*. 1999;81:7.
52. Aufiero E, Stitik TP, Foye PM, Chen B. Pyridoxine hydrochloride treatment of carpal tunnel syndrome: a review. *Nutr Rev*. 2004;62:96.
53. Wyatt KM, Dimmock PW, Jones PW, et al. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. *BMJ*. 1999;318:1375.
54. Malouf R, Grimley Evans J. The effect of vitamin B6 on cognition. *Cochrane Database Syst Rev*. 2003;(4):CD004393.
55. Schaumberg H, Kaplan J, Windebank A, et al. Sensory neuropathy from pyridoxine abuse. A new megavitamin syndrome. *N Engl J Med*. 1983;309:445.
56. Botto LD, Moore CA, Khoury MJ, et al. Neural-tube defects. *N Engl J Med*. 1999;341:1509.
57. Cesari M, Rossi GP, Sticchi D, Pessina AC. Is homocysteine important as risk factor for coronary artery disease? *Nutr Metab Cardiovasc Dis*. 2005;15:140.
58. Bailey LB. Dietary reference intakes for folate: the debut of dietary folate equivalents. *Nutr Rev*. 1998;56:294.
59. Lewis CJ, Crane NT, Wilson DB, et al. Estimated folate intakes: data updated to reflect food fortification, increased bioavailability, and dietary supplement use. *Am J Clin Nutr*. 1999;70:198.
60. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. *Arch Intern Med*. 1999;159:1289.
61. Koontz JL, Phillips KM, Wunderlich KM, et al. Comparison of total folate concentrations in foods determined by microbiological assay at several experienced U.S. commercial laboratories. *J AOAC Int*. 2005;88:805.
62. DeVries JW, Rader JI, Keagy PM, et al. Microbiological assay-trienzyme procedure for total folates in cereals and cereal foods: collaborative study. *J AOAC Int*. 2005;88:5.
63. Laurence VA, Loewenstein JE, Eichner ER. Aspirin and folate binding: *in vivo* and *in vitro* studies of serum binding and urinary excretion of endogenous folate. *J Lab Clin Med*. 1984;103:944.
64. Weir DG, McGing PG, Scott JM. Folate metabolism, the enterohepatic circulation and alcohol. *Biochem Pharmacol*. 1985;34:1.
65. Klee GG. Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B(12) and folate. *Clin Chem*. 2000;46:1277.
66. Ubbink JB, Delport R, Riezler R, et al. Comparison of three different plasma homocysteine assays with gas chromatography-mass spectrometry. *Clin Chem*. 1999;45:670.
67. Selhub J, Jacques PF, Rosenberg IH, et al. Serum total homocysteine concentrations in the Third National Health and Nutrition Examination Survey (1991–1994): population reference ranges and contribution of vitamin status to high serum concentrations. *Ann Intern Med*. 1999;131:331.
68. Ganapathy V, Smith SB, Prasad PD. SLC19: the folate/thiamine transporter family. *Pflugers Arch-Eur J Physiol*. 2004;447:641.

69. Moestrup SK. New insights into carrier binding and epithelial uptake of the erythropoietic nutrients cobalamin and folate. *Curr Opin Hematol.* 2006;13:119.
70. Birn H, Spiegelstein O, Christensen EI, Finnell RH. Renal tubular reabsorption of folate mediated by folate binding protein 1. *J Am Soc Nephrol.* 2005;16:608.
71. Said HM, Mohammed ZM. Intestinal absorption of water-soluble vitamins: an update. *Curr Opin Gastroenterol.* 2006;22:140.
72. Davis RE. Clinical chemistry of folic acid. *Adv Clin Chem.* 1986;25:233.
73. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet.* 1991;338:131.
74. Czeizel AE, Dudas I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med.* 1992;327:1832.
75. Berry RJ, Li Z, Erickson JD, et al. Prevention of neural-tube defects with folic acid in China. *N Engl J Med.* 1999;341:1485.
76. Tamura T, Picciano MF. Folate and human reproduction. *Am J Clin Nutr.* 2006;83:993.
77. Bailey LB, Rampersaud GC, Kauwell GP. Folic acid supplements and fortification affect the risk for neural tube defects, vascular disease and cancer: evolving science. *J Nutr.* 2003;133:1961S.
78. Eichholzer M, Tonz O, Zimmerman R. Folic acid: a public-health challenge. *Lancet.* 2006;22:1352.
79. Ueland PM, Monsen AL. Hyperhomocysteinemia and B-vitamin deficiencies in infants and children. *Clin Chem Lab Med.* 2003;41:1418.
80. Ramaekers VT, Rothenberg SP, Sequira JM, et al. Autoantibodies to folate receptors in the cerebral folate deficiency syndrome. *N Engl J Med.* 2005;352:1985.
81. McCully KS. Hyperhomocysteinemia and arteriosclerosis: historical perspectives. *Clin Chem Lab Med.* 2005;43:980.
82. Verhoef P, de Groot LC. Dietary determinants of plasma homocysteine concentrations. *Semin Vasc Med.* 2005;5:110.
83. Olthof MR, van Vliet T, Verhoef P, et al. Effect of homocysteine-lowering nutrients on blood lipids: results from four randomized, placebo-controlled studies in healthy humans. *PLoS Medicine.* 2005;2:e135.
84. Bostom AG, Silbershatz H, Rosenberg IH, et al. Nonfasting plasma total homocysteine levels and all-cause and cardiovascular mortality in elderly Framingham men and women. *Arch Intern Med.* 1999;159:1077.
85. Ridker PM, Manson JE, Buring JE, et al. Homocysteine and risk of cardiovascular disease among postmenopausal women. *JAMA.* 1999;281:1817.
86. Hackam DG, Anand SS. Emerging risk factors for atherosclerotic vascular disease: a critical review of the evidence. *JAMA.* 2003;290:932.
87. Voutilainen S, Jirtanen JK, Rissanen TH, et al. Serum folate and homocysteine and the incidence of acute coronary events: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am J Clin Nutr.* 2004;80:317.
88. Soinio M, Marniemi J, Laakso M, et al. Elevated plasma homocysteine level is an independent predictor of coronary heart disease events in patients with type 2 diabetes mellitus. *Ann Intern Med.* 2004;140:94.
89. Ganji V, Kafai MR. Demographic, health, lifestyle, and blood vitamin determinants of serum total homocysteine concentration in the Third National Health & Nutrition Survey 1988–1994. *Am J Clin Nutr.* 2003;77:826.
90. Lewis SJ, Ebrahim S, Davey Smith G. Meta-analysis of MTHFR 677C→T polymorphism and coronary heart disease: does totality of evidence support causal role for homocysteine and preventive potential of folate? *BMJ.* 2005;331:1053.
91. The Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke. A meta-analysis. *JAMA.* 2002;288:2015.
92. Homocysteine Lowering Trialists' Collaboration. Dose-dependent effects of folic acid on blood concentrations of homocysteine: a meta-analysis of the randomized trials. *Am J Clin Nutr.* 2005;82:806.
93. B-vitamin treatment Trialists' Collaboration. Homocysteine-lowering trials for prevention of cardiovascular events: a review of the design and power of the large randomized trials. *Am Heart J.* 2006;151:282.
94. The Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med.* 2006;354:1567.
95. Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med.* 2006;354:1578.
96. Schwammental Y, Tanne D. Homocysteine, B-vitamin supplementation and stroke prevention: from observational status to interventional trials. *Lancet Neurol.* 2004;3:493.
97. Bazzano LA, Reynolds K, Holder KN, He J. Effect of folic acid supplementation on risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. *JAMA.* 2006;296:2720.
98. Malinow MR, Bostom AG, Krauss RM. Homocysteine, diet, and cardiovascular diseases, a statement for healthcare professionals from the nutrition committee, American Heart Association. *Circulation.* 1999;99:178.
99. Chamberlain KL. Homocysteine and cardiovascular disease: a review of current recommendations for screening and treatment. *J Am Acad Nurse Pract.* 2005;17:90.
100. Mooijaart SP, Gussekloo J, Frolich M, et al. Homocysteine, vitamin B-12, and folic acid and the risk of cognitive decline in old age: the Leiden 80-plus study. *Am J Clin Nutr.* 2005;82:866.
101. Malouf M, Grimley EJ, Areosa SA. Folic acid with or without vitamin B12 for cognition and anemia. *Cochrane Database Syst Rev.* 2003;(4):CD004514.

102. Tucker KL, Qiao N, Scott T, et al. High homocysteine and low B vitamins predict cognitive decline in aging men: the Veterans Affairs Normative Aging Study. *Am J Clin Nutr.* 2005;82:627.
103. Taylor MJ, Carney SM, Goodwin GM, Geddes JR. Folate for depressive disorders: systematic review and meta-analysis of randomized controlled trials. *J Psychopharmacol.* 2004;18:251.
104. Bottiglieri T. Homocysteine and folate metabolism in depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2005;29:1103.
105. Giovannucci E, Stampfer MJ, Colditz GA, et al. Multivitamin use, folate, and colon cancer in women in the Nurse's Health Study. *Ann Intern Med.* 1998;129:517.
106. Larsson SC, Giovannucci E, Wolk A. A prospective study of dietary folate intake and risk of colorectal cancer: modification by caffeine intake and cigarette smoking. *Cancer Epidemiol Biomarkers Prev.* 2005;14:740.
107. Bingham S. The fibre-folate debate in colo-rectal cancer. *Proc Nutr Soc.* 2006;65:19.
108. Khosraviani K, Weir HP, Hamilton P, et al. Effect of folate supplementation on mucosal cell proliferation in high risk patients for colon cancer. *Gut.* 2002;51:195.
109. Pufulete M, Al-Ghnaniem R, Khushal A, et al. Effect of folic acid supplementation on genomic DNA methylation in patients with colorectal adenoma. *Gut.* 2005;54:648.
110. Mills JL. Fortification of foods with folic acid—how much is enough? *N Engl J Med.* 2000;342:1442.
111. Malinow MR, Duell PB, Hess DL, et al. Reduction of plasma homocysteine levels by breakfast cereal fortified with folic acid in patients with coronary artery disease. *N Engl J Med.* 1998;338:1009.
112. Jacques PF, Selhub J, Bostom AG, et al. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. *N Engl J Med.* 1999;340:1449.
113. Mix JA. Do megadoses of vitamin C compromise folic acid's role in the metabolism of plasma homocysteine? *Nutr Res.* 1999;19:161.
114. Mills JL, Von Kohorn I, Conley MR, et al. Low vitamin B-12 concentrations in patients without anemia: the effect of folic acid fortification of grain. *Am J Clin Nutr.* 2003;77:1474.
115. Metz J, McNeil AR, Levin M. The relationship between serum cobalamin concentration and mean red cell volume at varying concentrations of serum folate. *Clin Lab Haematol.* 2004;26:323.
116. Herbert V. Recommended dietary intakes (RDI) of folate in humans. *Am J Clin Nutr.* 1987;45:661.
117. Sesin GP, Kirschenbaum H. Folic acid hypersensitivity and fever: a case report. *Am J Hosp Pharm.* 1979;36:1565.
118. Ho C, Kauwell GPA, Bailey LB. Practitioners' guide to meeting the vitamin B-12 recommended dietary allowance for people aged 61 years and older. *J Am Diet Assoc.* 1999;99:725.
119. Yamada K, Yamada Y, Fukuda M, et al. Bioavailability of dried asakusanori *(Porphyra tenera)* as a source of cobalamin (vitamin B-12). *Int J Vitam Nutr Res.* 1999;69:412.
120. Fairbanks VF, Wahner HW, Phyliky RL. Tests for pernicious anemia: the "Schilling test." *Mayo Clin Proc.* 1983;58:541.
121. Miller A, Furlong D, Burrows BA, et al. Bound vitamin B_{12} absorption in patients with low serum B_{12} levels. *Am J Hematol.* 1992;40:163.
122. Obeid R, Morkbak AL, Munz W, et al. The cobalamin-binding proteins transcobalamin and haptocorrin in maternal and cord blood sera at birth. *Clin Chem.* 2006;52:263.
123. Carmel R. Mild transcobalamin I (haptocorrin) deficiency and low serum cobalamin concentrations. *Clin Chem.* 2003;49:1367.
124. Lindenbaum J, Rosenberg IH, Wilson PW, et al. Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr.* 1994;60:2.
125. Ermens AAM, Vlasveld LT, Lindemans J. Significance of elevated cobalamin (vitamin B12) levels in blood. *Clin Biochem.* 2003;36:585.
126. Holleland G, Schneede J, Ueland PM, et al. Cobalamin deficiency in general practice. Assessment of the diagnostic utility and cost–benefit analysis of methylmalonic acid determination in relation to current diagnostic strategies. *Clin Chem.* 1999;45:189.
127. Loehrer FM, Schwab R, Angst CP, et al. Influence of oral S-adenosylmethionine on plasma 5-methyltetrahydrofolate, S-adenosylhomocysteine, homocysteine and methionine in healthy humans. *J Pharmacol Exp Ther.* 1997;282:845.
128. Refsum H, Johnston C, Guttormsen AB, Nexo E. Holotranscobalamin and total transcobalamin in human plasma: determination, determinants, and reference values in healthy adults. *Clin Chem.* 2006;52:129.
129. Miller JW, Garrod MG, Rockwood AL, et al. Measurement of total vitamin B12 and holotranscobalamin, singly and in combination, in screening for metabolic vitamin B12 deficiency. *Clin Chem.* 2006;52:2.
130. Shane B, Stokstad EL. Vitamin B_{12}–folate interrelationship. *Annu Rev Nutr.* 1985;5:115.
131. Seetharam B, Alpers DH. Cobalamin absorption. In: Field M, Frizzell RA, eds. *Handbook of physiology: the gastrointestinal system, section 6,* vol. IV. Bethesda, MD: American Physiological Society, 1991:437.
132. Alpers DH. What's new in vitamin B12? *Curr Op Gastroenterol.* 2005;21:183.
133. Wuerges J, Garau G, Geremia S, et al. Structural basis for mammalian vitamin B12 transport by transcobalamin. *Proc Natl Acad Sci U S A.* 2006;103:4386.
134. Oh RC, Brown DL. Vitamin B12 deficiency. *Am Fam Physician.* 2003;67:979.
135. Ermens AA, Sonneveld P, Michiels JJ, et al. Increased uptake and accumulation of cobalamin by multiple myeloma bone marrow cells as a possible cause of low serum cobalamin. *Eur J Haematol.* 1993;50:57.

136. Bauman WA, Shaw S, Jayatilleke E, et al. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. *Diabetes Care*. 2000;23:1227.
137. Miller A, Korem M, Almog R, Galboiz Y. Vitamin B12, demyelination, remyelination and repair in multiple sclerosis. *J Neurol Sci.* 2005;233:93.
138. Krishna KK, Arafat M, Ichaporia NR, Jain MM. MRI findings in cobalamin deficiency. *J Clin Neurosci.* 2003;10:84.
139. Healton EB, Savage DG, Grust JC, et al. Neurologic aspects of cobalamin deficiency. *Medicine (Baltimore)*. 1991;70:220.
140. Hutto BR. Folate and cobalamin in psychiatric illness. *Compr Psychiatry.* 1997;38:305.
141. Bernard MA, Nakonezny PA, Kashner TM. The effect of vitamin B-12 deficiency on older veterans and its relationship to health. *J Am Geriatr Soc.* 1998;46:1199.
142. Osimani A, Berger A, Friedman J, et al. Neuropsychology of vitamin B12 deficiency in elderly dementia patients and control subjects. *J Geriatr Psychiatry Neurol.* 2005;18:33.
143. Celik M, Barkut IK, Oncel C, Forta H. Involuntary movements associated with vitamin B12 deficiency. *Parkisonsim Relat Disord.* 2003;10:55.
144. Aaron S, Sudhir K, Vijayan J, et al. Clinical and laboratory features and response to treatment in patients presenting with vitamin B12 deficiency-related neurological syndromes. *Neurol India.* 2005;53:55.
145. Langman LJ, Cole DEC. Homocysteine: cholesterol of the 90s? *Clin Chim Acta.* 1999;286:63.
146. Kuwabara S, Nakazawa R, Azuma N, et al. Intravenous methylcobalamin treatment for uremic and diabetic neuropathy in chronic hemodialysis patients. *Intern Med.* 1999;38:472.
147. Sato Y, Honda Y, Iwamoto J, et al. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA.* 2005;293:1082.
148. Lederle FA. Oral cobalamin for pernicious anemia. Medicine's best kept secret? *JAMA.* 1991;265:94.
149. Kuzminski AM, Giacco EJD, Allen RH, et al. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood.* 1998;92:1191.
150. Butler CC, Vidal-Alaball J, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. *Family Pract.* 2006;23:279.
151. Anonymous. Vitamin B12 nasal spray. *The Medical Letter.* 2005;47:64.
152. Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. *Proc Natl Acad Sci U S A.* 1996;93:3704.
153. Lachance P, Langseth L. The RDA concept: time for a change? *Nutr Rev.* 1994;52:266.
154. Vanderslice JT, Higgs DJ. Vitamin C content of foods: ample variability. *Am J Clin Nutr.* 1991;54:1323S.
155. Ausman LM. Criteria and recommendations for vitamin C intake. *Nutr Rev* 1999;57:222.
156. Wilson JX. Regulation of vitamin C transport. *Annu Rev Nutr.* 2005;25:105.
157. Padayatty SJ, Sun H, Wang Y, et al. Vitamin C pharmacokinetics: evaluation of its role in disease prevention. *J Am Coll Nutr.* 2003;22:18.
158. Packer L, Fuchs J, eds. *Vitamin C in health and disease.* New York: Marcel Dekker Inc, 1997.
159. Fain O. Musculoskeletal manifestations of scurvy. *Joint, Bone, Spine.* 2005;72:124.
160. Francescone MA, Levitt J. Scurvy masquerading as leukocytoclastic vasculitis: a case report and review of the literature. *Cutis.* 2005;76:261.
161. Wintergerst ES, Maggini S, Hornig DH. Immune-enhancing role of vitamin C and zinc and effects on clinical conditions. *Ann Nutr Metab.* 2006;50:85.
162. Douglas RM, Hemila H, D'Souza R, et al. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev.* 2004;18(4):CD000980.
163. Bielory L, Gandhi R. Asthma and vitamin C. *Ann Allergy.* 1994;73:89.
164. Padayatty SJ, Katz A, Wang Y, et al. Vitamin C as an antioxidant: evaluation of its role in disease prevention. *J Am Coll Nutr.* 2003;22:18.
165. Ness AR, Powles JW, Khaw KT. Vitamin C and cardiovascular disease: a systematic review. *J Cardiovasc Risk.* 1996;3:513.
166. Czernichow S, Blacher J, Hercberg S. Antioxidant vitamins and blood pressure. *Curr Hypertens Rep.* 2004;6:27.
167. Muntwyler J, Hennekens CH, Manson JE, et al. Vitamin supplement use in a low-risk population of US male physicians and subsequent cardiovascular mortality. *Arch Intern Med.* 2002;162:1472.
168. Osganian SK, Stampfer MJ, Rimm E, et al. Vitamin C and risk of coronary heart disease in women. *J Am Coll Cardiol.* 2003;42:246.
169. Khaw KT, Bingham S, Welch A, et al. Relation between plasma ascorbic acid and mortality in men and women in EPIC-Norfolk prospective study: a prospective population study. *Lancet.* 2001;357:657.
170. Weber P, Bendich A, Shcalch W. Vitamin C and human health—a review of recent data relevant to human requirements. *Int J Vitam Nutr Res.* 1996;66:19.
171. Frei B. To C or not to C, that is the queston. *J Am Coll Cardiol.* 2003;42:253.
172. Teucher B, Olivares M, Cori H. Enhancers of iron absorption: ascorbic acid and other organic acids. *Int J Vitam Nutr Res.* 2004;74:403.
173. Johnston CS. Biomarkers for establishing a tolerable upper intake level for vitamin C. *Nutr Rev.* 1999;57:71.
174. Staggs CG, Sealey WM, McCabe BJ, et al. Determination of the biotin content of select foods using accurate and sensitive HPLC/avidin binding. *J Food Compost Anal.* 2004;17:767.

175. Zempleni J, Mock DM. Biotin biochemistry and human requirements. *J Nutr Biochem.* 1999;10:128.
176. Vlasova TI, Tratton SL, Wells AM, et al. Biotin deficiency reduces expression of SLC19A3, a potential biotin transporter, in leukocytes from human blood. *J Nutr.* 2005;135:42.
177. Said HM, Mohammed ZM. Intestinal absorption of water-soluble vitamins: an update. *Curr Opin Gastroenterol.* 2006;22:140.
178. Said HM. Biotin: the forgotten vitamin. *Am J Clin Nutr.* 2002;75:179.
179. Mock DM, de Lorimer AA, Liebman WM, et al. Biotin deficiency: an unusual complication of parenteral alimentation. *N Engl J Med.* 1981;304:820.
180. Zempleni J, Mock DM. Marginal biotin deficiency is teratogenic. *Proc Soc Exp Biol Med.* 2000;223:14.
181. Thoene J, Baker H, Yoshino M, et al. Biotin-responsive carboxylase deficiency associated with subnormal plasma and urinary biotin. *N Engl J Med.* 1981;304:817.
182. Friebel D, von der Hagen M, Baumgartner ER, et al. The first case of 3-methylcorotonyl-CoA carboxylase (MCC) deficiency responsive to biotin. *Neuropediatrics.* 2006;37:72.
183. Mardach R, Zemplini J, Wolf B, et al. Biotin dependency due to a defect in biotin transport. *J Clin Invest.* 2002;109:1617.
184. Wolf B, Heard G, Jefferson LG, et al. Clinical finding in four children with biotinidase deficiency detected through a statewide neonatal screening program. *N Engl J Med.* 1985;313:16.
185. Leonardi R, Zhang YM, Rock CO, Jackowski S. Coenzyme A: back in action. *Prog Lipid Res.* 2005;44:125.
186. Gregory A, Hayflick SJ. Neurodegeneration with brain iron accumulation. *Folia Neuropathol.* 2005;43:286.
187. Bonakdar RA, Guarneri E. Coenzyme Q10. *Complement Altern Med.* 2005;72:1065.
188. Anonymous, Coenzyme Q10. *The Medical Letter.* 2006;48:19.
189. Miles MV, Horn PS, Tang PH, et al. Age-related changes in plasma coenzyme Q10 concentrations and redox state in apparently healthy children and adults. *Clin Chim Acta.* 2004;347:139.
190. Horvath R, Schneiderat P, Schoser BGH, et al. Coenzyme Q10 deficiency and isolated myopathy. *Neurology* 2006;66:253.
191. Lamperti C, Naini A, Hirano M, et al. Cerebellar ataxia and coenzyme Q10 deficiency. *Neurology.* 2003;60:1206.
192. Schapira AHV. Mitochondrial disease. *Lancet.* 2006;368:70.
193. Sandor PS, Di Clemente L, Coppola G, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomised controlled trial. *Neurology.* 2005;64:713.
194. Langsjoen PH, Langsjoen AM. The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications. *BioFactors.* 2003;18:101.
195. Vogel JH, Bolling SF, Costello RB, et al. Integrating complementary medicine into cardiovascular medicine. *J Am Coll Cardiol.* 2005;46:184.
196. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.* Washington, DC: National Academies Press, 2001. Available on line at *www.nap.edu/books, Crawler list 0309072794.* Accessed May 30, 2001.
197. Cooper DA. Carotenoids in health and disease: recent scientific evaluation, research recommendations and the consumer. *J Nutr.* 2004;134:221S.
198. Brown L, Rimm EB, Seddon JM, et al. A prospective study of carotenoid intake and risk of cataract extraction in U.S. men. *Am J Clin Nutr.* 1999;70:517.
199. Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. *Biochem Pharmacol.* 2006;71:1397.
200. West CE, Eilander A, van Lieshout M. Letter to editor. *Am J Clin Nutr.* 2003;133:2917.
201. Harrison EH. Mechanisms of digestion and absorption of dietary vitamin A. *Annu Rev Nutr.* 2005;25:87.
202. Dimitrov NV, Meyer C, Ullrey DE, et al. Bioavailability of beta-carotene in humans. *Am J Clin Nutr.* 1988;48:298.
203. Rock CL, Swendseid ME. Plasma β-carotene response in humans after meals supplemented with dietary pectin. *Am J Clin Nutr.* 1992;55:96.
204. Elinder L, Hadell K, Johansson J, et al. Probucol treatment decreases serum concentrations of diet-derived antioxidants. *Arterioscler Thromb Vasc Biol.* 1995;15:1057.
205. Fredrikzon B, Hernell O, Blackberg L, et al. Bile salt-stimulated lipase in human milk: evidence of activity *in vivo* and of a role in the digestion of milk retinol esters. *Pediatr Res.* 1978;12:1048.
206. Tanumihardjo SA. Assessing vitamin A status: past, present and future. *J Nutr.* 2004;134:290S.
207. Stephenson CB. When does hyporetinolemia mean vitamin A deficiency? *Am J Clin Nutr.* 2000;72:1.
208. Underwood BA. Method for assessment of vitamin A status. *J Nutr.* 1990;120 [Suppl 11]:1459.
209. Blomhoff R, Green MH, Norum KR. Vitamin A: physiological and biochemical processing. *Annu Rev Nutr.* 1992;12:37.
210. Hicks VA, Gunning DB, Olson JA. Metabolism, plasma transport and biliary excretion of radioactive vitamin A and its metabolites as a function of liver reserves of vitamin A in the rat. *J Nutr.* 1984;114:1327.
211. Pryor WA, Stahl W, Rock CL. Beta carotene: from biochemistry to clinical trials. *Nutr Rev* 2000;58:39.

212. Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely low-birth-weight infants. *N Engl J Med*. 1999;340:1962.
213. Ross DA. Recommendations for vitamin A supplementation. *J Nutr*. 2002;131:2902S.
214. Zhou GB, Zhao WL, Wang ZY, et al. Retinoic acid and arsenic for treating acute promyelocytic leukemia. *PLoS Medicine*. 2005;2:33.
215. Mannisto S, Smith-Warner SA, Spiegelman D, et al. Dietary carotenoids and risk of lung cancer in a pooled analysis of seven cohort studies. *Cancer Epidemiol Biomarkers Prev*. 2004;13:40.
216. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. *Lancet*. 2004;364:1219.
217. Voutilainen S, Narmi T, Mursu J, Rissanen TH. Carotenoids and cardiovascular health. *Am J Clin Nutr*. 2006;83:1265.
218. Huiming Y, Chaomin W, Meng M. Vitamin A for treating measles in children. *Cochrane Database Syst Rev*. 2005;19:CD001479.
219. Rahmathullah L, Underwood BA, Thulasiraj R, et al. Reduced mortality among children in Southern India receiving a small weekly dose of vitamin A. *N Engl J Med*. 1990;323:929.
220. Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. *Am J Clin Nutr*. 2006;83:191.
221. Ovesen L. Vitamin therapy in the absence of obvious deficiency. What is the evidence? *Drugs*. 1984;27:148.
222. Melhus H, Michaelsson K, Kindmark A, et al. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. *Ann Intern Med*. 1998;129:770.
223. Oakley GP, Erickson JD. Vitamin A and birth defects: continuing caution is needed. *N Engl J Med*. 1995;333:1414.
224. Fenaux P, DeBooton S. Retinoic acid syndrome: Recognition, prevention and management. *Drug Saf*. 1998;18:273.
225. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr*. 2004;79:362.
226. Glerup H, Mikkelsen K, Pousen L, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. *J Intern Med*. 2000;247:260.
227. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr*. 2005;135:317.
228. Whiting SJ, Calvo MS. Dietary recommendations to meet both endocrine and autocrine needs of vitamin D. *J Steroid Biochem Molec Biol*. 2005;97:7.
229. Weaver CM, Fleet JC. Vitamin D requirements: current and future. *Am J Clin Nutr*. 2004;80:1735S.
230. Vieth R. Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. *J Nutr*. 2006;136:1117.
231. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. *Am J Clin Nutr*. 2004;79:717.
232. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. *Am J Clin Nutr*. 2004;80:1710S.
233. Tylavsky FA, Cheng S, Lyytikainen A, et al. Strategies to improve vitamin D status in Northern European children: exploring the merits of vitamin D fortification and supplementation. *J Nutr*. 2006;136:1130.
234. Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. *J Nutr*. 2005;135:310.
235. Looker AC, Gunter EW. Hypovitaminosis D in medical inpatients. *N Engl J Med*. 1998;339:344.
236. LeBoff MS, Kohlmeier L, Hurwitz S, et al. Occult vitamin D deficiency in postmenopausal U.S. women with acute hip fracture. *JAMA*. 1999;281:1505.
237. Hanley DA, Davison KS. Vitamin D insufficiency in North America. *J Nutr*. 2005;135:332.
238. Binkley N, Krueger D, Cowgill CS, et al. Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization. *J Clin Endocrinol Metab*. 2004;89:3152.
239. Carter GD, Carter R, Jones J, Berry J. How accurate are assays for 25-hydroxyvitamin D? Data from the International Vitamin D External Quality Assessment Scheme. *Clin Chem*. 2004;50:2195.
240. Avioli L, Haddad JG. The vitamin D family revisited. *N Engl J Med*. 1984;311:47.
241. Portale AA, Halloran BP, Murphy MM, et al. Oral intake of phosphorus can determine the serum concentration of 1,25-dihydroxyvitamin D by determining its production rate in humans. *J Clin Invest*. 1986;77:7.
242. Kumar R. Hepatic and intestinal osteodystrophy and the hepatobiliary metabolism of vitamin D. *Ann Intern Med*. 1983;98:662.
243. Smith GR, Collinson PO, Kiely PDW. Diagnosing hypovitaminosis D: serum measurements of calcium, phosphate, and alkaline phosphatase are unreliable, even in the presence of secondary hyperparathyroidism. *J Rheumatol*. 2005;32:684.
244. Sahota O, Masud T, San P, et al. Vitamin D insufficiency increases bone turnover markers and enhances bone loss at the hip in patients with established vertebral osteoporosis. *Clin Endocrinol*. 1999;51:217.
245. Whiting SJ, Calvo MS. Dietary recommendations for vitamin D: a critical need for functional end points to establish an estimated average requirement. *J Nutr*. 2005;135:304.
246. Jones G, Strugnell SA, DeLuca HF. Current understanding of the molecular actions of vitamin D. *Physiol Rev*. 1998;78:1193.

247. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr.* 2004;80:1698S.
248. Breitwieser GE. Calcium sensing receptors and calcium oscillations: calcium as a first messenger. *Curr Top Dev Biol.* 2006;73:85
249. Suda T, Ueno Y, Fujii K, et al. Vitamin D and bone. *J Cell Biochem.* 2002;88:259.
250. Peterlik M, Cross HS. Vitamin D and calcium deficits predispose for multiple chronic diseases. *Eur J Clin Invest.* 2005;35:290.
251. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African Americans and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr.* 2002;76:187.
252. Javorsky BR, Maybee N, Padia SH, Dalkin AC. Vitamin D deficiency in gastrointestinal disease. *Pract Gastroenterol.* 2006;19:52.
253. Henkel AS, Buchman AL. Nutritional support in patients with chronic liver disease. *Nat Clin Pract Gastroenterol Hepatol.* 2006;3:202.
254. Udall JN, Jr. Crohn disease early in life and hypovitaminosis D: where do we go from here? *Am J Clin Nutr.* 2002;76:909.
255. Weber P. The role of vitamins in the prevention of osteoporosis—a brief status report. *Int J Vitam Nutr Res.* 1999;69:194.
256. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D_3. *J Clin Invest.* 1985;76:1536.
257. Spencer H, Rubio N, Rubio E, et al. Chronic alcoholism. Frequently overlooked cause of osteoporosis in men. *Am J Med.* 1986;80:393.
258. Thomas MK, Lloyd-Jones DM, Thadhani RJ, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med.* 1998;338:777.
259. NIH Consensus Statement. Optimal calcium intake. 1994;12:1.
260. Vieth R. The role of vitamin D in the prevention of osteoporosis. *Ann Med.* 2005;37:278.
261. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA.* 2005;293:2257.
262. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D_3) for prevention of fractures in primary care. *BMJ* 2005;330:1003.
263. The RECORD trial group. Oral vitamin D_3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomized placebo-controlled trial. *Lancet.* 2005;365:1621.
264. Avenell A, Gillespie W, Gillespie L, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and postmenopausal osteoporosis. *Cochrane Database Syst Rev.* 2005;3:CD000227.
265. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med.* 2006;354:669.
266. Di Daniele N, Grazia Carbonelli M, Candeloro N, et al. Effect of supplementation of calcium and vitamin D on bone mineral density and bone mineral content in peri- and post-menopause women. A double-blind, randomized, controlled trial. *Pharmacol Res.* 2004;50:637.
267. Buckley LM, Leib ES, Cartularo KS, et al. Calcium and vitamin D_3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis. *Ann Intern Med.* 1996;125:961.
268. Nuti R, Martinin G, Giovani S, et al. Effect of treatment with calcitriol combined with low-dosage alendronate in involutional osteoporosis. *Clin Drug Invest.* 2000;19:55.
269. Janssen HCJP, Samson MM, Verhaar HJJ. Vitamin D deficiency, muscle function, and falls in elderly people. *Am J Clin Nutr.* 2002;75:611.
270. Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. *Am J Public Health.* 2006;96:252.
271. Wactawski-Wende J, Morley Kotchen J, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med.* 2006;354:684.
272. Zitterman A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr.* 2003;89:552.
273. Symposium: Vitamin D deficiency: a significant risk factor in chronic diseases and potential disease-specific biomarkers of vitamin D sufficiency. *J Nutr.* 2005;135:301.
274. Shoji T, Shinohara K, Kimoto E, et al. Lower risk for cardiovascular mortality in oral 1α-hydroxy vitamin D3 users in a haemodialysis population. *Nephrol Dial Transplant.* 2004;19:179.
275. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science.* 2006;311:1770.
276. Soilu-Hanninen M, Airas L, Mononen I, et al. 25-hydroxyvitamin D levels in serum at the onset of multiple sclerosis. *Mult Scler.* 2005;11:266.
277. Lim WC, Hanauer SB, Li YC. Mechanisms of disease: vitamin D and inflammatory bowel disease. *Nat Clin Pract Gastroenterol Hepatol.* 2005;2:308.
278. Schleitoff SS, Zitterman A,Tenderich G, et al. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr.* 2006;83:754.

279. Cooper L, Clifton-Bligh PB, Nery ML, et al. Vitamin D supplementation and bone mineral density in early postmenopausal women. *Am J Clin Nutr.* 2003;77:1324.
280. Heaney RP. The vitamin D requirement in health and disease. *J Steroid Biochem Mol Biol.* 2005;97:13.
281. Rhode CM, DeLuca HF. All-trans retinoic acid antagonizes the action of calciferol and its active metabolite, 1,25-dihydroxycalciferol in rats. *J Nutr.* 2005;135:1647.
282. Slatopolsky E, Weerts C, Thielan J, et al. Marked suppression of secondary hyperparathyroidism by intravenous administration of 1,25-dihyroxy-cholecalciferol in uremic patients. *J Clin Invest.* 1984;74:2136.
283. Wu-Wong JR, Tian J, Goltzman D. Vitamin D analogs as therapeutic agents: a clinical study update. *Curr Opin Investig Drugs.* 2004;5:320.
294. Brown AJ, Dusso S, Slatopolsky E. Vitamin D analogues for secondary hyperparathyroidism. *Nephrol Dial Transplant.* 2002;17 (Suppl 10):10.
285. Levin A, Li YC. Vitamin D and its analogues: Do they protect against cardiovascular disease in patients with kidney disease? *Kidney Int.* 2005;68:1973.
286. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr.* 1999;69:842.
287. Weber P, Bendich A, Machlin LJ. Vitamin E and human health: rationale for determining recommended intake levels. *Nutrition.* 1997;13:450.
288. Brigelius-Flohe R, Kelly FJ, Salonen JT, et al. The European perspective on vitamin E: current knowledge and future research. *Am J Clin Nutr.* 2002;76:703.
289. Jiang Q, Christen S, Shegenaga MK, Ames BN. γ-tocopherol, the major form of vitamin E in the US diet, deserves more attention. *Am J Clin Nutr.* 2001;74:714.
290. Bruno RS, Traber MG. Cigarette smoke alters human vitamin E requirement. *J Nutr.* 2005;135:671.
291. Bauernfeind JC. The tocopherol content of food and influencing factors. *Crit Rev Food Sci Nutr.* 1977;8:337.
292. Maguire LS, O'Sullivan SM, Galvin K, et al. Fatty acid profile, tocopherol, squalene and phytosterol content of walnuts, almonds, peanuts, hazelnuts and the macadamia nut. *Int J Food Sci Nutr.* 2004;55:171.
293. McLaughlin PJ, Weihrauch JL. Vitamin E content of foods. *J Am Diet Assoc.* 1979;75:647.
294. Ford ES, Ajani UA, Mokdad AH. Brief communication: The prevalence of high intake of vitamin E from the use of supplements among U.S. adults. *Ann Intern Med.* 2005;143:116.
295. Schwarzpaul S, Strassburg A, Luhrmann PM, Neurhauser-Berthold M. Intake of vitamin and mineral supplements in an elderly German population. *Ann Nutr Metab.* 2006;50:155.
296. Ford ES, Sowell A. Serum alpha-tocopherol status in the United States population: findings from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol.* 1999;150:290.
297. Thurnham DI, Davies JA, Crump BJ, et al. The use of different lipids to express serum tocopherol:lipid ratios for the measurement of vitamin E status. *Ann Clin Biochem.* 1986;23:514.
298. Refat M, Moore TJ, Kazui M, et al. Utility of breath ethane as a noninvasive biomarker of vitamin E status in children. *Pediatr Res.* 1991;30:396.
299. Knutson MD, Handelman GJ, Viteri FE. Methods for measuring ethane and pentane in expired air from rats and humans. *Free Radic Biol Med.* 2000;28:514.
300. Chan AC. Vitamin E and atherosclerosis. *J Nutr.* 1998;128:1593.
301. Steiner M. Vitamin E, a modifier of platelet function: rationale and use in cardiovascular and cerebrovascular disease. *Nutr Rev.* 1999;57:306.
302. Hacquebard M, Carpentier YA. Vitamin E: absorption, plasma transport and cell uptake. *Curr Opin Clin Nutr Metab Care.* 2005;8:133.
303. Leonard SW, Good CK, Gugger ET, Traber MG. Vitamin E bioavailability from fortified breakfast cereal is greater than that from encapsulated supplements. *Am J Clin Nutr.* 2004;79:86.
304. Berdanier CD. *Advanced nutrition: micronutrients.* Boca Raton, FL: CRC Press, 1998.
305. Williams MT, Hord NG. The role of dietary factors in cancer prevention: beyond fruits and vegetables. *Nutr Clin Pract.* 2005;20:451.
306. Kelemen LE, Cerhan JR, Lim U, et al. Vegetables, fruit, and antioxidant-related nutrients and risk of non-Hodgkin lymphoma: a National Cancer Institute-Surveillance, Epidemiology, and End Results population-based case-control study. *Am J Clin Nutr.* 2006;83:1401.
307. Park EJ, Pezzuto JM. Botanicals in cancer chemoprevention. *Cancer Metastasis Rev.* 2002;21:231.
308. Halvorsen BL, Carlsen MH, Phillips KM, et al. Content of redox-active compounds (i.e., antioxidants) in foods consumed in the United States. *Am J Clin Nutr.* 2006;84:95.
309. Heinecke JW. Lipoprotein oxidation in cardiovascular disease: chief culprit or innocent bystander? *JEM.* 2006;203:813.
310. Nutritional status: blood vitamins A, E, B_6, B_{12}, folic acid, and carotene. Euronut SENECA investigators. *Eur J Clin Nutr.* 1991;45:63.
311. Rosenblum JL, Keating JP, Prensky AL, et al. A progressive neurologic syndrome in children with chronic liver disease. *N Engl J Med.* 1981;304:503.
312. Tanyel MC, Mancano LD. Neurologic findings in vitamin E deficiency. *Am Fam Physician.* 1997;55:197.
313. Jialal I, Devaraj S. Scientific evidence to support a vitamin E and heart disease health claim: research needs. *J Nutr.* 2005;135:348.
314. Knekt P, Ritz J, Pereira MA, et al. Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. *Am J Clin Nutr.* 2004;80:1508.

315. Kris-Etherton PM, Lichtenstein AH, Howard BV, et al. for the Nutrition Committee of the American Heart Associatioin Council on Nutrition, Physical Activity, and Metabolism. Antioxidant vitamin supplements and cardiovascular disease. *Circulation.* 2004;110:637.
316. Ascherio A, Rimm EB, Hernan MA, et al. Relation of consumption of vitamin E, vitamin C, and carotenoids to risk for stroke among men in the United States. *Ann Intern Med.* 1999;130:963.
317. Devaraj S, Jialal I. Failure of vitamin E in clinical trials: is gamma-tocopherol the answer? *Nutr Rev.* 2005;63:290.
318. Hercberg S, Galan P, Preziosi P, et al. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med.* 2004;164:2335.
319. Pham DQ, Plakogiannis R. Vitamin E supplementation in cardiovascular disease and cancer prevention: part 1. *Ann Pharmacotherapy.* 2005;39:1870.
320. The HOPE and HOPE-TOO trial investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer. *JAMA.* 2005;293:1338.
321. Cho E, Hunter DJ, Spiegelman D, et al. Intakes of vitamins A, C and E and folate and multivitamins and lung cancer: a pooled analysis of 8 prospective studies. *Int J Cancer.* 2006;118:970.
322. Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest.* 2004;114:147.
323. Bugianesi E, Marzocchi R, Villanova N, Marchesini G. Non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH): treatment. *Best Pract & Res Clin Gastroenterol.* 2004;18:1105.
324. Harrison SA, Torgerson S, Hayashi P, et al. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. *Am J Gastroenterol.* 2003;98:2485.
325. Bugianesi E, Gentilcore E, Manini R, et al. A randomized controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. *Am J Gastroenterol.* 2005;100:1082.
326. Paquot N, Delwaide J. *Curr Opin Nutr Metab Care.* 2005;8:183.
327. Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: part 2. *Ann Pharmacother.* 2005;39:2065.
328. Petersib RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cogjtive impairment. *N Engl J Med.* 2005;352:23.
329. Berman K, Brodaty H. Tocopherol (vitamin E) in Alzheimer's disease and other neurodegenerative disorders. *CNS Drugs.* 2004;18:807.
330. Rumbold AR, Crowther CA, Haslam RR, et al. Vitamins C and E and the risks of preeclampsia and perinatal complications. *N Engl J Med.* 2006;354:17.
331. Roonpraiwan R, Suthutvoravut U, Feungpean B, Phuapradit P. Effect of oral vitamin E supplementation in children with cholestasis. *J Med Assoc Thai.* 2002;85 Suppl 4:S1199.
332. Argyriou AA, Chroni E, Koutras A, et al. Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. *Neurology.* 2005;64:26.
333. Thiele JJ, Hsieh SN, Ekanayake-Mudiyanselage S. Vitamin E: Critical review or its current use in cosmetic and clinical dermatology. *Dermatol Surg.* 2005;31:805.
334. Horwitt MK. Therapeutic uses of vitamin E in medicine. *Nutr Rev.* 1980;38:105.
335. Sokol RJ, Guggenheim MA, Iannaccone ST, et al. Improved neurologic function after long-term correction of vitamin E deficiency in children with chronic cholestasis. *N Engl J Med.* 1985;313:1580.
336. Sokol RJ, Butler-Simon N, Conner C, et al. Multicenter trial of *d*-alpha-tocopheryl polyethylene glycol 1000 succinate for treatment of vitamin E deficiency in children with chronic cholestasis. *Gastroenterology.* 1993;104:1727.
337. Sitrin MD, Lieberman F, Jensen WE, et al. Vitamin E deficiency and neurologic disease in adults with cystic fibrosis. *Ann Intern Med.* 1987;107:51.
338. Hittner HM, Godio LB, Rudolph AJ, et al. Retrolental fibroplasia: efficacy of vitamin E in a double-blind clinical study of preterm infants. *N Engl J Med.* 1981;305:1365.
339. Corash L, Spielberg S, Bartsocass C, et al. Reduced chronic hemolysis during high-dose vitamin E administration in Mediterranean-type glucose-6-phosphate dehydrogenase deficiency. *N Engl J Med.* 1980;303:416.
340. Natta CL, Machlin LJ, Brin M. A decrease in irreversibly sickled erythrocytes in sickle cell anemia patients given vitamin E. *Am J Clin Nutr.* 1980;33:968.
341. Spencer AP, Carson DS, Crouch MA. Vitamin E and coronary artery disease. *Arch Intern Med.* 1999;159:1313.
342. Bendich A. Safety issues regarding the use of vitamin supplements. *Ann N Y Acad Sci.* 1992;669:300.
343. Miller ER III, Pastor-Barriuso R, Dalal D, et al. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med.* 2005;142:37.
344. Adams J, Pepping J. Vitamin K in the treatment and prevention of osteoporosis and arterial calcification. *Am J Health-Syst Pharm.* 2005;62:1574.
345. Olson RE, Chao J, Graham D, et al. Total body phylloquinone and its turnover in human subjects at two levels of vitamin K intake. *Br J Nutr.* 2002;87:543.
346. Booth SL, Suttie JW. Dietary intake and adequacy of vitamin K. *J Nutr* 1998;128:785.
347. Helphingstine CJ, Bistrian BR. New Food and Drug Administration requirements for inclusion of vitamin K in adult parenteral multivitamins. *JPEN J Parenter Enteral Nutr.* 2003;27:220.
348. Bolton-Smith C, Price RJG, Fenton ST, et al. Compilation of a provisional UK database for the phylloquinone (vitamin K_1) content of foods. *Br J Nutr.* 2000;83:389.

349. Booth SL, Pennington JA, Sadowski JA. Food sources and dietary intakes of vitamin K-1 (phylloquinone) in the American diet: data from the FDA Tsotal Diet Study. *J Am Diet Assoc.* 1996;96:149.
350. Elder SJ, Haytowitz DB, Howe J, et al. Vitamin K contents of meat, dairy, and fast food in the U.S. diet. *J Agric Food Chem.* 2006;54:463.
351. Booth SL, Centurelli MA. Vitamin K: a practical guide to the dietary management of patients on warfarin. *Nutr Rev.* 1999;57:288.
352. Johnson MA. Influence of vitamin K on anticoagulant therapy depends on vitamin K status and the source and chemical forms of vitamin K. *Nutr Rev.* 2005;63:91.
353. Vermeer C, Shearer MJ, Zittermann A, et al. Beyond deficiency: potential benefits of increased intakes of vitamin K for bone and vascular health. Eur J Nutr 2004;43:325.
354. Stafford DW. The vitamin K cycle. *J Thromb Haemost.* 2005;3:1873.
355. Spronk HM, Sourte BA, Schurgers LJ, et al. Tissue-specific utilization of menaquinone-4 results in the prevention of arterial calcification in warfarin-treated rats. *J Vasc Res.* 2003;40:531.
356. Wallin R, Hutson SM. Warfarin and the vitamin K-dependent γ-carboxylation system. *Trends Molec Med.* 2004;7:299.
357. Hey E. Vitamin K—what, why, and when. *Arch Dis Child Fetal Neonatal Ed.* 2003;88:F80.
358. Booth SL, Tucker KL, Chen H, et al. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. *Am J Clin Nutr.* 2000;71:1201.
359. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteroporosis Prevention Study. *Am J Med.* 2004;117:549.
360. Feskanich D, Willett WW, Rockett H, et al. Vitamin K intake and hip fractures in women: a prospective study. *Am J Clin Nutr.* 1999;69:74.
361. Jamal SA, Browner WS, Bauer DC, et al. Warfarin use and risk for osteoporosis in elderly women. *Ann Intern Med.* 1998;128:829.
362. Caraballo PJ, Heit JA, Atkinson EJ, et al. Long-term use of oral anticoagulants and the risk of fracture. *Arch Intern Med.* 1999;159;1750.
363. Brown JP, Josse RG, for the Scientific Advisory Council of the Osteoporosis Society of Canada. *CMAJ.* 2002;167 (10 Suppl):S1.
364. Duggan P, O'Brien M, Kiely M, et al. Vitamin K status in patients with Crohn's disease and relationship to bone turnover. *Am J Gastroenterol.* 2004;99:2178.
365. Orbak Z, Selimoglu A, Doneray H. Inherited vitamin K deficiency: case report and review of literature. *Yonsei Med J.* 2003;44:923.
366. Fiore LD, Scola MA, Cantillon CE, Brophy MT. Anaphylactoid reactions to vitamin K. *J Thromb Thrombolysis.* 2001;11:175.

7 MINERALS

FACTORS INVOLVED IN MINERAL DEFICIENCY AND OVERLOAD

The minerals important in human nutrition can be classified into three groups: those stored in the body in large quantities (Na, K, Ca, Mg, P); those present in trace amounts whose role in human nutrition has been determined (Fe, Zn, Cu, I, F, Se, Cr); and those present in trace amounts (Co, Mo, Mn, Cd, As, Si, V, Ni) that are clearly important in laboratory animals but whose role in human nutrition is uncertain. Of this last group, only manganese is discussed in detail in this chapter because some deficiency of that element has been demonstrated in humans.

Intestinal Absorption and Secretion

Divalent Cations

The major divalent cations (Ca, Mg, Zn, Cu) are not absorbed efficiently. They are ingested in forms that are poorly soluble and must be converted to more soluble salts, and transport

across the apical membrane is relatively slow. Moreover, significant amounts of these ions are secreted into the intestinal lumen each day via intestinal, pancreatic, and biliary juices. Thus, deficiency develops in the setting of either diarrhea or malabsorption. Iron is absorbed best in its divalent form and is lost mainly through bleeding into the gastrointestinal tract or from the uterus.

Monovalent Cations

The major monovalent cations (Na, K) are also secreted in digestive juices, but they are very efficiently reabsorbed. Nonetheless, their concentrations are so high that deficiency can develop when large amounts of body fluids are lost. Therefore, intestinal diseases often lead to decreases in the body stores of many minerals. Many minerals are reabsorbed by renal (Na, K, Ca, Mg, P) as well as intestinal cells. Thus, the potential for loss is great when these organs are diseased.

Effect of Diet on Acid-Base Balance and Renal Acid Excretion

Foods that contain an excess of fixed anions (Cl, P, S) over fixed cations (Na, K, Ca, Mg) can promote acidification of body fluids. The intestine can exchange chloride for bicarbonate, and so modify the effect of ingested anions. Moreover, the liver can produce sulfate from sulfur-containing amino acids, or produce bicarbonate from citrate. Thus, the effect of diet on overall acid-base status is complex. A potential renal acid load of foods (PRAL) has been calculated. Fruits and vegetables reduce renal acid secretion, milk and yogurt provide mild acid loads, and meat, fish, poultry, cheese, and some grain products with higher P and S content can provide >3.5 mEq per 100 g of serving (1). Total net acid excretion and urinary pH can be influenced by the diet and can account for much of the variability in acid excretion in normal subjects.

Evaluation of Deficiency

Body Stores

Only in the case of iron do blood levels correlate with body stores. Bone is the major storage site of several minerals (Ca, P, Mg, F), and levels of these minerals in bone do not equilibrate rapidly with blood levels. In the case of some minerals (Na, K, Ca), many compensatory mechanisms exist to maintain blood levels within the normal range. These mechanisms are designed to regulate extracellular fluid concentrations rather than body stores. Because blood levels do not usually correlate well with body stores, deficiencies of many minerals are difficult to assess from a practical point of view. The diagnosis of mineral deficiency should be suspected first by the presence of appropriate symptoms or signs in a high-risk setting. Table 7-1 outlines these general features. The details of each deficiency state are described in the sections on each mineral.

Water Balance

In normal adults total body water accounts for ~60% of body weight, being somewhat lower in women and in the elderly, who can have smaller muscle mass and larger fat stores. Two-thirds of the water is intracellular, and only ~7% is intravascular, and water moves freely between body compartments according to the effective osmotic pressure (2). The major extracellular ions are sodium, potassium, chloride, and bicarbonate. Thus, changes in volume status can lead to changes in ion concentrations, most rapidly in the plasma. Weight gain is the best measure of volume overload, but edema may not be apparent until 2 to 4 kg of water have been retained (3). Other features of water overload may be anxiety or agitation, but if sodium overload is the cause of increased fluid retention, then signs of congestive heart failure or dependent edema may develop. The best measure of volume depletion in adults is postural hypotension, manifested by a fall in systolic blood pressure of >15 mm Hg and/or an increase in pulse of >15 beats per minute immediately after a shift in position. Other features of volume depletion include decreased skin turgor, dry mouth, thirst, and oliguria. When severe, weakness, lethargy or coma, and anuria may develop.

Water Requirements

Total water intake includes water in beverages (including drinking water), and water in food. On average, water in beverages accounts for ~80% of water intake in adults (2). The

TABLE 7-1. Clinical Manifestations of Mineral Deficiency and Toxicity States

Mineral	Major functions	Major causes of deficiency	Clinical signs	
			Deficiency	Toxicity
Na	ECF volume, muscle and nerve function, nutrient absorption	GI, renal, and skin losses	Hypovolemia, weakness, nausea	Confusion, stupor
K	Acid/base balance, membrane transport, muscle contraction, protein synthesis	GI (nausea, diarrhea) renal (diuretics) losses	Arrhythmias, muscle weakness, nausea, irritability	Paresthesias, confusion, cardiac depression
Cl	Acid–base balance, osmotic pressure, HCl in stomach	GI (vomiting, diarrhea), renal (diuretics) losses	Alkalosis, muscle cramps, anorexia	Acidosis with renal failure
Ca	Bone/tooth formation, blood clotting, nerve transmission, muscle contraction, secretion	↓ Intake, malabsorption, ↑ PTH	Tetany, arrhythmia, osteomalacia	Anorexia, constipation, vomiting, coma
Mg	Cell metabolism, enzyme activation, nerve/muscle action	Malabsorption, renal tubular leak, EtOH	Muscle twitching, arrhythmia, nausea, weakness, confusion	Nausea, ↓ BP, confusion, ↓ reflexes
P	Bone/tooth formation, metabolic functions, nucleic acid formation	↑ renal excretion, wasting diseases	Weakness, bone pain, rhabdomyolysis,	Secondary ↑ parathyroidism
Fe	Heme formation, enzyme cofactor	Blood loss (GI, gynecologic) ↑ needs (pregnancy), ↓ intake (infants)	Anemia, increased infection (children)	Cirrhosis, heart failure, skin pigmentation
Zn	Enzyme cofactor, CO_2 transfer, DNA function, wound healing	Diarrhea, malabsorption	Stunted growth, skin changes, anorexia, lethargy, alopecia, photophobia	Cu deficiency, ↓ immunity, gastric erosions
Cu	Enzyme cofactor function of nerves, vascular/bone structure	Malnutrition, prematurity	Anemia, neutropenia, skeletal defects, nerve degeneration	Vomiting, cardiomyopathy, congestive heart failure
I	Thyroxine synthesis	↓ Intake	Goiter, hypothyroidism	Hyperthyroidism
Mn	Enzyme cofactor	One case reported	↑ Cholesterol, weight loss, dermatitis, change in hair color	Neural damage (e.g., Wilson disease)
Cr	Insulin cofactor	TPN	Glucose intolerance, ↑ lipids, peripheral neuropathy	None for trivalent Cr
F	Bone/tooth formation	↓ Intake	Dental caries	Brittle bones, thickened cortex, mouth numbness, salty taste, diarrhea
Se	GSH peroxidase cofactor	↓ Intake, TPN	Cardiomyopathy, locomotor disturbance	Hair loss, fatigue, polyneuritis, gastroenteritis
Mo	Cofactor for oxidases (sulfite, xanthine, aldehyde)	Metabolic defect in Mo cofactcor	Neurologic abnormalities	None

BP, blood pressure; ECF, extracellular fluid; EtOH, ethyl alcohol; GI, gastrointestinal; GSH, reduced glutathione; PTH, parathyroid hormone; TPN, total parenteral nutrition.

"requirement" for water is established in the form of an adequate intake (AI), set to prevent the acute effects of dehydration. The amount of water required may increase over the AI due to physical activity and environmental conditions. Whether sodium and other minerals are needed along with water to maintain plasma osmolality depends upon whether fluid is lost from the lungs (mostly water), sweat (low sodium content), or gastrointestinal tract from vomiting (half isosmolar sodium and chloride) or from diarrhea (isosmolar sodium along with potassium and some bicarbonate). The AI for total water intake is based on median intake from the U.S. Third National Health and Nutrition Examination Survey (NHANES III). AI for men and women age 19 to 70 is 3.7 and 2.7 L per day, respectively (2). The amount needed to achieve this AI from total beverages should be ~3.0 L (~13 cups) and 2.2 L (~9 cups) per day for men and women, respectively.

Mineral/Metal Overload and Toxicity

Many minerals are widely available in foods; moreover, they are easily provided as supplements. For these reasons, and because it is difficult to assess body stores, it is not surprising that overload syndromes occur more frequently in the case of minerals than of vitamins. Sodium, potassium, calcium, iron, and fluoride are the minerals most commonly involved in overload syndromes. Table 7-1 outlines the general features of overload syndromes.

There are some metals that cause toxicity in humans, but are not required nutrients, yet toxic amounts can be ingested in foods (2). Organic arsenic can be found in fish, meat and poultry, dairy products, grains and cereals, and fats and oil; inorganic arsenic is found in rice, flour, and grape juice. Arsenic toxicity is manifested by vomiting, colic, diarrhea, and renal failure. Boron is found most concentrated in fruit-based beverages, tubers, and legumes, but toxic amounts could only be ingested as boric tartrate, used for epilepsy at doses >20 mg per kg per day. Nickel is most abundant in nuts and legumes, sweeteners, and chocolates, but toxicity (nausea, abdominal pain, diarrhea, vomiting) has occurred only after ingestion of water contaminated with nickel sulfate. Vanadium content is highest in mushrooms, shellfish, some spices including black pepper, and some processed foods, but vanadyl sulfate (up to 100 mg per day) and sodium metavanadate (up to 125 mg per day) have been used as supplements for diabetics and by weight-training athletes, with possible effects on renal morphology and serum urea concentration.

Toxicity from other heavy metals in food includes syndromes due to ingestion of cadmium (Cd), mercury (Hg), thallium (Tl), tin (Sn), and lead (Pb) occurring due to contamination with industrial waste (Cd, Hg, Tl), fungicides (Hg), elution from metal containers (Sn), or from calcium supplements derived from limestone (Pb) (4). Cadmium can be ingested in shellfish, grains, and peanuts, and causes nausea, vomiting, myalgia, abdominal pain, and renal failure. Mercury is found in contaminated fish and in grains treated with fungicide, causing numbness, weakness, spastic paralysis, blindness, and coma. Thallium can be transferred from soil to food crops, and excessive intake from crops grown on contaminated land can cause nausea, vomiting, diarrhea, parasthesias, hair loss, and polyneuropathy. Tin can contaminate foods stored in tin cans, but the decreased use of these has led to falling levels of ingestion. Tin toxicity can cause nausea, vomiting, and diarrhea. Lead used to contaminate some wines by elution at acid pH from brass tubing, but such tubing has been removed from commercial wine production. The only significant source of dietary lead in the U.S. diet is from calcium-supplemented food where the calcium is derived from limestone (5). Chronic lead toxicity in children can cause weight loss, weakness, and anemia.

Treatment of Mineral Deficiency

Oral therapy is discussed in detail in this chapter. Parenteral therapy with major minerals (Na, K, Ca, Mg, P) is discussed in Chapter 11. Most healthy people do not require mineral supplements. However, certain groups of patients at high risk for deficiency of individual minerals should receive supplements. In infancy, iron may be needed at 6 to 8 weeks of life, especially if the mother has been deficient. Low-birth-weight infants require zinc. Iron supplements are often required by women after menarche and before menopause. More iron and calcium are needed during pregnancy because requirements are increased (see also Chapter 4). Persons who consume little or no milk require calcium; those on vegetable diets require iron. Patients with malabsorption may require calcium, magnesium, and zinc.

In acute disorders characterized by severe vomiting or diarrhea, sodium and potassium must be replaced. Patients with chronic gastrointestinal bleeding may require iron replacement. Elderly patients whose calcium intake is decreased or who have osteopenia may require calcium supplements. The sections on the individual minerals should be consulted for details.

MAJOR MINERALS

Sodium (and Chloride)

Requirements

Sodium and chloride are found together in most foods, and the requirements are therefore considered together (2). There are examples in which one or the other mineral can be lost in excess of the other, or where the physiology of transport differs, and these differences will be discussed. Total body sodium levels range from 52 to 60 mmol per kg in male adults and from 48 to 55 mmol per kg in female adults. The body of a 70-kg man may contain between 3,600 and 4,200 mmol of sodium (83 and 97 g). About one-fourth of this, largely in the skeleton, is not exchangeable. Exchangeable sodium averages 40 mmol per kg in males and 37 mmol per kg in females. Changes in sodium concentration are corrected even at the expense of volume distribution. The kidney regulates sodium excretion by producing aldosterone. When sodium intake decreases, aldosterone levels increase, and urinary excretion of sodium falls. When sodium intake is high, urinary excretion rises. Thus, obligatory sodium losses are small in comparison with body stores. Minimal urinary and fecal losses are each about 23 mg (1 mmol) daily. Total body water losses contain from 46 to 92 mg of sodium (2 to 4 mmol) daily.

Adequate Intake. Minimal sodium needs in normal persons, when adaptation is maximal and sweating is minimal, can be met by an intake of 4 to no more than 8 mmol (92 to 184 mg) daily. The requirement increases when the production of sweat (containing 25 mmol of sodium per liter) increases or losses in the urine or stool increase in disease states. Because of wide variations in physical activity and ambient temperatures, the AI is set for young adults, age 19 to 50, at 1.5 g (65 mmol) per day (2). For children and adolescents age 9 to 18 the AI is the same, based on extrapolation from the adult AI, based on energy intake. The sodium requirement in children is set somewhat below that for adults: 120 mg for infants ages 0 to 6 months, 370 mg for infants ages 7 to 12 months, 1.0 g for children 1 to 3 years old, and 1.2 g for children 4 to 8 years old. The requirement in infants is largely provided by human milk (7 mmol per L) or cow's milk (21 mmol per L). In pregnancy, another 11 kg is added to the mother's body weight, of which 35% to 40% is extracellular fluid. This amounts to an additional 700 mmol of sodium, or 3 mmol (69 mg) per day, throughout the pregnancy. However, the AI for healthy adults is considered adequate to cover these needs during pregnancy and lactation. The AI for sodium (and chloride) for older adults and for the elderly is somewhat less, being 1.3 g (55 mmol) per day for adults aged 50 to 70 years, and 1.2 g (50 mmol) per day for men and women >71 years old. The AI for chloride is set at a molar equivalent to that of sodium, so the AI for chloride for adults age 19 to 50 is 2.3 g (65 mmol) per day, equivalent to 3.8 g of sodium chloride. Although this value is not a recommended dietary intake, there are no data to suggest that more is needed.

Tolerable Upper Intake Level (UL). The DRI committee used the adverse effects of high sodium intake on blood pressure to establish the rationale for setting the UL for salt intake. Review of 10 meta-analyses of studies on salt intake and blood pressure determined that there was a direct and dose-related relationship between these factors throughout the whole spectrum of salt intake (2). Below an intake of 2.3 g (100 mmol) of sodium per day (3.8 g of salt), the effect of sodium restriction was larger. However, many of these interventional trials were for periods of less than 6 months. Patients with idiopathic hypertension, diabetes, and chronic renal disease, and older persons or African Americans are more sensitive to the effects of increased salt intake. The situation is further confounded by the observation that this rise in blood pressure can be altered by diets low

in fat, or high in potassium or other minerals. Other factors, such as weight, level of exercise, genetic differences, and alcohol intake also affect the response to salt. Although the DRI Committee recognized the imprecision behind the estimate, they set the UL at 2.3 g (100 mmol) of sodium per day (3.8 g of salt). The comparable molar UL for chloride is 3.5 g per day.

One view states that sodium is only one of many factors in hypertension, and that even randomized interventions (30% to 50% decrease in sodium intake) produce very modest changes (decrease of ~1 mm Hg in systolic pressure) (6). The Dietary Approaches to Stop Hypertension (DASH) study compared a typical American diet (high in fat, low in fiber, low in potassium and calcium) with a diet rich in fruits and vegetables, both without and with low-fat dairy products (DASH diet); sodium intake and weight were kept stable throughout the 8-week trial in patients with systolic pressures below 160 mm Hg and diastolic pressures between 80 and 95 mm Hg (7). The DASH diet lowered systolic blood pressure by 11.4 mm Hg and diastolic blood pressure by 5.5 mm, much better results than those obtained with low-sodium diets. The National Heart, Lung, and Blood Institute 1999 Workshop on Sodium and Blood Pressure agreed that sodium restriction is most beneficial for older persons with established hypertension, but that only a small percentage of the U.S. population is sensitive to the hypertensive effect of sodium (6). Moreover, much of the effect may represent a lower intake of potassium, calcium, and other minerals, rather than an excessive intake of sodium. In the DASH-sodium diet, the average intake was 1.5 g (65 mmol), estimated by mean urinary excretion (7). A later study by the DASH-Sodium Collaborative Research Group studied 412 subjects who ate low, medium, and high sodium foods for 30 days in random order, both with the DASH and control diets (8). At each sodium level, systolic blood pressure was lower with the DASH diet group, the drop being 11.5 mm Hg in patients with hypertension, and 7.1 mm Hg in those without. The decrease in sodium intake associated with a fall in systolic blood pressure was weakly correlated with a decrease in plasma sodium, suggesting a mechanism (decreased extracellular fluid volume) that could explain the blood pressure findings (9).

Proponents of the other point of view discount the small effects of randomized low-sodium trials because of their short time frame and cite data suggesting a high prevalence of sodium sensitivity (10). This argument has received support from the Cochrane systematic review that analyzed 11 trials (three in normotensives and eight in hypertensives) with follow up from 6 months to 7 years, and found only a modest reduction in blood pressure (1.1 mm Hg systolic) that was not related to reduction in sodium intake (11). However, another systematic review accepting trials of a minimum of 4 weeks duration (17 normotensive, 11 hypertensive) found a correlation between the magnitude of salt reduction and that of blood pressure (12). Studies of other factors, such as loss of weight, increased physical activity, and moderation of alcohol intake show that blood-pressure-lowering effects can be as low as those found using medications (13). For these reasons, and because most people do not reach the currently recommended level of sodium intake, the issue is still unresolved, but both groups agree that sodium restriction for elderly hypertensives is a reasonable approach.

Food Sources

In Western societies, an adult with free access to salt consumes from 2.3 to 6.9 g (100 to 300 mmol) of sodium per day, or from 8 to 12 g (140 to 250 mmol) of sodium chloride. Daily sodium intake alone can increase to 12 g (250 mmol) in very hot climates when hard work increases sweating (14). Most of the sodium is added to foods as salt (NaCl). Of total dietary sodium, about one-third comes from the shaker, one-third from processing, and one-third from the food itself. Cheese, milk, and shellfish, in addition to meat, fish, and eggs, are good natural sources of sodium. Cereals, fruits, and vegetables are low in salt unless it is added during processing. The amount of salt added in processing can be considerable.

Salt is added to foods to extract moisture from the food, in order to prevent spoiling. High salt concentrations may also prevent growth of some bacteria. In addition, salt adds flavor to processed foods, and adds texture to dried foods, such as crackers. Table 7-2 lists the sodium content of some foods at different stages of preparation and preservation.

Normally, sodium must be added to some cereals, such as those containing bran or fiber, to increase palatability. In other cereals (e.g., wheat cereals), the range of sodium content is very wide. The sodium content of some natural foods is listed in Table 7-3.

TABLE 7-2. Effect of Food Processing on Sodium Content

Food	State	Portion	Na content (mg)[a]
Corn	Fresh kernels	1/2 cup	12
	Canned kernels	1/2 cup	190
	Canned, creamed	1/2 cup	365
Potato	Baked	1 each	16
	Mashed, instant	1 cup	733
	Chips	14 chips	133
Tomato	Fresh chopped	1 cup	11
	Canned whole	1 cup	390
	Juice	1 cup	881

[a] These are representative figures, not brand-specific.

Much sodium can be added to foods in the form of condiments, fats, and salad dressings. Some of the most commonly used products are listed in Table 7-4.

A full list of the sodium content of foods is presented in the U.S. Department of Agriculture (USDA) booklet entitled *The Sodium Content of Your Food* (Home and Garden Bulletin No. 233, U.S. Government Printing Office, Washington, DC). Some labels express sodium content in grams or milligrams. Some diets list salt content or milliequivalents of sodium. To convert salt to sodium content, multiply milligrams of salt by 0.4, the fraction of sodium chloride weight that represents sodium. To convert sodium in milligrams to milliequivalents, divide milligrams by 23, the atomic weight of sodium. 1 tsp of salt = 2,325 mg of sodium.

Sodium in Prepared Foods. In food preparation, a number of compounds are added besides sodium chloride to increase the sodium content. These are listed below as they appear on labels:

Monosodium glutamate (MSG)—in packaged and frozen foods
Baking powder—in breads and cakes
Baking soda (sodium bicarbonate)—in breads and cakes. 1 tsp = 1,000 mg of sodium
Brine—in processed foods (e.g., pickles)
Disodium phosphate—in quick-cooking cereals and cheeses
Sodium alginate or caseinate—as thickener and binder
Sodium benzoate or nitrite—as preservative
Sodium hydroxide—to soften skins of fruits and olives
Sodium propionate—to inhibit mold in cheeses
Sodium sulfite—as preservative in dried fruit
Sodium citrate—as buffer for canned and bottled citrus drinks

For practical advice on following a low sodium diet, see Chapter 12.

Sodium in Water and Medications. In addition to food, sodium is present in drinking water and in medications. Water may contain very little sodium or as much as 1,500 mg per L, depending on the degree of softening, a process that raises the sodium content of water. The various departments of public health can usually supply information on the sodium content of local water supplies.

Most medications do not contain enough sodium to present a problem, but a few are very high in sodium. Table 7-5 lists some of these. In general, liquid formulas contain more sodium than do capsules or tablets.

Assessment

Clinical. The signs of total body sodium excess are weight gain and edema. The signs of total body sodium deficiency are manifestations of hypovolemia and can include decreased

TABLE 7-3. Approximate Sodium Content of Natural Foods

Negligible	2–5 mg	5–9 mg	25–60 mg	≥120 mg
Butter, unsalted	Fruits (1/2 cup)	Bread without salt (slice)	Muscle or organ meat (1 oz)	Milk (1 cup)
Cream (tbs)	Corn, potato, peas, beans (1/2 cup)	Selected dry cereals (puffed rice, puffed wheat, shredded wheat (1 cup)	1 egg Fish (1 oz) Root vegetables (celery, beets, turnip)	Salted butter (1 oz) Vegetable margarines (1 oz)
	Nuts (raw)			Processed meats (1 oz)
Cooking fat (tsp)		Most vegetables (1/2 cup)	Artichoke	

skin turgor, hypotension, tachycardia, dry tongue or axillae, sunken eyes, and weight loss. In older adults, other explanations are often present for all these signs (15). Orthostatic hypotension is often used, defined in the American Academy of Neurology consensus statement as a decrease in systolic blood pressure of 20 mm Hg or in diastolic blood pressure of 10 mm Hg within 3 minutes of standing (16). Some clinicians prefer an increase in the pulse rate of 5 to 12 beats per minute (17). However, postprandial hypotension resulting from splanchnic blood pooling is common in older patients, and blood loss is a common cause of postural hypotension. Usually, the decision to proceed with hydration therapy depends on a consideration of all the findings of the clinical and laboratory evaluation.

Serum Sodium and Chloride. Sodium and chloride are measured by ion-selective electrodes in either clotted blood or anticoagulated blood (not ethylenediaminetetraacetic

TABLE 7-4. Representative Sodium Content of Condiments

Product	Portion	Na content (mg)	Na content (mmol)
Baking powder	1 tsp	339	15
Baking soda	1 tsp	821	36
Catsup	1 tbs	202	9
Chili powder	1 tsp	25	1
Garlic salt	1 tsp	1,620	70
Meat tenderizer	1 tsp	1,750	76
Monosodium glutamate	1 tsp	492	21
Mustard, prepared	1 tsp	65	3
Onion salt	1 tsp	1,650	72
Olives, green	10 ea	936	41
Pickle, dill	1 medium	928	41
Pickle, sweet	1 tbs	107	40
Table salt	1 tsp	1,938	84
A-1 sauce	1 tbs	275	12
Barbecue sauce	1 tbs	130	6
Soy sauce, regular	1 tbs	1,029	45
Soy sauce, low-sodium	1 tbs	300	13
Worcestershire sauce	1 tbs	206	9
Butter, regular	1 tbs	116	5
Margarine	1 tbs	140	6
Salad dressing, bottled	1 tbs	109–224	5–10

TABLE 7-5. Sodium Content in Selected Medications (Sodium per Therapeutic Unit[a])

<5 mg	5–25 mg	25–100 mg	>100 mg
Penicillin, potassium	Phenytoin	Penicillin, sodium	Alka-Seltzer (521 per tablet)
Analgesics (most)	Maalox liquid	Synthetic penicillins, sodium	Bromo-Seltzer (717 per tablet)
Nonpenicillin antibiotic tablets	Amphojel suspension	Dramamine	Sal Hepatica (1,000 per tsp)
Vitamin tablets	Titralac liquid[a]	Antibiotic suspensions	Oral phosphate for colonoscopy
Metamucil	Kaopectate	Colace	Sodium bicarbonate
Diuretics	Milk of magnesia		
Antihypertensives	Metamucil instant mix		
Antihistamines	Endocrine agents		
$Mg/Al(OH)_3$ antacid tablets (many)	Cold syrups		
Mylanta liquid	Sedative elixirs		
Riopan liquid	Liquid vitamins		
Laxatives (many)	Di-Gel liquid		
Psychoactive drugs			
Sedative capsules			

[a] The therapeutic unit of antacids is considered to be 30 mL of liquid or 2 tablets. The therapeutic dose of Titralac is 5 mL.

acid, or EDTA). The serum sodium level (normal, 135 to 145 mmol per L) and chloride level (normal, 99 to 110 mmol per L) does not reflect the total body sodium but rather the relationship between total body sodium and extracellular fluid (ECF) volume. A patient with excess total body sodium, manifested by edema, may have a low, normal, or high serum level of sodium depending on whether ECF volume is increased to a level in excess of, even with, or less than that of the total body sodium. Thus, a patient with edema and a serum sodium level of 125 mmol per L has a total body excess of sodium, but the serum sodium level is low because of retained water in excess of sodium. The serum sodium level can be high in hyperadrenalism, severe dehydration, diabetic coma, or treatment with sodium salts. Serum values >160 mmol per L or <120 mmol per L are usually associated with symptoms and must be verified and corrected. Serum chloride levels fall when chloride is lost in excess of sodium, e.g., following extensive vomiting. Serum chloride levels rise when the anion cannot be excreted, as in chronic renal failure, or when chloride is reabsorbed in excess, in some patients with uretero-ileal anastomoses in ileal bladders.

Other Laboratory Evaluation. Laboratory findings associated with hypovolemia include a high urine specific gravity, elevated hematocrit, and a blood urea nitrogen (BUN) elevated in excess of the serum creatinine level. The urinary sodium level does not correlate with intake or body stores except in the normal condition when excess sodium is excreted. The normal range is 27 to 287 mmol per 24 hours. In sodium retention syndromes, the urinary sodium level can be low when stores are high; in renal salt wasting, the urinary sodium level can be elevated when body stores are low. For acute assessment, the body weight provides a better measure of extracellular volume. When the glomerular filtration rate (GFR) per nephron ratio is decreased, as in prerenal azotemia, the urinary–plasma (U/P) creatinine ratio is greater than 20 (range, 20 to 50) and the urine sodium concentration is greater than 20 mEq per L. The fractional excretion of sodium is defined as $100 \times (U/P_{sodium} \div U/P_{creatinine})$ and is less than 1% in prerenal azotemia or total body sodium deficiency. In acute renal failure, the fractional excretion of sodium is more than 4%, the U/P creatinine ratio is less than 10, and the urinary sodium level is >40 mmol per L.

Physiology

Sodium and Chloride Transport and Absorption. Transport of sodium and chloride across epithelium generates membrane potentials and osmotic gradients that drive transmembranous and paracellular fluid movement. Sodium uptake occurs in the small intestine

through transporters that are coupled to sodium movement, including cotransporters for glucose-galactose (SGLT1 and 2), for amino acids (B0AT/SLC6 family of transporters), and bile salts (ASBT/SLC10A2) (18). Much of the apical sodium transport not linked to solute occurs via the amiloride-sensitive epithelial sodium channel (EnaC) that is electrogenically coupled to Na+/K+-ATPase (19). The rest of the sodium moves through the sodium/hydrogen exchange (NHE) gene family that includes exchangers located apically (NH2), basolaterally (NH1), and recycling (NH3), as well as intracellular isoforms (NH6,7,9) (20). These latter two mechanisms are dominant in the colon where solute-coupled sodium absorption is minimal. In the proximal colon, sodium is reabsorbed mainly via the NHE family, and in the distal colon via EnaC sodium channels.

Chloride transport across the apical membrane is mediated by a series of mechanisms, including the cAMP-dependent Cystic Fibrosis Transmembrane Conductance regulator (CFTR) channel (21), voltage-dependent Cl channels, the ClC family of chloride channels (22), calcium activated Cl channels, CaCC and outward rectifying channels (ORCC) (13d, 13f), ligand-gated (e.g., glycine) Cl channels (23), and the SLC4 and SLC26 family of multifunctional anion exchangers, mostly Cl^-/HCO_3^- (24,25). This bewildering array is likely to grow larger, as there seems to be no common structure for chloride channels. Because mutations in many of these channels cause disease, it is not clear whether any of them are dominant in function in a given cell. CFTR modulates ATP release and regulates the calcium-dependent channels, CaCC and ORCC, and inhibits sodium absorption via EnaC (21). The ClC channels move H^+ and Cl^- ions in opposite directions, as do the Cl^-/HCO_3^- exchangers. Mutations in chloride channels produce cystic fibrosis (CFTR), but also many myopathies (ClC-1), epilepsy (ClC-2), Bartter syndrome (ClC-Kb), Dent disease (X-linked nephrolithiasis) (ClC-5), osteopetrosis (ClC-7), and hereditary hyperekplexia or startle disease (glycine-Cl channel) (22,23). All of these channels are located on the plasma membrane of cells, except for ClC-5 and -7 that are on endosomal membranes. The most important chloride channels for intestinal absorption are probably CFTR, NHE2, and SLC26A3. When mutated SLC26A3 produce congenital chloride diarrhea (18). One of the voltage dependent chloride channels, ClC-2, is located apically and is activated by a bicyclic fatty acid, lubiprostone, an orally administered drug that increases intestinal secretion in patients with constipation (26). The significance of this channel in normal fluid secretion is not known. The Na/K-2Cl-symporter channel permits cotransport of sodium, potassium, and chloride bilaterally across the basolateral membrane. Water follows passively along the osmotic gradients produced by sodium and chloride movement, either via paracellular or transcellular (via aquaporins) pathways.

Ion Excretion. Sodium and anions, usually chloride or bicarbonate, are present in most body secretions. Excessive loss of sodium can occur when any of these secretions is lost in large amounts from the body. The secretions and their ion contents are listed in Table 7-6. Only the kidney (and the colon and terminal ileum to a limited extent) is able to restrict or increase its loss of sodium. Because the urinary sodium level is so variable, it is not included in the list. Renal conservation involves a balance between filtration and reabsorption. The urinary sodium level reflects the sodium that escapes reabsorption in the nephron; therefore, sodium excretion depends on the GFR. Thus, renal regulation is well adapted to conserving the major extracellular cation.

Intestinal Reabsorption. The small bowel reabsorbs most of the electrolytes and water from luminal secretions under normal circumstances. Most of the sodium is absorbed from the jejunum and ileum by solute-dependent sodium cotransport along with sugars and amino acids. Non–nutrient-dependent sodium absorption in the proximal small intestine occurs mainly by Na/H exchange. The ileum and colon absorb sodium actively by a coupled Na/Cl cotransport and also secrete bicarbonate in exchange for chloride. The colon retains sodium most avidly and secretes potassium into the lumen. In small-bowel malabsorption, the colon is presented with an increased sodium load, which it reabsorbs at least partially. The colon and terminal ileum can respond to aldosterone but are not able to retain sodium as efficiently as the kidney. Sodium absorption in the rectum occurs mainly through apically located sodium channels.

When diarrhea is mild or moderate and the colon is intact, sodium losses are moderate and proportional to the stool volume (Table 7-7). Potassium losses are also proportional to

TABLE 7-6. Electrolyte Concentrations in Gastrointestinal Fluids and Sweat

Fluid source	Na		K		Cl		HCO_3	
	(mmol/L)	(mmol/d)	(mmol/L)	(mmol/d)	(mmol/L)	(mmol/d)	(mmol/L)	(mmol/d)
Sweat	30–50	15–25	5	2.5	45–55	25	—	—
Saliva	45	35–55	20	15–25	45	35–55	60	45–75
Stomach[a]	40–65	40–100	10	10–15	100–140	140–200	—	—
Bile	135–150	150–170	4	5	80–110	100–140	35–50	40–60
Pancreas[b]	135–150	120–130	7	6	60–80	55–70	70–90	80–100
Duodenum	90	180	15	30	90	180	90	180
Mid-small bowel	140	280	6	12	100	200	20	40
Terminal ileum	140	70	8	4	60	30	70	35
Rectum/stool	40	10	90	23	15	4	30	8
Diarrhea, moderate	50–100		20–30		50–100		<20	
Diarrhea, severe	100–140		20–40		80–100		30–50	

[a] Na and Cl vary inversely according to the rate of H^+ secretion.
[b] Cl and HCO_3 vary inversely according to the rate of secretion.

TABLE 7-7. Common Metabolic Consequences of Electrolyte Depletion Syndromes

Syndrome	Major ions lost	Acid–base status	ECF volume	Renal response	[K]
Vomiting	H, Cl, K > Na	Alkalosis	↓	Na, HCO_3 Retained K lost	↓
Pancreatic fistula	Na, HCO_3	Acidosis	↓↓	Na, Cl retained	NL
Malabsorption	Na, Cl, K All > HCO_3	NL, alkalosis	↓	Na, Cl retained, K lost	↓
Ileostomy	Na, Cl > HCO_3	Alkalosis	↓	Na, HCO_3 retained, K lost	NL, ↓
Diarrhea, moderate	Na, K	NL	NL	K retained	NL, ↓
Diarrhea, severe	Na, HCO_3, K, Cl	Acidosis	↓↓	Na, Cl retained	↓
Salt wasting	Na, Cl	Alkalosis	↓	None	NL, ↑
↑ Sweating	Na, Cl	Alkalosis	↓	Na, Cl retained,	NL, ↓
↑ Diuretics	Na, K, Cl	Alkalosis	↓	None	↓

ECF, extracellular fluid; NL, normal.

the stool volume when it is not excessive (<3 L per day). Chloride is lost as the predominant anion, and systemic alkalosis develops, so that the potassium loss is exacerbated through increased urinary excretion. In secretory diarrheas, stool sodium is <70 mEq per L; in osmotic diarrhea, sodium is usually less than 70 mEq per L.

When diarrhea is severe, the colon is maximally stimulated to conserve sodium chloride. In the process, it secretes more potassium and bicarbonate. The result is greater loss of sodium (because the colonic capacity is exceeded) and greater loss of potassium. Sodium loss can increase without limit, depending on fecal volume. Large amounts of sodium can be lost in a short time whenever intestinal secretions are lost in large quantities. Sodium is the major extracellular cation and is involved in the maintenance of electrogenic potentials across the cell membrane. Because the body preserves serum sodium concentration at the expense of extravascular volume, early sodium deficiency is accompanied by signs of volume depletion rather than by hyponatremia.

Potassium loss is limited somewhat by the degree of sodium exchange, and the potassium concentration tends to plateau when fecal volumes are >3 L per day. Bicarbonate losses can be large in severe diarrhea, and metabolic acidosis may result.

Deficiency

Sodium deficiency is nearly always the result of excessive losses and results in hypovolemia and dehydration (see the section on Assessment). Hyponatremia may accompany signs of dehydration. These signs (seen especially in children) include dry mucous membranes when dehydration is mild, sunken eyes and loss of skin turgor (moderate dehydration), and rapid faint pulse, cyanosis, rapid breathing, and lethargy (severe dehydration). The differential diagnosis of hyponatremia with contracted ECF volumes is aided by determining the urinary sodium levels. When the urinary sodium concentration is less than 10 mmol per L, sodium intake may be inadequate, but hypovolemia resulting from excessive sodium loss (sweating, diarrhea) is a more likely cause. When the urinary sodium concentration is more than 10 mmol per L, vomiting or excessive urinary loss of sodium may be the likely cause. When the cause of hyponatremia is not clear, the serum osmolality should be measured. Normal osmolality can be associated with hyperlipidemia or markedly elevated glucose or urea levels *(pseudohyponatremia)*. To ascertain whether the serum sodium concentration is normal in the presence of hyperglycemia or an elevated BUN value, the serum osmolarity can be estimated (normal, 275 to 295 mOsmol per kg):

$$\text{Serum osmolality} = 2 \times [\text{Na}] + ([\text{glucose}] \div 18) + ([\text{BUN}] \div 2.8)$$

where [Na] is expressed in mmol/L and [glucose] and [BUN] are expressed in mg/dL.

TABLE 7-8. Causes of Dilutional Hyponatremia

Pathophysiology	ECF volume	Causes
Renal sodium loss	↓	Diuretic drugs, adrenal insufficiency, nephropathy, osmotic diuresis
Intestinal sodium loss	↓	Diarrhea, vomiting, blood loss
Skin sodium loss	↓	Excessive sweating/climatic heat
Fluid sequestration	↓	Burns, pancreatitis, bowel obstruction
Renal sodium retention	↑	CHF, cirrhosis, renal failure, pregnancy
Inappropriate antidiuretic	NL	Cancer, CNS lesions and disorders, medications, pulmonary conditions, postoperative, HIV hormone
↓Solute intake	NL	Beer potomania, tea-and-toast diet
Excessive water intake	NL	Primary polydipsia, dilute infant formula

CNS, central nervous system; CHF, congestive heart failure; ECF, extracellular fluid; NL, normal; HIV, human immunodeficiency virus.

Dilutional (hypotonic) hyponatremia occurs when water is retained in excess of existing sodium stores. Although sodium depletion is a major cause of this syndrome, any water-retaining disorder may present with a similar serum sodium profile, although signs of dehydration are not present. Both sodium depletion and retention syndromes are characterized by low urinary sodium levels and an impaired capacity for renal water excretion.

The serum sodium level is not a guide for volume loss, but symptoms (confusion, anorexia, lethargy, vomiting, seizures) can develop when the serum sodium level falls below 120 to 125 mEq per L. Other metabolic consequences accompany clinical situations in which sodium depletion develops (Table 7-8). These situations largely involve losses from the gastrointestinal tract. Losses of sodium from the gastrointestinal tract are proportional to the volume lost. The other ions lost (K, Cl, HCO_3) are determined by the source of the fluid. The serum sodium level is normal or low in these syndromes depending on how rapidly the losses occur. With large losses of gastric secretions, hypochloremia and alkalosis ensue. With severe losses from diarrhea, metabolic acidosis can develop when the colon is intact to generate bicarbonate. In mild to moderate cases of diarrhea, chloride is lost in proportion to or in excess of bicarbonate, and alkalosis is present if any acid–base disturbance is noted.

Therapy

In sodium replacement, the amount given depends on the salt administered. Because 1 g of sodium equals 43 mmol of sodium and 1 g of sodium chloride equals 17 mmol of sodium, a 4-g sodium diet is roughly equivalent to a 10-g salt (NaCl) diet. Each gram of sodium bicarbonate represents 12 mmol of sodium. Sodium preparations are listed in Table 7-9.

Parenteral Replacement. When hyponatremia causes symptoms (lethargy, seizures), intravenous (IV) treatment is needed with normal or hypertonic saline solution. Replacement should raise the serum concentration to >120 mmol per L but should not increase it by more than 24 mmol per L in the first 24 hours. Permanent neurologic damage has been attributed to excessively rapid sodium replacement when deficiency is severe. When IV fluid is needed, the choice of additive or solution used (Table 7-9) sometimes depends on the source of lost fluid (Tables 7-6 and 7-8). When signs of volume depletion are obviously present, at least a 10% reduction in the ECF volume has occurred. In a normal person, the ECF volume is about 20% of body weight. Because the sodium concentration is 135 to 146 mmol per L of ECF fluid, the milliequivalents of sodium required can be estimated to replace 10% of the

TABLE 7-9. Sodium Supplements

Product	Anion	Na per dose (mmol)	Na per dose (mg)	ECF distribution (%)
Oral supplements				
NaCl	Cl	17/1-g tablet	391	100
$NaHCO_3$	HCO_3	7.8/0.650-g tablet	138	?
Parenteral fluids				
Normal saline	Cl	154/L	3,541	100
3% Saline	Cl	513/L	11,891	100
$NaHCO_3$	HCO_3	44.6/50 mL or 50/50 mL		?
Lactated Ringer solution	Lactate	130/L	2,990	97
0.45% Saline in water	Cl	77/L	1,771	73

ECF, extracellular fluid.

ECF volume or 20% if the signs of volume depletion are severe. The sodium deficit can be estimated as follows:

$$\text{Na deficit (mmol)} = ([Na]_{desired} - [Na]_{observed}) \times 0.6 \times \text{weight (kg)}$$

Alternatively, one can estimate the effect on the serum sodium concentration of adding 1 L of infusate:

$$\text{Change in } [Na]_{serum} = [Na]_{infusate} - [Na]_{serum} \div (\text{total body water} + 1)$$

where total body water is estimated in liters as a fraction of body weight (0.6 for children; 0.6 and 0.5 for nonelderly men and women, respectively; 0.5 and 0.45 for elderly men and women, respectively) (27).

Oral Replacement

Oral replacement solutions. In general, oral therapy is effective, less costly, and as effective as parenteral therapy for dehydration. Many oral rehydration solutions are available, but they are often underutilized in young children and infants because of concern that they are not as efficient as IV solutions (28), and in adults because of the general availability of IV solutions in hospitals (29) (Table 7-10). The mechanism of oral substitution is to restore fluid and electrolyte content by driving water across intestinal mucosa following sodium-coupled glucose uptake via the sodium–glucose cotransporter, SGLT1. The exact composition of the oral replacement solution for infants is still being debated because diarrheal stool sodium concentration is lower in children than in adults. Thus, when dehydration is severe, too much sodium (90 mmol per L) in a short time can occasionally cause hypernatremia. In this situation, solutions with 40 to 60 mEq per L are recommended (28,30). However, for children with mild to moderate dehydration and for adults with a normal intestine, the World Health Organization (WHO) solution containing 90 mmol per L is probably just as good. The use of rice-based and other cereal-based (as a substitute for glucose) oral rehydration solutions (glucose, e.g., Ceralyte, Ricelyte) is thought to reduce diarrhea by providing glucose slowly in the gut lumen without increasing osmolarity. Fecal losses have been reduced by adding resistant starch to the oral rehydration solution in the form of high-amylose maize starch, which allows colonic fermentation to short-chain fatty acid and sodium and fluid absorption in the colon (31). Fructo-oligosaccharides have been used in some preparations (e.g., Equalyte) because they can be fermented to short-chain fatty acids by colonic bacteria, thus providing the metabolic fuel preferred by colonocytes (but not small bowel epithelia).

TABLE 7-10. Composition of Selected Oral Rehydration Solutions

Solution	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Base (mmol/L)	Glucose mmol/L (g/L)	Osmolality (mOsm/kg)
Rehydration						
WHO packet	90	20	80	30	111[a] (20)	310
Rehydrylyte	75	20	65	30	139 (25)	310
CeraLyte 70/90	70/90	20	60	30	222 (40)[b]	260/275
EquaLyte	78	22	68	32	139 (25)[d]	305
Washington U[e]	105	0	100	10	111 (20)	250
Maintenance[f]						
ESPGHN	60	20	60	30	90 (16)	240
Pedialyte	45	20	35	30	139 (25)	269
Resol	50	20	50	34	111 (20)	265
Infalyte (former Ricelyte)	50	20	40	30	111 (20)	270
Lytren	50	25	45	30	111 (20)	?
Naturalyte	45	20	35	48	139 (25)	?
Diocalm Junior[c]	60	20	50	10	111 (20)	251
Dioralyte[c]	60	20	60	10	90 (16)	240
Electrolade[c]	50	20	40	30	111 (20)	251
Rapolyte[c]	60	20	50	10	111 (20)	251
Unsuitable						
Gatorade	20	3	27	3	278 (45)[c]	330–380
Colas	1.6	<1	—	13.4	(5–15)	550–750
Orange juice	<1	50	—	50	666 (12)	High
Apple juice	<1	44	45	—	666 (12)	730
Chicken broth	250	8	—	0	0	500

[a] May contain glucose or sucrose.
[b] Rice-based carbohydrate.
[c] Available in the United Kingdom.
[d] Also contains fructo-oligosaccharides.
[e] Washington University formula: Mix 3/4 tsp NaCl, 1/2 tsp sodium citrate, and 3 tbs + 1 tsp Polycose powder in 1 L (4 1/4 cups) of distilled water, add Crystal Light to taste (especially lemon or orange-pineapple). Potassium may need to be added.
[f] Reduced-sodium ORS is indicated for maintenance in adults, in children with mild/moderate dehydration, or for replacement therapy in infants or children with severe dehydration.
ESPGHN, European Society of Pediatric Gastroenterology, Hepatology, and Nutrition; WHO, World Health Organization.

Solutions with higher sodium and glucose concentrations are used for rehydration, although whether 75 or 90 mEq of sodium per liter is better is unclear. The Washington University formula has been developed for patients with short-bowel syndrome who require IV rehydration. The higher sodium concentration has been shown to convert such patients from fluid secretors to fluid absorbers (32). The oral rehydration solutions with lower sodium and glucose contents are used for maintenance. The WHO oral rehydration solution can be bought in many countries in dried packets to be rehydrated at home, or can be made from ingredients readily available at home. Recent modifications of the WHO solution contain less glucose to avoid osmotic diarrhea, and less sodium (50 mEq per L) to avoid hypernatremia and convulsions. The standard recipe involves 3/4 tsp of salt, 1/2 tsp of baking soda (or 1 tsp of baking powder), 4 tbs of table sugar, and 8 oz of orange juice (to provide potassium), diluted in 1 L (4 1/4 cups) of water. A Crystal-Light packet (or other product without sugar or electrolytes) can be added for flavor if needed.

The daily dose for adults is 2 to 3 L, for children 1 L plus food, and for infants 0.5 L plus food. The more substrate present, the better the cotransport of sodium. For this reason and to replace deficits resulting from malnutrition, infants and children should also be fed the regular diets appropriate for their age.

Food-based solutions. Food-based solutions may be less practical because the sodium and fluid may not be so readily available for rapid absorption. Most sodas contain 1 to 4 mEq of sodium per liter and 0.1 to 0.6 mEq of potassium per liter along with about 10% carbohydrate usually supplied as fructose-rich carbohydrate derived from corn syrup. Because they do not contain enough sodium, and because fructose is not absorbed by the SGLT1 glucose-Na cotransporter, they are inadequate for the treatment of dehydration. Fluid replacement drinks are available in grocery stores. The characteristics of some of these preparations are listed in Table 7-10. Gatorade® was designed to provide energy and replace electrolytes lost in sweat, and consequently the sodium concentration is too low to treat significant dehydration. However, it is isotonic, and all therapeutic oral replacement solutions are isotonic or mildly hypotonic. When fluid loss from vomiting or diarrhea is not severe in adults, Gatorade or similar beverages may be well tolerated because of their near-isotonicity. These products are helpful in maintaining fluid volume but not in treating volume depletion because the sodium concentration is too low. If fluid loss is moderate to severe, one of the other solutions is indicated.

Toxicity

Sodium toxicity presents in two clinical syndromes: hypernatremia (usually with decreased body water), and dilutional hyponatremia (always with increased body water due to excessive sodium retention).

Hypernatremia. Sodium may be ingested or provided in excess of water to cause hypernatremia. Hypertonic sodium gain can be caused by the use of hypertonic IV or feeding solutions, ingestion of sodium chloride tablets, or the administration of hypertonic dialysis or saline enemas (33). Much more commonly, hypernatremia develops during net water loss (usually renal) in diabetes insipidus, the use of loop diuretics, osmotic diuresis, postobstructive diuresis, the polyuric phase of acute tubular necrosis, and intrinsic renal disease. The loss of hyponatremic gastrointestinal fluids (e.g., in vomiting) can also cause hypernatremia. The major signs of hypernatremia are evidenced in the central nervous system by confusion, obtundation, stupor, and even coma. These signs are similar to those of other hyperosmolar syndromes (e.g., hyperglycemia). The effect on serum sodium of 1 L of any infusion can be estimated by using the formula presented in the section on parenteral replacement in sodium deficiency. When water loss is the cause of hypernatremia, the amount of water required to correct the loss can be calculated as follows:

$$\text{Water deficit} = [([\text{Na}]_{\text{plasma}} - 140)] \div 140 \times \text{total body water (L)}$$

where total body water is estimated as a fraction of body weight that is 0.6 for children, 0.6 and 0.5 for nonelderly men and women, respectively, and 0.5 and 0.45 for elderly men and women, respectively (27).

The rapid correction or overcorrection of hypernatremia should be avoided because shifts in cerebral edema can have major clinical consequences (33). The deficit should be

corrected over 2 to 3 days, and should not lower the serum sodium by >12 mmol per L during the first day. To avoid rapid shifts in serum sodium, it is better to deliver the water orally or enterally rather than intravenously.

Abnormal Sodium Retention. Abnormal sodium retention, as in conditions associated with edema, is the more common cause of sodium overload (toxicity). Signs and symptoms are related to fluid overload. Treatment involves decreasing dietary or infused sodium and the use of diuretics. Booklets with low-sodium diets are available from the dietary divisions of most hospitals. The principles involved in dietary management are discussed in Chapter 12 in the section on low-sodium diets. Seasoning food can be a problem. Salt substitutes can be used, and other spices can be very helpful in making food more palatable. Table 7-11 outlines alternative seasonings and their suggested uses. Many commercial products are available offering various combinations of these spices.

Potassium

Requirements

The requirements for potassium are not as clearly defined as those for sodium because of adjustments in urinary excretion that follow changes in intake. The DRI Committee recommended AI values for potassium, the observed average or experimentally determined intake that maintains a defined status in a specific population. It is not the same as a recommended dietary allowance. The AI is set at 4.7 (120 mmol) per day for adolescents aged 14 to 18 and for adults over age 18. This intake is based on evidence that it will lower blood pressure, perhaps by blocking the effect of sodium chloride, will reduce the risk of kidney stones, and may possibly reduce bone loss (2). These beneficial effects appear to be associated with forms of potassium found naturally in foods (e.g., fruits and vegetables), including anions that are bicarbonate precursors. This AI is not meant to be satisfied by preparations of potassium chloride. The AI for infants 0 to 6 months of age is 0.4 g per day, and for infants of 7 to 12 months is 0.7 g per day, based on the average consumption of human milk and other foods. The AI of children is derived from extrapolating the adult AI based on energy intake relative to adults, and is set at 3.0, 3.8, and 4.5 g per day for children age 1 to 3years, 4 to 8 years, and 9 to 13 years, respectively.

All but a small amount of potassium is normally absorbed by the gastrointestinal tract. The kidney is the major excretory organ for potassium and regulates output. The normal kidney can adjust the amount of potassium excretion from 5 to 1,000 mEq per day. Moreover, sodium intake determines, in part, the amount of potassium excreted, as both are affected by the action of aldosterone. Thus, the sodium–potassium ratio in the diet is a factor in defining the daily excretion rate and the AI.

Potassium excretion is affected by changes in recent dietary intake. Maximal values for potassium excretion occur early after a few days of adaptation to a high intake of

TABLE 7-11. Natural Low-sodium Seasonings that Can Be Substituted for Salt

Uses	Alternate seasonings
General cooking	Lemon juice, garlic, onion, and sour cream the most useful; pepper and chili powder good if tolerated
Meat	Lemon, garlic, onion, pepper, oregano, curry powder, rosemary, thyme, paprika, ginger, sour cream
Fish and poultry	Lemon, garlic, onion, pepper, ginger, oregano, paprika, parsley, sesame seed, savory, tarragon, thyme
Egg dishes	Pepper (red or black), basil, marjoram, onion, oregano, tarragon, thyme
Vegetables	Pepper, basil (especially for tomatoes), dill, thyme, oregano, chervil, rosemary, sour cream (potatoes especially)
Soups	Garlic, onion, pepper, bay leaf, basil, thyme

potassium. On the other hand, sodium excretion increases within hours of a sodium load. With potassium restriction, maximal renal preservation occurs after 1 to 2 weeks, whereas sodium adaptation is more rapid. These considerations further confuse the determination of minimal daily requirements based on urinary excretion. Therefore, the DRI Committee elected not to set an estimated adequate requirement (EAR) because a dietary intake could not be calculated that would provide an adequate intake for half of the population (2).

Food Sources

Intake of potassium in adults varies from 2,000 to 6,000 mg per day (50 to 150 mmol per day), but the median intake in the United States is well below the AI, being 2.8 to 3.3 g per day for men and 2.2 to 2.4 g per day for women (2). Hospitalized patients generally receive adequate dietary sources of potassium. The average hospital diet provides about 4,000 to 4,800 mg. Low-sodium diets provide 3,800 to 4,000 mg, and full-liquid diets supply the same amount. Because potassium is an intracellular ion, meat is a rich source. Therefore, low-protein and low-calorie diets provide somewhat less potassium (2,000 to 3,000 mg). A clear liquid diet is low in potassium (~750 mg) and in other essential nutrients.

In natural foods, potassium is available primarily in complexes with anions that generate bicarbonate, such as citrate, or with phosphate. In most supplements or foods to which potassium has been added, the form of the salt is potassium chloride. Table 7-12 lists some good sources of potassium. Meat, fluid milk, and fruits are good sources. The highest content of potassium (mg per 100 kcal) is in leafy greens such as spinach, cabbage, lettuce, and kale, but the caloric provision of these foods is low. It is more practical to consider the content of potassium and other nutrients per serving. In general, fruits and meats provide 200 to 400 mg of potassium per serving, vegetables slightly more, milk 370 mg per glass, and dried fruits, nuts, and juices somewhat more. However, high protein foods, such as meat and dairy, and high protein grains do not contain as much of the bicarbonate precursor anions as is present in fruits and vegetables, although the exact content is not known. Thus, it is possible that bioavailability of potassium from those sources may not be quite so high (2). Foods high in sodium, processed foods, and diets low in fruits, vegetables, dairy, and whole grains may not provide enough potassium to meet minimum requirements. Because many potassium-rich foods also contain fiber and other vitamins and minerals, the consumption of dietary fruits, vegetables, and dairy products should be encouraged, rather than the use of potassium supplements.

The effect of food processing on potassium content can be significant, as it is on sodium. Potassium content can increase or decrease with processing, but not so much as sodium content (Table 7-2). Water itself contains very little potassium and does not affect food content after cooking. Table 7-13 lists some examples of the effects of processing on potassium content.

Assessment

Ionic potassium is measured in serum or plasma with the use of ion-selective electrodes. Hemolysis elevates values through the release of intracellular potassium. Of all the potassium in the body (~54 mmol per kg of body weight), only about 10% is extracellular. Moreover, only about 0.4% (0.2 mEq per kg) is found in the plasma or serum. The distribution of potassium depends on an energy-consuming process in which sodium is extruded from cells and potassium enters. At normal rates of dietary intake, the transfer of ingested potassium into cells occurs so rapidly that extracellular concentrations do not change noticeably.

Body Stores. The serum potassium concentration (normal, 3.5 to 4.5 mmol per L) reflects both total body stores and availability of energy (glucose). Values from 3.0 to 3.5 mmol per L correspond to mild hypokalemia, and values <2.5 mmol per L define severe hypokalemia. The serum potassium level does reflect body stores in the absence of impaired energy utilization, (e.g., diabetes mellitus). It does not reflect changes in recent or chronic intake because the plasma level is adjusted fairly rapidly. However, the serum potassium level, at best, provides only an approximation of total body stores. A serum level not below 3.3 mmol per L often corresponds to a loss of 10% of body potassium; a level

TABLE 7-12. Food Sources of Potassium

Food	Portion	Potassium content (mg)
Grains		
White bread	1 slice	28
Whole wheat bread	1 slice	62
Rice, cooked	1 cup	80
Spaghetti noodles, cooked	1 cup	43
Meats		
Muscle red meats, broiled	3 oz	250
Organ meats	3 oz	250–300
Bacon, cooked	3 slices	92
Fish, broiled	3 oz	340–400
Chicken, white meat roasted	3 oz	209
Vegetables		
Asparagus, fresh, cooked	1/2 cup	279
Avocado	1/2 medium	530
Broccoli, cooked	1 cup	456
Brussels sprouts	1/2 cup	250
Celery	1/2 cup	186
Cucumber, sliced	1/2 cup	80
Green beans, cooked	1 cup	373
Kidney beans	1 cup	713
Mushrooms	1 cup	550
Tomato	1 each	273
Tomato juice	1 cup	537
Fruits		
Applesauce, canned	1 cup	295
Cantaloupe	1 cup	494
Banana	1 medium	451
Dried apricots	10 each	482
Orange	1 medium	273
Grapefruit, white	1/2 grapefruit	175
Grapefruit juice, canned	1 cup	378
Orange juice, frozen	1 cup	474
Prunes	5	313
Raisins	1/3 cup	373
Watermelon slice	1 cup	186
Dairy products		
Milk	1 cup	350–370
Cheese	1 oz	25–40
Egg	1 each	63
Other		
Nuts (peanuts, almonds)	1 oz	180–220
Coffee, brewed	4 oz	80
Tea, brewed	4 oz	16

below 3.0 mmol per L suggests a loss greater than 20%. Small shifts in the transport of potassium can rapidly shift the equilibrium between intracellular and extracellular compartments. Hypokalemia also may occur during acute alkalosis or acute attacks of familial periodic paralysis. Conversely, the serum potassium level may be normal when body stores are low (or high) as measured by isotope studies.

Losses From the Body. Urinary potassium levels reflect excretion on any given day (K^+ excretion = Uvol × $[K^+]$). However, the ability of the kidney to alter potassium excretion is great, and adults on an average diet excrete 25 to 125 mmol per day (34). Therefore, the urinary potassium level may be useful in assessing losses from the body when potassium

Table 7-13. Effect of Processing on Potassium Content of Food

Food	Portion	Potassium content (mg)
Potato		
Fresh baked	1 each	844
Instant mashed	1 cup	428
Canned	2 each	160
Chips	14 (1 oz)	369
Tomato		
Sliced	1 cup	400
Canned	1 cup	529
Catsup	1 tbs	82
Peas, green		
Fresh cooked	1 cup	434
Frozen, cooked	1 cup	268
Canned, without liquid	1 cup	194

depletion is present. When the kidney is normal, potassium excretion should be low but still significant (10 to 20 mmol per day). When losses from the gastrointestinal tract occur, the measurement of potassium in the appropriate fluid provides an additional assessment of the requirement for that patient (see Table 7-6 for the average daily potassium content of gastrointestinal fluids). Once hypokalemia is detected, measurement of the urinary potassium level may be helpful in determining the source of loss. A low urinary potassium level (<15 mmol per L) implies near-maximal renal conservation and suggests an extrarenal source of depletion. This interpretation is correct only if the patient has not been treated recently with diuretics. After diuretics are discontinued, the kidney responds to induced hypokalemia with maximal potassium conservation. However, if the urinary potassium level is high (>30 mmol per L), then renal conservation is inadequate, and this result suggests that the kidney is the source of potassium loss.

To distinguish the mechanism for excessive potassium secretion the transtubular K^+ concentration gradient (TTKG) is used. TTKG calculates the ratio of potassium concentration in the lumen of the collecting duct compared with that in the plasma. To estimate the concentration in the lumen, a correction is made to account for the amount of water reabsorbed in the medullary collecting duct by dividing the urinary $[K^+]$ by the quotient of urine and plasma osmolality, since the osmolality of the fluid in the cortical collecting duct equals plasma osmolality when antidiuretic hormone is active (35). Thus,

$$\text{TTKG} = ([K^+]_u) \div (U_{osm}/P_{osm}) \div [K^+]_p$$

Tests to measure potassium excretion when hypo- and hyperkalemia are present are shown in Table 7-14.

Physiology

Potassium is the major intracellular cation, maintained at an intracellular concentration of ~145 mmol per L. Along with sodium and calcium, it is responsible for the maintenance of normal electric potentials across cell membranes. The membrane depolarization needed for muscle contraction depends on an influx of sodium into the cell coupled with an efflux of potassium. Membrane repolarization involves the reverse process. Thus, potassium helps to regulate neuromuscular contraction in addition to glycogen formation, protein synthesis, and acid–base balance.

Absorption. Potassium must be absorbed from the diet and from gastrointestinal secretions, from which it must be reabsorbed (Table 7-6). More than 85 potassium channels have been identified in all tissue cells (www.genenames.org/genefamily/KCN.php). When sodium moves into the small intestinal cell with transporters coupled to glucose and amino acids, the entry of a positive net charge depolarizes the apical membrane, leading to

TABLE 7-14. Tests for Determining K+ Excretion when Hypo- or Hyperkalemia Is Present

Test	Expected values	Advantages	Disadvantages
24 h K^+ excretion or K^+/creatinine	60–80 mmol/day 6–8 mmol/mmol Cr Hypokalemia <10 mmol/d Hyperkalemia >150 mmol/d	Overall renal response	Mechanism-independent Need 24-hour collection
Spot urine [K^+]	Hypokalemia <20 mmol/L if due to K deprivation Hypokalemia >20 mmol/L if due to a renal cause	Convenience	Affected by K^+ secretion and water reabsorption so wide variability
TTKG	Non-renal hypokalemia <2 Non-renal hyperkalemia >10	Corrects for water reabsorption	Assumptions are made in the calculation

Adapted from Halperin ML, Kamel KS. Potassium. *Lancet.* 1998;352:135.
TTKG, transtubular [K^+] gradient.

an electrogenic transport of chloride. Basolateral K^+ channels open to hyperpolarize the cell, and the K^+ is recycled by the Na^+/K^+ ATPase. The luminal membrane is then hyperpolarized and apical electrogenic transport is initiated across the apical and basolateral membranes in order to repolarize the membrane voltage (36). K^+ channels probably play a role in restoring the absorbing cell size to normal, after being swollen during solute and fluid absorption. The types of K^+ channels present in the small intestine are still incompletely understood, but probably include a large conductance channel, calcium-activated small-conductance channels, and KATP-like channels.

Excretion. The kidney is the major regulatory site of potassium excretion, through the action of aldosterone, accounting for 77% to 90% of dietary potassium (1). Potassium excretion by the kidney is regulated by a secretory process, largely independent of the GFR and the amount of filtered potassium. Most filtered potassium (70% to 80%) is reabsorbed in the proximal nephron. The amount in the urine is regulated by the potassium ion concentration in the cells of the distal tubule and is high when the intracellular concentration is high. Thus, excretion is regulated in part by the intracellular content of renal cells. The kidney responds rapidly to alterations in potassium intake.

In contrast with the small intestine, the colon secretes potassium, especially in response to a high potassium intake and/or high aldosterone concentrations. The overall mechanism involves electro-neutral transcellular secretion of KCl, rather than the Cl^- absorption and paracellular sodium absorption seen in the small intestine. Apical channels active in the colonic mucosa include large-conductance channels, a pH-sensitive ROMK-type channel, maxi K^+ channels, and KCNQ1 (36). In the colon, potassium secretion is aided by the electronegativity of the intestinal lumen. Ordinarily, stool volumes are low, so the relatively high potassium concentrations in stool are not the cause of serious losses. In diarrhea, large potassium losses may occur. Changes in colonic secretion do not alter the overall potassium balance unless the colon is removed, when losses through the ileostomy can be significant.

Deficiency

If one assumes that no metabolic factors are altering the serum potassium level, each decrease of 1 mmol per L corresponds to a loss of body potassium of 200 to 300 mmol. The major causes of deficiency include increased renal excretion and extrarenal losses, largely intestinal. Because of the widespread presence of potassium in foods, decreased intake is an uncommon cause of deficiency. However, clear liquid diets are low in potassium and may lead to deficiency after prolonged use.

Increased renal excretion, one cause of deficiency, may be secondary to the use of potent diuretics, chronic metabolic alkalosis (e.g., chronic obstructive pulmonary disease), diabetic ketoacidosis (with osmotic diuresis), and states associated with the development of edema. Distal renal tubular acidosis also can lead to large losses of potassium. Potassium can be lost at the rate of 150 to 300 mmol per day in these situations. Major causes of extrarenal losses include gastric or biliary drainage and chronic diarrhea. Because potassium is secreted by the colon, moderate diarrhea can lead to hypokalemia before sodium or volume depletion is clinically evident. The concentration of potassium in sweat is low (5 to 10 mEq per L), so large losses are not common with increased sweating. Nondiuretic medications, such as steroids, digoxin, and excess natural licorice, may cause an increase in potassium excretion (37).

The loss of 5% to 10% of body stores (200 to 300 mmol) may occur without hypokalemia and is tolerated without many symptoms. Elevated blood pressure may occur, especially changes that are sensitive to changes in salt intake. Manifestations of hypokalemia usually appear at serum levels <2.5 to 3.0 mmol per L. If the loss of potassium is rapid, symptoms may develop at a higher serum level. Prominent symptoms include weakness, paresthesias, orthostatic hypotension, and cardiovascular abnormalities. With depletion, the membrane electrical potential gradient increases, and muscle contraction is impaired. Muscle weakness and delayed cardiac repolarization are early effects. Electrocardiographic abnormalities include depressed ST segments, low T waves, and the presence of U waves. However, these findings are neither constant nor specific and cannot be relied on for diagnosis. The effects of digitalis are exaggerated by potassium deficiency. If depletion is chronic, the concentrating ability of the kidneys is impaired and polyuria results. Glucose intolerance, polydipsia, constipation, ileus, and metabolic alkalosis can occur. Common causes of depletion are gastrointestinal (vomiting and diarrhea) and urinary (diuretics) losses, glucocorticoid excess, and inadequate intake in the face of obligatory urinary excretion.

Potassium supplementation is associated with a significant but small reduction in systolic (3 mm Hg) and diastolic (2 mm Hg) pressures (38,39). This effect is noted most in patients with a high intake of sodium. However, in the DASH study, in which the diet of participants was rich in fruits and vegetables (average potassium intake of 4,100 mg per d), blood pressures fell (6). This diet also included low-fat dairy foods and reduced amounts of saturated and unsaturated fat, so the role of potassium alone is not clear. It is usually not necessary to prescribe potassium supplements for hypertensive patients except when hypokalemia is present.

Treatment

Hypokalemia is treated by oral replacement if possible. The reason for choosing this route is to allow the serum potassium level to rise slowly in equilibrium with the intracellular component. For mild deficiency, table foods may be adequate (Table 7-12). Foods high in potassium are those with more than 300 mg per portion.

Supplements. The Food and Drug Administration (FDA) now allows manufacturers to claim on the labels of certain "foods that are good sources of potassium and low in sodium may reduce the risk of high blood pressure and stroke." To qualify, the food must contain more than 10% of the recommended dietary value of potassium (or 350 mg), be low in sodium (<140 mg), and also be low in fat, saturated fat, and cholesterol, as defined by the FDA.

Potassium salts (gluconate, aspartate, citrate, chloride) are available as liquid, tablets, and capsules. Individual doses of nonprescription preparations are limited by the FDA to less than 99 mg (~2.5 mmol) because of the dangers associated with self-dosing. The salt most often used to treat moderate deficiency is potassium chloride. However, it has a bitter taste, and if it is not well tolerated, other salts are available. If the source of the potassium loss is in the intestine, fixed base will also be lost, so that a basic salt of potassium (e.g., potassium gluconate) may be more appropriate as replacement therapy. Although the risk for mucosal damage in the gastrointestinal tract caused by potassium chloride, a sclerotic agent, is smaller with currently available slow-release, wax matrix, and microencapsulated forms than with liquid potassium chloride, esophageal and small-bowel damage does still occur when slow-release tablets containing high doses of potassium

chloride are ingested. Such preparations should not be used by patients with any condition that may delay transit through the gastrointestinal tract. For such patients, the gluconate or citrate salt is more appropriate. Liquid or effervescent preparations are preferable if they are well tolerated and should be mixed in 3 to 8 oz of water or juice and drunk slowly. Potassium chloride can be given IV to severely depleted patients if the salt is diluted to 20 to 40 mmol per L of fluid, no more than 40 mmol is administered per hour, and electrocardiographic monitoring is provided. Without such monitoring, replacement should not exceed 20 mmol per hour. A partial list of oral potassium preparations available by prescription is given in Table 7-15.

Salt Substitutes. Many patients who require potassium supplements are also on a low-sodium diet. As part of this diet, they may be using a salt substitute. The potassium content of salt substitutes is considerable. If significant amounts of these salts are used, they may contribute a major supplementary source of potassium and should be considered in the overall oral intake. In addition, potassium chloride in the form of commercial salt substitutes is 10 times less expensive than potassium chloride solutions and powders. Characteristics of the salt substitutes are listed in Table 7-16. "No salt" products are the only ones with a nutritionally significant potassium content and an acceptably low sodium content but are poorly accepted by patients who find them unpalatable.

Toxicity

Toxicity occurs when hyperkalemia develops (serum level >5.0 to 5.5 mEq per L). Because of the largely intracellular distribution of potassium, toxicity can be manifested without significant changes in total body levels of potassium.

Causes

Impaired renal excretion. Impaired renal excretion is the major cause of hyperkalemia because this mechanism is so important for normal function. When diuretics are used, potassium often must be replaced. Potassium-sparing diuretics increase potassium retention and can cause hyperkalemia. The concurrent use of angiotensin-converting enzyme (ACE) inhibitors may lead to hyperkalemia in certain patients.

Increased potassium intake. Increased potassium intake may also produce hyperkalemia, especially the use of prescription supplements. An increase in oral intake of 50 to 100 mEq within a short period can raise the serum potassium level by 0.5–1 mEq/L, but the abnormality is transient once cellular redistribution occurs. The use of salt substitutes along with other potassium supplements can result in excessive intake. Many herbal medications now contain potassium, including alfalfa, dandelion, horsetail, nettle, milkweed, and hawthorne berries. Increased endogenous potassium load can occur during prolonged exercise and/or if hemolysis, rhabdomyolysis, and gastrointestinal bleeding occur.

Other causes. Potassium penicillin contains 1.7 mEq per million units and can provide a large dose of potassium. The sudden breakdown of cells with disruption of the transcellular gradients can acutely raise the serum potassium level and produce toxic effects in the absence of changes in total body potassium. Transcellular shifts in potassium may also occur during hyperglycemia and acute metabolic acidosis due to addition of mineral acids, with the use of nonselective β-blockers or somatostatin, with mannitol infusion, and due to drugs or herbals that inhibit Na/K ATPase. Such inhibitors include digoxin, toad skin, oleander, yew berry, lily of the valley, dogbane, Siberian ginseng, and red squill (40).

Signs and Symptoms. Signs and symptoms of hyperkalemia include those associated with decreased membrane potential, rapid repolarization, and slowed conduction velocity. Neuromuscular effects include paresthesias, weakness, mental confusion, and paralysis. The cardiovascular effects are a decrease in blood pressure and direct cardiac effects. The electrocardiogram shows peaked T waves, loss of P waves, a depressed ST segment, widened QRS complex, and prolongation of the PR interval. If severe, these features lead to heart block, atrial arrest, and asystole. The rate of onset of hyperkalemia, accompanying acid–base disturbances, and use of other drugs modify the degree of cardiac toxicity. In general, cardiac toxicity is rare when the serum potassium level is below 6.5 mEq per L, and common when it is above 8.0 mEq per L.

TABLE 7-15. Potassium Supplement Preparations[a]

Usual preparation[b]	Anion	K^+ content/unit dose (mmol/15 mL or per tablet)
Liquids		
Kaochlor 10%	Cl	20
Kaon Cl 20%	Cl	40
Kay Ciel	Cl	20
Klorvess 10%	Cl	20
Klor-Con 10%		20
Rum-K	Cl	20
Potassium chloride solution 5%, 10%, or 20%	Cl	20
Kaon Elixir	Gluconate	20
Kolyum	Gluconate/Cl	20
Potassium triplex (Tri-K)	Acetate, HCO_3, citrate	45
Twin-K	Gluconate, citrate	20
Polycitra-K	Citrate, citric acid	30
Tablets[c]		
Effer K	HCO_3, citrate	25
K+ Care	HCO_3	20, 25
Slow-K	Cl	8
Klotrix	Cl	10 in wax matrix
Klor-Con/EF	HCO_3, citrate	25
Klor-Con 10	Cl	10 in wax matrix
Micro-K Extencaps	Cl	8, 10 controlled-release
K-tab	Cl	10
Kaon	Gluconate	5
K-lyte Effervescent	HCO_3, citrate	25 (DS = 50)
Klorvess Effervescent	HCO_3, Cl	20
K-Dur	Cl	10, 20 microencapsulated
Potassium chloride	Cl	10 in wax matrix, controlled-release, or microencapsulated
Powder		
Effervescent Kaon-Cl	Cl	6, 7, 10
K+ Care	Cl	15, 20, 25
K-Lor	Cl	15, 20
Klor-Con	Cl	20, 25
K-Lyte/Cl	Cl	25 (DS = 50)
Kay Ciel	Cl	20
Kolyum	Gluconate/Cl	20
Klorvess Effervescent	HCO_3, Cl	20
Micro-K LS	Cl	20 (extended-release)
Potassium chloride	Cl	20

DS, double strength.
All liquid preparations should be diluted in juice or water (4 oz for each 20-mmol dose). All packets or effervescent tablets should be dissolved in the same amount of liquid. Tablets (slow release in wax matrix or microencapsulated) should be swallowed whole with 4 oz of liquid.
[a] The K content (mmol/g) of potassium salts is K gluconate, 4.3; K citrate, 9.8; K bicarbonate, 10; K acetate, 10.2; K chloride, 13.4.
[b] Many preparations are available in liquid, tablet, and powder forms.
[c] Most tablets are either covered by wax matrix, microencapsulated, or in controlled-release forms.

Treatment. Treatment should be started immediately. For mild hyperkalemia, cessation of potassium intake may be enough if renal function is normal. With more severe toxicity, active intervention should be used.

Calcium gluconate. If ECG abnormalities are present, 10 to 30 mL of 10% calcium gluconate should be given IV over a few minutes, but the effect is transient (1 to 2 hours).

TABLE 7-16. Characteristics of Salt Substitutes[a]

Product	Na content (mmol/g)	K content (mmol/g)	Na:K ratio
Table salt	16.6	0.004	4150
Flavored salt	11.9	0.049	243
Monosodium glutamate	5.3	0.004	1325
Seasonings and marinades	7.0	0.087	80
Lemon pepper	4.4	—	—
Marinades	1.4	—	—
Meat tenderizer	12.0	—	—
"Low salt" substitutes	9.45	5.29	1.8
"No salt" substitutes[b]	0.014	12.8	<0.01
Adolph's salt substitute	—	12.8	—
Adolph's seasoned salt substitute	—	7	—
Morton's salt substitute	—	12.8	—
Morton's seasoned salt substitute	—	11.2	—
Nosalt	—	12.8	—
Neocurtasal	—	12	—
Nu-salt	—	13.6	—
Lawry's seasoned salt-free	—	6	—

[a] Mean values for classes of products are listed.
Adapted from Greenfield H, et al., *Med J Aust* 1984;140:460 and from Hands ES. *Food finder,* 2nd ed. Salem, OR.: ESHA Research, 1990.
[b] Data for salt substitutes adapted from Cannon-Babb MT, Schwartz AB, *Hosp Pract* 1986;21:99, and from *Drugs: Facts and Comparisons*. St Louis: C.V. Mosby, 1998.

Glucose and insulin. Glucose and insulin can be used to drive the potassium intracellularly and can be given at the same time as calcium gluconate. A dose of 10 to 20 U of insulin per 100 g of glucose can be given after the glucose is started, and the effect lasts 6 to 12 hours. The glucose is not needed initially if the patient is hyperglycemic.

Sodium bicarbonate. Sodium bicarbonate is used when systemic acidosis is present. Two ampules (90 to 100 mEq) can be given IV over 5 to 10 minutes.

Potassium removal from the body. Oral exchange can be accomplished by giving the resin sodium polystyrene sulfonate (Kayexalate) orally (20 to 30 g in 70% sorbitol) or by enema (50 to 100 g in 200 mL), as indicated by the serum potassium level. This dose can be repeated every 2 hours as needed. In severe toxicity or renal failure, hemodialysis is used.

Calcium

Requirement

Calcium is the major cation of bone. Calcium, like iron, is a threshold nutrient. This means that below a critical value the ability of calcium to increase bone mass is limited by available mineral, whereas above the threshold no further increase in intake results in functional benefit. Three factors define the requirements for calcium and explain the discrepancy between the actual requirement and the larger dietary reference intake (DRI): (a) Calcium is needed in increased amounts during periods of growth or new bone formation. (b) Because absorption is not efficient (~30%), the amount ingested must exceed the actual requirement. (c) There is an obligatory daily loss of calcium in the stool and urine. Thus, the requirement is greatest during childhood, adolescence, pregnancy, and lactation. The fact that bone mass is measured so long after the critical periods of growth of bone mass, and that calcium is a nutrient that improves function only below a given

threshold may account for the difficulty in demonstrating a role for calcium in modifying bone mass in adults.

Other factors can play a role in the amount of calcium required for positive balance. The role of fiber is quite variable and is generally small. Wheat bran, but not fiber in green, leafy vegetables reduces absorption of calcium (41). A high intake of phytate may decrease calcium absorption by binding to calcium (42). Beans contain both phytate and oxalate, but in spinach and rhubarb the calcium is bound to oxalate. The calcium bound to oxalate is less available than that bound to phytate. Animal data suggest that the optimal dietary calcium–phosphorus ratio is from 2:1 to 1:2. The ratio of the average U.S. diet is 1:1.5. Although phosphate is an additive in many processed foods, especially canned foods and soft drinks, the effect of the added phosphorus on calcium absorption is unclear. At a luminal pH above 6, calcium forms complexes with phosphorus and with other anions. Thus, fecal calcium and phosphorus are usually correlated. However, various calcium phosphate salts are absorbed at about the same (low) rate as other calcium salts. Calcium phosphate is one of the major calcium salts in milk, the food that has the most bioavailable source of calcium. Because calcium absorption is inefficient in adults, changes in the phosphorus intake increase the fecal output relatively little. There is no evidence that calcium absorption is altered by changing the Ca:P ratio from 0.2 to 2.0, providing that adequate calcium intake is maintained (41).

Urinary calcium excretion increases as protein intake increases, but the effect is not always proportional to the protein intake. In balance studies, when phosphorus intake was stable, 1 g of dietary protein increased urinary calcium excretion by 1 to 1.5 mg (43). Thus, diets high in protein but with limited calcium intake (e.g., high in meat, low in dairy products) may increase urinary calcium loss and alter daily requirements. The source of calcium is assumed to be the skeleton, but some of the calcium may come from increased calcium absorption (44). Calcium and sodium share the same transport system in the proximal tubule. Every gram of sodium excreted carries about 8 to 25 mg of calcium with it. Sodium bicarbonate does not have the same effect on urinary calcium loss as sodium chloride (41). In addition, 1 mg of calcium is lost with each 1 g of protein metabolized in the body. This effect may be related to calcium binding to the sulfate derived from sulfur-containing amino acids. The practical significance of this effect in making diet recommendations is not clear because diets with low intakes of calcium should be avoided. However, at low salt and protein intake the minimum calcium requirement may be as low as 450 mg per day for a small female, and as large as 2 g per day, if protein and sodium intake are high. Each gram of sodium leads to the urinary excretion of about 15 mg of calcium when calcium intake is high or moderate (43). This problem persists when Western diets are consumed, as they are high in sodium and low in available calcium.

Until puberty, calcium absorption is increased up to twofold (60%) in comparison with absorption in adults. In pregnancy absorption and retention of calcium are increased. After the age of 60, calcium absorption decreases, and the ability of the intestine to respond to a low-calcium diet by increasing the rate of absorption is impaired. The bowel and kidney excrete about 160 mg of calcium daily even when calcium intake is low. In addition, about 40 mg is lost per day through the skin (45). Thus, an intake of 200 mg per day is needed to offset these obligatory losses. Net calcium absorption will not occur until these obligatory losses have been satisfied.

Dietary Reference Intake

Bone density increases during the first 25 to 30 years of life and decreases thereafter. The FDA has approved the claim that the use of calcium supplements reduces the risk for osteoporosis (46). The revised dietary recommendations for calcium intake (43) are close to those formulated by the National Institutes of Health consensus development conference on optimal calcium intake (47).

The recommendations in Table 7-17 are meant to be reflections of national policy. They are not intended to be nutrient requirements for individuals. This issue is particularly troublesome for calcium because a long time may elapse before the effects of calcium deficiency are noted. Thus, an optimal intake is better stated for populations than for individuals. The debate over calcium guidelines continues to stress the need for calcium intake versus the complex relationship between calcium intake and bone health (48). The

TABLE 7-17. Dietary Reference Intakes for Calcium

Age group	DRI (mg/day)
0–6 months	210
7–12 months	270
1–3 years	500
4–8 years	800
9–18 years	1,300
19–50 years[a]	1,000
51+ years	1,200

[a] No alterations for pregnancy or lactation are recommended.
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: National Academies Press, 1997.

increased recommendation for adolescents is based on their rapid growth of bone. The increased recommendation for older persons is based on data showing that their rate of calcium absorption is decreased.

The current recommendations imply that a single universal requirement exists for calcium, regardless of the intake of protein, sodium, and fiber/phytate. This view has been challenged because of the fact that calcium intake is low in parts of the world where fracture rates are low, and high where fracture rates are high (45). In fact, a review of 58 studies of dairy or dietary calcium intake in children and young adults found no relationship between dairy or dietary calcium intake and bone mineralization or fracture rate (49). It has been estimated that a diet low in sodium and protein can reduce the calcium requirement by as much as 200 to 300 mg per day. These considerations have not been included in the DRI calculations of the U.S./Canadian Committee (43).

Food and Dietary Sources. Primitive diets containing vegetables, bones of small animals or fish, and possibly insects have a high calcium density that approaches 80 to 100 mg per 100 kcal (47). In contrast, the median calcium density of the diet of women in NHANES III was only about 36 mg per 100 kcal, and the new DRIs suggest about 50 mg of calcium per 100 kcal (45). Milk contains 350 mg of calcium per 100 kcal (~300 mg per cup), and thus, dairy products are the most calcium-dense foods in the diets of most countries. Shellfish contain much calcium, but calcium levels are low in most meats, fish, or poultry. Three hundred milligrams of calcium can be found in 1 1/2 oz of cheese, 1 3/4 cup of ice cream, 6 oz of low-fat yogurt, 1 1/2 cup of cooked greens (e.g., kale, spinach, bok choy), and 5 oz of canned salmon. Other foods that contribute to daily calcium intake include dried beans, broccoli, and tofu (chemically set with calcium). However, the calcium in beans is only about 50% as available as that from animal sources. In animal products, calcium is bound largely to protein, which must first be digested before calcium can be absorbed. Organic anions, such as phytates and oxalates, are found in many green leafy vegetables and inhibit calcium absorption either partially (phytate) or nearly completely (oxalate), so bioavailability is variable. Table 7-18 lists the calcium content of selected foods.

Calcium-fortified foods (e.g., fortified orange juice) contain up to 350 mg of calcium per 8 oz and may constitute a major source of dietary calcium for persons who do not use dairy products. Other sources of fortified calcium include soft drinks and breakfast cereals. However, adding mineral salts to foods can possibly decrease the bioavailability of natural minerals in the food. Interactions between calcium, iron, and zinc have been documented in humans (50). If intake of zinc is limited, high calcium intake can decrease uptake of zinc, especially in children. Because 29% of the body content of zinc is in bones, zinc status may be as important as calcium status in overall bone health. There is also a small but significant inverse relationship between calcium intake and iron body stores (42).

TABLE 7-18. Calcium Content of Selected Foods

Food	Serving size	Calcium content (mg)
Calcium-fortified orange juice	1 cup	up to 350
Milk, all types (liquid)	1 cup	280–300
Yogurt, plain	1 cup	274–315
Hard cheeses	1 oz	213–287
Soft cheeses	1 oz	159–219
Figs, dried	10	269
Tofu, raw, firm	1/2 cup	258
Calcium-fortified cereals	3/4 cup	250
Spinach, cooked	1 cup	244
Collards, cooked	1/2 cup	179
Cottage cheese	1 cup	126–180
Ice cream	1 cup	176
Peanuts, roasted	1 cup	126
Beans (navy, pinto)	1 cup	80–120
Salmon, canned with bones	1 oz	110
Sardines, in oil	Two	92
Vegetables (carrots, kale, broccoli)	1/2 cup	36–52
Fruits	1 cup/piece	18–25
Pasta, rice	1 cup	10–23
Bread, white	Slice	35
Meat, fish	3 oz	3–10

Data from Hands ES, *Food Finder*, 2nd ed. Salem, OR: ESHA Research, 1990; Pennington JAT. *Bowes and Church's Food Values of Portions Commonly Used*. 17th ed. Philadelphia: Lippincott-Raven, 1998.

Supplementation with calcium is the most widely available means to increase calcium intake. There are at least 22 forms of calcium approved for supplement use by the U.S. FDA, and these differ in formulation and bioavailability (42). Factors that affect bioavailability include dissolution time, solubility, co-ingestion of food, and timing of dose. However, solubility and bioavailability are not proportionately related in the case of all salts. There are sparse data available to allow an informed choice about the proper salt to use for supplementation and how to dose it. Calcium carbonate is preferred by consumers because of its high content (40% mg per kg), but its absorption may not be optimal.

Assessment

Intake/absorption. Intake/absorption is best measured by 24-hour urinary calcium excretion. This varies from 100 to 240 mg per day, with much individual variation noted. In adults, the amount excreted correlates with calcium absorption above 2 mg per kg per day (i.e., intake >6 mg per kg per day) because only about 30% is absorbed. When calcium intake or absorption is low, urinary calcium does not decline proportionally. The range of values for urinary calcium found with an inadequate calcium intake of less than 200 mg per day (30 to 160 mg of urinary calcium per day) overlaps with the range of values found with a normal calcium intake (100 to 240 mg per day). Thus, the values for urinary calcium excretion should not be interpreted too rigorously. Even when net calcium absorption is zero, the obligatory loss of urinary calcium continues. This situation is in contrast to what is observed with other minerals, such as sodium, potassium, magnesium, and phosphorus, the urinary excretion of which is regulated at low levels of intake/absorption. Thus, urinary excretion is not a good test for calcium deficiency; it is better used to monitor the adequacy of calcium intake when supplemental calcium is prescribed. It should be measured only after 3 to 4 days on a constant calcium intake and when drugs that alter urinary calcium (e.g., thiazide diuretics, tetracycline, glucocorticoids) are not being taken. A high intake of protein or renal leak may increase calcium excretion. Treatment with

1,25-dihydroxyvitamin D_3 can cause bone resorption and an increased urinary calcium that is unrelated to calcium absorption. In patients with bone disease, urinary calcium excretion may be constant and independent of calcium absorption.

Calcium Determination. Serum calcium and alkaline phosphatase measurements are the conventionally used tests of calcium status but are inadequate for this purpose. Ionized calcium is maintained within a very narrow range as calcium is mobilized from the bones. The non-ionized calcium is protein-bound and pH-dependent, increasing with alkalosis and decreasing with acidosis. Thus, alkalosis or hyperproteinemia can cause a false-positive result for hypercalcemia, and acidosis or hypoproteinemia a false-positive result for hypocalcemia.

Calcium is measured by rapid automated procedures; the *o*-cresolphthalein complex method is used most often, and sometimes flame photometry or atomic absorption spectroscopy (34). Normal values for serum calcium are given in Table 7-19. Because of the tight metabolic regulation of serum calcium, values outside this range cannot be interpreted according to nutritional status; rather, they usually suggest a pathologic mechanism. Ionized calcium levels reflect calcium metabolism better than total calcium does. Serum levels of ionized calcium can be low when calcium (or vitamin D) deficiency is severe and skeletal pools of calcium are low, but this is a late finding. Hypocalcemia is defined as less than 2.18 mmol per L (<85 mg per L), and hypercalcemia as more than 2.6 mmol per L (>105 mg per L).

Alkaline Phosphatase. Activity in serum represents the sum of liver and bone isozyme activity. During active bone resorption, alkaline phosphatase activity in serum increases, but this result is neither sensitive nor specific, even in the presence of secondary hyperparathyroidism (51). Origin of the enzyme in bone can be suggested by heat inactivation at 56°C (<15% remaining indicates origin in bone), or by determination of γ-glutamyl transpeptidase, a bile canalicular enzyme present in liver and biliary tissue but not in bone. When calcium deficiency is advanced and osteomalacic bone disease is present, alkaline phosphatase is elevated. The enzyme level is high in any condition in which bone remodeling is taking place, so that it is elevated in children and adolescents and in patients with metastatic bone disease or Paget disease.

Bone Density Measurements. Changes in bone density (usually by dual-energy X-ray absorptiometry (DEXA) are measured for several years to follow the effects of dietary calcium supplements and other interventions on bone density, especially in the prevention and treatment of postmenopausal osteoporosis in women. The measure is not recommended for routine screening but may be useful in guiding treatment decisions for selected postmenopausal women (52,53,54). The National Osteoporosis Foundation (NOF) recommends testing for postmenopausal women age 65 or over, or age <65 with one or more clinical risk factors (e.g., smoking, weight <57 kg, and a personal or family history of fractures due to fragile bones) (53). The International Osteoporosis Foundation (IOF) recommends screening for postmenopausal women with one or more clinical risk factors, and includes height loss,

TABLE 7-19. Serum Calcium Biochemical Parameters

Parameter	Young men	Young women	Adults	Elderly
Total calcium (mmol/L)	2.41 ± 0.2	2.40 ± 0.2	2.43 ± 0.02	2.28 ± 0.12
Ionized calcium (mmol/L)	1.48	1.21	1.25 ± 0.04	1.24 ± 0.07
Alkaline phosphatase (IU/L)	63 (21–155)		80 (43–110)	

Modified from Sauberlich HE. *Laboratory Tests for the Assessment of Nutritional Status.* 2nd ed. Boca Raton, FL: CRC Press, 1999.

or radiographic osteopenia, or the need for prolonged hormone replacement therapy. The International Society for Clinical Densitometry (ISCD) has similar recommendations, but includes diseases known to be associated with bone loss as a risk factor. The WHO study group has emphasized the differences that may occur depending on the site tested for bone density and warns against using density to assess fracture risk, although a low bone density is one of the strongest risk factors for fracture. The WHO has suggested that intervention be recommended for persons with a T-score value less than 2.5 SD below the age-adjusted mean, but the USDA has accepted a score less than 2.0 SD below the mean. The WHO criteria suggest that a T-score <2.5 at either lumbar or femoral site can be used to diagnose osteopenia, but some evidence suggests that the lumbar site is more sensitive for younger patients (men <60, women <70 years), and the femoral site for older patients (55).

Guidelines for the use of bone density measurement (BMD). In 1996, the American Association of Clinical Endocrinologists (AACE) developed guidelines for the treatment of osteoporosis that included bone density measurement (56). They recommended bone density measurement to assess risk in perimenopausal or postmenopausal women concerned about osteoporosis. They also recommended testing for women with radiographic evidence of the diagnosis, undergoing treatment for osteoporosis, with asymptomatic primary hyperparathyroidism, or receiving long-term glucocorticoid therapy, situations in which evidence of skeletal loss might alter clinical strategy. In 1996, the European Foundation for Osteoporosis and Bone Disease (EFFO) also published practical guidelines for the use of bone density measurement (57). These guidelines were similar but did not include a recommendation to perform a baseline hip measurement. All these guidelines recommend the use of multiple skeletal sites, with the caveat that each site (e.g., spine, hip) best predicts fractures at that site but not at others (58). The USDA recommends bone density measurement if "it is reasonable and necessary for diagnosing, treating, or monitoring the condition of a beneficiary" as indicated in "estrogen deficiency...vertebral abnormalities...glucocorticoid (steroid) therapy...hyperparathyroidism" (59). Potentially modifiable features in postmenopausal women (and others) that might encourage testing include current cigarette smoking, low body weight, estrogen deficiency, low calcium intake (lifelong), alcoholism, recurrent falls, inadequate physical activity, and glucocorticoid therapy (60).

On a regular basis the ISCD holds Position Development Conferences to review the guidelines for indications and interpretation of bone density tests. The 2003 and 2005 conferences recommended measuring bone density at both posterior-anterior spine and hip, or in forearm when the other sites were not available (61,62). In addition, in healthy premenopausal women, Z-scores rather than T-scores should be used.

Factors other than BMD alone are considered risk factors for fractures. Chief among these is body mass index (BMI), particularly at low values (63,64). Mineral crystallinity, that is not measured by BMD, rather than mineral content itself is thought to account for some of the discrepancy between fracture rate and BMD (65). Although peak bone mass was formerly felt to be an independent risk factor, it is now considered that bone mass is more related to bone size or muscle function (66). It is worth remembering that when a BMD is done for the first time in a menopausal woman, 50% of women will have a negative T-score, but this does not imply recent bone loss (67).

Method. Most centers now use dual-energy absorptiometry (DEXA) to assess trabecular bone in the vertebrae and hips. The X-ray source in DEXA, which replaced the isotopic source of the original dual-photon absorptiometry, is preferable because of its wider range and shorter scanning speed. Precision standards for DEXA measurement have been published by the ICSD (68). Peripheral DEXA (P-DEXA) measures density in bones that are not at risk to fracture from fragility, but the machines are portable and units can be used in an office (www.webmd.com/hw/osteoporosis/hw3738.asp). If spine or hip DEXA is available, P-DEXA is not needed. Quantitative computed tomography (QCT) is also useful for the spine and peripheral QCT for the wrist. Peripheral QCT is promising for assessing bone mass in children, in whom DEXA is still the gold standard, but is not as predictive of future fracture risk as in adults (69). Bone mass values from DEXA or QCT are difficult to interpret if metal in the spine, contrast material in the gastrointestinal tract or spinal canal, or focal bone lesions are present. Aortic calcification and prior spinal bone surgery can affect the measurement, although

QCT is more useful with aortic calcification. Accuracy is only about 90% because of variation in marrow fat content. More radiation is delivered by QCT than by DEXA, about 250 mrad.

Other techniques have been used in order to improve the fracture predictability that is still a problem with DEXA. Quantitative ultrasound is used mostly in the heel. Infrared imaging spectroscopy has been used in an attempt to assess mineral crytallinity as well as mineral content, although no variations in crystallinity were produced by raloxifene (65,70).

Bone Biopsy. Calcium (or vitamin D) deficiency can sometimes be diagnosed by bone biopsy, which can demonstrate increased osteoid seams. Tetracycline labeling allows a distinction to be made between delayed mineralization (osteomalacia) and increased osteoid synthesis (bone remodeling states) by revealing the calcification front. This technique is not often needed to make clinical decisions.

Physiology

Calcium provides part of the matrix structure of bone. It is necessary for blood coagulation and for controlling membrane potential and the excitability of nerves and muscles. Through the protein calmodulin, it helps to control myocardial function and contractility. It supports membrane integrity and is a second messenger for many secretory processes. It helps to maintain intracellular integrity and intercellular tight junctions (60). Because of the importance of all these functions, serum levels are maintained with precision at the expense of bone matrix if exogenous calcium is not available. The major systems involved in regulating calcium homeostasis include the parathyroid hormone, vitamin D, and calcitonin (71). Apical calcium entry channels have been found in calcium transporting epithelia, CaT1 (ECaC2, TRPV6) in the intestine, and ECaC (ECaC1, TRPV5) as well as TRP6 and 7 in the kidney. The G-protein coupled calcium sensing receptor (CaR) is responsible for the tightly regulated secretion of parathormone from the parathyroid gland, responsive to small changes in serum calcium (72). The CaR also regulates calcium and magnesium excretion by the kidney, calcium reabsorption by the intestine, and bone remodeling. The calcium content of the human adult body is about 1,000 mg. More than 99% of this is in the skeleton. Young adults typically retain about 68 mg of calcium per day, with average retention efficiency of about 7.6% (60). About half of circulating calcium is turning over in the bone.

Absorption. When calcium intake is adequate, differences in calcium bioavailability probably play little role (73). When dietary calcium is low, however, or ingested in poorly soluble forms (e.g., green vegetables), then availability may be a problem. Absorption of vegetable calcium has proved to be quite variable because effective digestion is difficult to predict and assess (60). The high solubility of dairy calcium has been attributed to its presence as the citrate salt, and also to the presence of peptides, amino acids, and lactose. Milk substitutes lack many of these features and are not as good a source of available calcium and phosphorus as milk or milk products. Synthetic triglycerides improve calcium absorption (60). Gastric acid does not have much effect on the absorption of dietary calcium when the calcium is ingested with a meal (74). However, when calcium enters the relatively alkaline lumen of the duodenum, less calcium is solubilized, and calcium carbonate, when taken alone, is poorly absorbed.

Active calcium absorption (entry and secretion) depends on vitamin D intake and the presence of calbindin in duodenal enterocytes (60). Most calcium is absorbed passively in the jejunum and ileum because transit time through the duodenum is so short. The degree of passive ileal absorption depends on many factors, including luminal solubility, residence time in the lumen, and the rate of paracellular diffusion. Only a small amount ($<10\%$) of calcium is absorbed in the human colon, all of it passively; active transport of larger amounts occurs in rat and sheep. The two apical calcium channels show 75% homology, and belong to the super family of the transient receptor potential (TRP) channels. Entry across the apical intestinal membrane via CaT1 is driven by a favorable electrochemical gradient. Inside the cell calcium is bound to calbindins, vitamin D-dependent proteins that deliver calcium to the basolateral membrane (71,75). Intracellular calcium is in the nanomolar range, whereas extracellular calcium is millimolar. Thus, extrusion from the cell is

mediated against this electrochemical gradient by the calcium pump, consisting of an ATP-dependent Ca^{+}-ATPase, and a Na^{+}-Ca^{++} exchanger, NCX1. About 4 mmol (~140 mg) of calcium is absorbed each day into the extracellular fluid, a compartment that contains about 25 mmol of calcium (61). Fourteen millimoles of calcium enter bone and is mobilized from it each day, but the largest movement of calcium occurs in the kidney, where 270 mmol is filtered each day, and 266 mmol is reabsorbed, via CaT1 and ECaC and the active calcium pump in the proximal tubules (70%), the ascending limb (20%), the distal convoluted tubule and connecting tubule (71,75).

Enteroenteric Circulation. About 300 to 400 mg of calcium is absorbed each day in a normal adult, but 200 to 300 mg is re-excreted into the lumen via pancreatic, biliary, and intestinal secretions. The newly absorbed calcium in the blood mixes with an exchangeable pool of about 1 g. The calcium pool is filtered through the kidney many times, so that 10 g is filtered each day, of which 99% is absorbed secondary to the action of parathyroid hormone and 100 mg is excreted in urine. When intestinal or urinary losses are excessive, the rate of bone resorption increases until it cannot compensate for the losses and hypocalcemia develops.

Deficiency

Incidence. Dietary deficiency of calcium is more common than magnesium or phosphorus deficiency; dietary sources of calcium are more limited than those of magnesium and phosphorus, absorption is not as good as that of phosphorus, and the obligatory daily excretion (300 mg in stool, 100 mg in urine) is large in comparison with the exchangeable pool size (1 g) and the daily flux from bone (200 to 300 mg). Dietary deficiency is most likely to develop during infancy, adolescence, and pregnancy (when requirements are large) and during old age (when absorption is decreased and bone mass is lower).

Hypocalcemia. The usual causes of hypocalcemia are not related to deficiency but to metabolism. Hypocalcemia leads to enhanced neuromuscular transmission, tetany, altered myocardial function and arrhythmias (prolonged QT interval), and altered nerve conduction. Severe weight loss (e.g., anorexia nervosa) can lead to a prolonged QT interval and arrhythmia by a mechanism that is not explained by hypocalcemia (76).

Chronic Deficiency. The body contains about 1,000 g of calcium. A net loss of 100 mg per day would lead to a 20% (detectable) loss of bone calcium in about 2,000 days, or 6 years. Because bone loss is a slow process, the state of calcium nutrition at the time of clinical presentation, such as fracture, may bear little relationship to an earlier cause of bone loss. Thus, calcium intake should aim to achieve a peak bone density at ages 25 to 30 as well as to alter the rate of bone loss with aging (77). The expected rate of bone loss with aging is 0.5% yearly after age 40, except for the 5 years after menopause, when it increases to 2% annually. The major mechanisms that lead to bone loss greater than expected for age include failure to achieve an optimal bone mass during growth and development, excessive bone resorption, and inadequate replacement of lost bone.

Osteopenia can occur unevenly in different bones, so the bone density analysis must be performed on those most at risk in a given patient. As a person ages, however, the bone loss from various sites tends to equalize. Thus, measurements of density in the spine, proximal femur, middle portion of the radius, and os calcis all reflect similar degrees of bone loss in the elderly. In women 20 to 45 years old, the site of measurement may be critical (58). The spine is most often followed in postmenopausal osteoporosis; the rate of bone turnover in trabecular bone, such as that of the spine, is high, and measurement with DEXA is most precise in the spine.

Causes. Malabsorption of calcium usually occurs in short-bowel syndrome and untreated celiac disease, but malabsorption may be of many causes. Renal failure and vitamin D deficiency lead to hypocalcemia and bone disease. The factors most often associated with low bone mass (not necessarily calcium deficiency) are postmenopausal osteoporosis (especially if the patient or a first-degree relative has a history of fracture), Caucasian race, female sex, advanced age, dementia, low body weight, current cigarette smoking, low calcium intake (lifelong), alcoholism, and poor general health. Gastric bypass surgery

for morbid obesity can lead to an increase in bone turnover and a decrease in bone mass that can occur within 9 months of surgery, despite an increase in dietary calcium and vitamin D (78).

Treatment

Any patient with calcium deficiency should also be evaluated for vitamin D deficiency (see Chapter 6), and if this is present, it should be treated.

Hypocalcemia. Acute symptomatic hypocalcemia (ionized calcium <1.12 mmol per L) is a medical emergency (79). It should be treated with 10 to 20 mL of a 10% solution of calcium gluconate (90 to 180 mg of elemental calcium) administered IV over 10 to 15 minutes. When the initial [iCa]s is <1 mmol per L, twice that amount can be given. This initial therapy should be followed by more prolonged IV infusion (e.g., 6 to 8 10-mL ampules of 10% calcium gluconate per liter in D5W) until serum calcium levels can be maintained with oral supplements. Frequent ionized calcium and phosphorus determinations should be made, and electrocardiographic monitoring is indicated until serum calcium returns toward normal.

Nutritional Deficiency. Nutritional rickets still occurs in Third World nations. When rickets was caused by a low intake of calcium (200 mg per day), it responded better to treatment with calcium alone (1,000 mg per day) or in combination with vitamin D than to vitamin D alone (80). When calcium intake was below recommended levels but not very low (e.g., 800 mg per day) in mothers who were lactating or postweaning, supplementation with calcium (1,000 mg per day) enhanced bone density only modestly (~5%) in 6 months (81).

Osteoporosis in Medical Disorders. In certain intestinal diseases, fecal calcium loss is increased by diarrhea or malabsorption; patients with such diseases should undergo bone density screening, and any osteoporosis should be treated. Clinical risk factors are not good predictors of bone mass in these patients, and the threshold for measuring bone density should be low. Patients with celiac disease and inflammatory bowel disease (IBD) should be given adequate dietary calcium and supplementation to 1,500 mg per day in the form of tablets if necessary (82). Vitamin D deficiency should be sought and treated (see Chapter 6). If patients are on glucocorticoids, the dose taken should be the lowest required to obtain benefit, and it should be taken for the shortest possible time. Physical activity and adequate nutrition should be promoted, and cigarette smoking should be discouraged (83). Studies suggest that supplementation with calcium, vitamin D, or both prevents bone loss in patients with Crohn disease (84). If low bone density persists, drug therapy for osteoporosis should be provided, with the addition of hormone replacement therapy for postmenopausal women, testosterone for men with low testosterone levels, and biphosphonates or calcitonin for others as indicated.

Osteoporosis. Good evidence is available to support the role of calcium supplementation in improving bone density in elderly and adolescent populations (39). This relationship has been supported by the FDA, the National Institutes of Health, and the National Academy of Sciences. The beneficial effect of 1,000 mg of supplemental calcium, with or without vitamin D, has been seen in early postmenopausal women, even those with good initial calcium and vitamin D status. Some studies also show a decrease in the fracture rate with calcium alone (1,200 mg per day for 4 years) (85). Studies assessing the efficacy of estrogen therapy in postmenopausal women showed improved bone density in those whose dietary calcium exceeded 1,000 mg per day, but not in those whose dietary calcium was only half that amount (41,86). When adequate calcium (>1,000 mg per day) and vitamin D (to maintain 25-hydroxyvitamin D levels ≥ 75 nmol per L) were taken, bone sparing with low-dose hormone replacement therapy was as good as that achieved with high-dose hormone replacement therapy (87). However, one cannot assume that routine supplementation of postmenopausal women with 1,000 mg of calcium and 800 IU of vitamin D will be effective in prevention of fractures, either as primary (88) or secondary (89) prevention. The possible reasons for such failure are many and incompletely understood, but the message is clear that routine supplementation in unstratified elderly women is not likely to be

successful. Whether replacing vitamin D adequately (see Chapter 6) or treating only those with vitamin D deficiency is the answer is still unknown.

Hypertension. A small decrease in systolic, but not diastolic, pressure was observed with calcium supplementation between 500 and 2,000 mg per day (90,91). However, use of the DASH diet, low in fat and rich in fruits, vegetables, whole grains, and low-fat dairy products that provide 1,265 mg of calcium per day, produced a greater fall in pressure (6). The major problem is the variable calcium excretion related to the high sodium intake and relatively low calcium intake that characterize Western diets (41). Thus, calcium supplements are not often indicated for the treatment of hypertension.

Colon Cancer. Controlled studies measuring the effect of calcium on colonic proliferative rates have provided mixed answers (92) (see also Chapter 14). One large study showed a modest effect of calcium supplementation (1,200 mg per day) for 4 years in preventing colorectal polyps (93).

Premenstrual Syndrome. The use of 1,200 mg of calcium per day for three cycles led to fewer symptoms in women ages 18 to 45 years (94). The use of calcium for this condition should still be considered uncertain until more studies have been reported.

Oral Preparations. Calcium carbonate is given to most patients because it contains the largest amount of elemental calcium per unit weight. However, it is less soluble than some other salts (glubionate, gluconate, citrate), which may be useful in selected cases because they are better absorbed (95). Calcium carbonate contains 40% elemental calcium. Tricalcium phosphate contains 33% elemental calcium, acetate 25%, dibasic phosphate 23%, citrate 21%, lactate 13%, gluconate 9%, and glubionate 6.5%. Table 7-20 lists some of the available preparations.

Toxicity

The tolerable upper intake level (UL) for calcium has been set for adults at 1,200 mg per day (43) (Appendix B). When intake exceeds 4,000 mg per day, hypercalcemia develops, along with renal damage and metastatic calcification.

Populations at Risk. In patients on thiazide diuretics or with renal disease, urinary calcium excretion may be decreased. Patients with absorptive or renal hypercalciuria are at an increased risk for kidney stones, although normal persons are not (96). Patients with primary hyperthyroidism and sarcoidosis are at risk for hypercalcemia and should avoid calcium supplements. Patients with calcium oxalate stones, especially if they are secondary to malabsorption of fat, should be treated with oral calcium to precipitate the soluble sodium oxalate in the intestinal lumen.

Interference with Absorption. Oral calcium may interfere with the absorption of many drugs (e.g., salicylates, bisphosphonates, fluoride, tetracyclines, atenolol, iron). Calcium supplements should not be taken at the same time as iron and other medications. Calcium supplements do not interfere with magnesium absorption in normal persons but may do so in cases of magnesium depletion, as in patients with diabetes, malabsorption, or acute alcoholic intake. In such cases, 100 mg of magnesium should be provided for every 500 mg of supplemental calcium used (96).

Hypercalcemia. Serum calcium levels above 11 mg per dL can be associated with symptoms related to decreased neuromuscular transmission and muscle contraction. These include weakness, ileus, altered cardiac conductivity, anorexia, nausea, vomiting, constipation, dry mouth, polyuria, and thirst. Serum calcium levels above 12 mg per dL can produce confusion, delirium, stupor, and coma, especially in the elderly. Changes on the electrocardiogram include short PR, ST, and QT intervals, with a prolonged QRS complex. Arrhythmias can occur, especially at levels above 13 mg per dL. The treatment of severe exogenous hypercalcemia should begin with IV normal saline solution (500 to 750 mL per hour or as tolerated) and furosemide (80 to 120 mg per hour) if renal function is adequate. These measures are usually rapidly effective. Long-term management consists of adjusting the doses of exogenous calcium, vitamin D, or both.

TABLE 7-20. Selected Calcium-containing Products for Oral Use

Calcium supplement	Elemental calcium (mg per tablet)	Vitamin D (IU per tablet)
Calcium carbonate		
Alka 2	200	—
Alka-Mints	340	—
Biocal	250, 500	—
Calburst	500	200
Calciday	667	—
Calsup	300, 600	200
Caltrate + D	600	200
Os-Cal + D	250, 500	200
Oystercal	250, 375, 500	—
Titralac	200 (405/5 mL)	—
Tums	200, 500	—
Viactiv	500	100
Calcium citrate		
Citracal	200 (500 per effervescent tablet)	—
Citracal + D	315	200
Calcium citrate + D	315	200
Calcium complex/components		
Calcium acetate	167–668 mg	—
Calcet (carbonate, lactate, gluconate)	150	100
Calcium gluconate	45/500 mg	—
Calcium lactate	42/325 mg	—
Ca Plus (protein)	280	—
Calcium glubionate		
Neo-Calglucon	115/5 ml)	—
Calcium phosphate		
Dical-D	350	400
Posture-D	600	125

Magnesium

Requirement

Magnesium requirements have been determined by balance studies and urinary measurements because the kidney is the main excretory organ. With an average U.S. dietary intake of 120 mg per 1,000 kcal per day and maintenance of the serum concentration at 2 mg per dL (~1.7 mEq per L), the mean urinary excretion is about 72 mg per day. Because average absorption is 30% to 40%, the daily requirement should be about 200 mg for an adult. However, the requirements for infants and children have not been accurately assessed. Estimates of net magnesium accretion over all of childhood are ~4 mg per day (43). Magnesium replacement for infants is still uncertain (97). Human milk contains 40 mg of magnesium per liter, and the average infant ingests about 850 mL per day. The 1997 DRIs are noted in Table 7-21.

Food Sources

Magnesium is bound to protein and phosphate ions, and to porphyrin in green leafy plants and vegetables. Hard water and mineral waters can contain as much as 120 mg per L. The sources of magnesium are widespread. Good dietary sources include whole grains, legumes, dark green leafy vegetables, nuts, fish, whole grains, and cocoa. Dairy products, meat, and eggs contain lesser amounts of magnesium. The use of calcium supplements without magnesium is controversial. There is a theoretical interaction between the ions for absorption, but practically the risk of producing deficiency in humans (particularly children) is not

TABLE 7-21. Dietary Reference Intakes of Magnesium

Life stage group	Magnesium (mg/day)	Life stage group	Magnesium (mg/day)
Infants		**Females**	
0–6 months	30[a]	9–13 years	240
7–12 months	75[a]	14–18 years	360
		19–30 years	310
Children		31–>70 years	320
1–3 years	80		
4–8 years	130	**Pregnancy**	
		≤18 years	400
Males		19–30 years	350
9–13 years	240	31–50 years	360
14–18 years	410		
19–30 years	400	**Lactation**	
31–>70 years	420	≤18 years	360
		19–30 years	310
		31–50 years	320

[a] Adequate intake (AI) is estimated from ingestion of human milk content. Other values reflect recommended dietary allowance (RDA).
Modified from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: National Academies Press, 1997.

demonstrated (50). In the United States the FDA encourages the use of foods with a low sodium content and a high content of calcium, magnesium, or potassium (by allowing health claims to be used for such products) (98). Table 7-22 lists the magnesium content of selected foods.

Assessment

Intake and Absorption. When dietary information is available, urinary magnesium can be helpful because dietary intake and urinary excretion are strongly correlated (34). The kidney avidly retains magnesium when dietary intake is low, and urinary levels fall. However, dietary deficiency of magnesium is uncommon because the mineral is widely distributed among foods. Thus, low urinary levels of magnesium usually reflect disease (e.g., prolonged diarrhea). Elevated urinary levels of magnesium often reflect diuretic therapy, not high dietary intake.

TABLE 7-22. Magnesium Content of Selected Foods

Food	Serving size	Magnesium content (mg)
Cereals	3 oz	90–120
Legumes	1 cup	80–120
Nuts	1/2 cup	130–210
Fish, cooked	3 oz	20–60
Baked potato with skin	One	55
Spinach, cooked	1/2 cup	80
Vegetables, cooked	1 cup	5–30
Fruit	1 cup	20–30
Meat, cooked	3 oz	10–20
Milk	1 cup	28–33
Yogurt	1 cup	27–40
Beer	12 oz	23

Body Stores. Serum magnesium is measured by colorimetric or fluorometric methods, although atomic absorption spectroscopy is more reliable. Hemolysis falsely elevates serum magnesium levels because the mineral is an intracellular cation. Extracellular ionized magnesium (filterable magnesium) is the biologically active fraction, so that the total serum magnesium level does not reflect total stores in a reliable fashion. As with calcium, ionized magnesium cannot be estimated using a correction for albumin. Magnesium-selective electrodes are available and have been incorporated into commercially available instruments (34). About 70% of the total magnesium in plasma is ionized, but the usefulness of measuring ionized magnesium in disease states is not well studied. Studies differ on whether total serum magnesium can predict changes in ionized magnesium, or whether ionized magnesium can predict clinical outcomes (99). Current electrodes used for ionized magnesium do not adequately select for magnesium over calcium, so results have to be corrected for ionized calcium. Moreover, the life span of existing electrodes is variable, and further standardization is needed. Hypomagnesemia, defined as levels below 1.25 to 1.50 mEq per L or 0.62 to 0.75 mmol per L (Table 7-23), is often accompanied by hypokalemia and hypocalcemia. Low levels can occur with pregnancy, malabsorption, reduced intake, diabetes mellitus, severe illness, acute alcoholism, or renal leak (or diuretic use). A normal level does not rule out deficient stores because the serum level is corrected by the action of parathyroid hormone and calcitonin. Hypermagnesemia is found in renal failure and with the use of magnesium-containing antacids or laxatives.

Tissue magnesium levels should be the best measure of body stores of this intracellular cation, but practical methods are not available. Red and white cells have been isolated for this purpose, but the results are not sufficiently consistent for general use (99). The magnesium loading test has been used to assess deficiency (34). Thirty millimoles of magnesium chloride is infused over 12 hours, and urine is collected for 24 hours. Magnesium status is based on the amount of magnesium retained in the body. Normally, only 5% to 6% is retained. Another paradigm infuses 2.4 mmol per kg of parenteral magnesium, and retention of >20% suggests magnesium deficiency (99). However, the care required to perform the test has limited its clinical usefulness.

Physiology

Magnesium is the fourth most abundant cation in the body, after sodium, potassium, and calcium. The 70-kg adult body contains about 2,000 mEq of magnesium, or 21 to 28 g. About 60% is in the bone, with the rest distributed equally between muscle and other soft tissues. Less than 5% is in the extracellular fluid. The exchangeable magnesium pool is about 5 g, but extracellular magnesium is only about 250 mg. Magnesium flux from bone replenishes the exchangeable pool, but the daily rate of this flux is not precisely known.

TABLE 7-23. Reference Values for Magnesium Assessment

Parameter	Magnesium levels (mmol/L)	Magnesium levels (mEq/L)
Serum magnesium (adult)	0.75–1.25	1.5–2.5
NHANES I (18–74 years)	0.75–0.96	1.5–1.92
Hypomagnesemia	>0.62–0.75	<1.25–1.5
Hypermagnesemia	>1.25	>1.5
Serum ionized magnesium	0.58 ± 0.006	
Erythrocyte magnesium (adult)	1.88 ± 0.12	
	Magnesium urinary excretion per day	
Magnesium load test	94%–95% (normal)	33%–69% (deficient)

NHANES, National Health and Nutrition Examination Survey.
Modified from Sauberlich HE. *Laboratory Tests for the Assessment of Nutritional Status.* 2nd ed. Boca Raton, FL: CRC Press, 1999.

Function. More than 300 enzymatic reactions require magnesium. These involve transfer of phosphate groups, acylation of coenzyme A, hydrolysis of phosphates and pyrophosphates, and nucleic acid synthesis. All enzymatic reactions in which adenosine triphosphate is involved require magnesium. In addition, the cation is necessary for ribosomal RNA and DNA stability, activation of amino acids, degradation of DNA, neurotransmission, regulation of smooth muscle tone, and immune function. Magnesium is a calcium antagonist in some reactions, and interacts with potassium, pyridoxine, and boron.

Absorption. Magnesium is absorbed by two processes: nonsaturable passive paracellular diffusion (90%) and saturable active transport (10%). Paracellular absorption is impaired in the rare autosomal recessive disorder, primary hypomagnesemia, associated with a defect in a tight junction protein called paracellin 1 (PCLN1) or claudin 16 (100). Active transport of magnesium is mediated by a member of the cation channel transient receptor potential (TRP) family, TRPM6. Mutations in this protein are found in the inherited disorder of hypomagnesemia with secondary hypocalcemia (101). The TRPM6 transporter is located apically in all parts of the intestine and in cells of the distal renal tubule. A portion of magnesium is absorbed in the colon, by a mechanism as yet unknown (102). Absorption varies from 30% to 70% of ingested magnesium, depending on how much magnesium is presented to the gut. At the usual intake levels of 300 mg per day, absorption is about 30% to 50%. Active magnesium absorption is more readily detected in magnesium-deficient states. At physiologic concentrations, the effect of 1,25-dihydroxyvitamin D_3 on magnesium absorption is very small and is probably related to changes in calcium or phosphorus uptake (103). Much of the magnesium ingested in medicinal form (oxide, hydroxide, chloride, citrate) is poorly soluble and is not absorbed to a great extent. Phosphate and organic chelators (e.g., oxalate, phytate) can delay absorption. Transit time is a major factor in determining the efficiency of magnesium absorption.

Urinary Excretion. The kidney is the major excretory organ. More than two-thirds of absorbed magnesium is excreted in the urine each day. Urinary excretion is about 80 to 120 mg (3% to 5%) of the filtered load of 2.4 g per day, and is increased in conditions associated with proteinuria. The proximal tubule reabsorbs 15% to 20% of filtered magnesium, and the thick ascending limb of the tubule absorbs 50% to 75%, so that excretion is reduced to less than 1 mmol per day. The distal tubule reabsorbs 5% to 10% of the ion and together with the thick ascending loop is the major site of magnesium regulation (104). The major regulator is the serum magnesium concentration, and regulation is mediated by Ca/Mg-sensing receptors located on the capillary side of cells of the thick ascending limb. Maximal excretion in response to magnesium loading can exceed 160 mmol per day. Magnesium excretion is increased by volume expansion, hypercalcemia, diuretics, alcohol, and phosphate depletion, and is decreased by the action of parathyroid hormone. Because of this tight urinary regulation, magnesium deficiency occurs rarely except when excessive amounts are lost from the body, in intestinal or renal disease.

Parathyroid Hormone Response. When hypomagnesemia is mild, parathyroid hormone is released and calcium is released from bone. However, the direct effect of hypomagnesemia on decreasing calcium mobilization from bone blunts this effect (105). When magnesium deficiency is severe and the serum concentration very low, parathyroid hormone secretion is impaired. Along with the direct effect of the hypomagnesemia on bone, calcium flux is lowered and hypocalcemia develops. In this case, hypocalcemia is less a manifestation of depleted calcium stores than of low stores of exchangeable magnesium. Thus, when magnesium deficiency is severe (e.g., in malabsorption), magnesium is required to treat the hypocalcemia.

Deficiency

Clinical Manifestations. Magnesium deficiency may not be associated with symptoms. Many of the symptoms of moderate or severe deficiency are nonspecific or are caused by associated electrolyte abnormalities, such as hypocalcemia, hypokalemia, and metabolic alkalosis (Table 7-24). The most common symptoms are muscular twitching and tremor, numbness, and tingling. Less common are muscle weakness, convulsions, apathy, depression, and delirium. Refractory hypokalemia can develop because magnesium plays a role

TABLE 7-24. Clinical Manifestations of Moderate/Severe Magnesium Deficiency

Symptoms	Signs	Laboratory abnormalities
Carpopedal spasm, tetany	Chvostek	Hypocalcemia
Seizures, tremor	Trousseau	Hypokalemia
Vertigo/ataxia	Arrhythmia, prolonged QT or PR interval wide QRS, peaked T wave, ST depression	Carbohydrate intolerance
Muscle weakness		ECG: wide QRS complex, prolonged PR interval, inverted T waves, U waves, ventricular arrhythmias
Numbness, tingling		
Depression, psychosis		

ECG, electrocardiogram.

in determining the intracellular–extracellular ratio of the two ions. If magnesium is deficient, potassium supplements can restore serum potassium, but not intracellular potassium (106). Common manifestations include Chvostek sign and premature ventricular beats. Ventricular premature complexes, and ventricular tachycardia or fibrillation are more serious complications. Magnesium therapy is recommended for treatment of torsade de pointes, but no randomized trials have proven its efficacy (107).

Causes. Most cases of magnesium deficiency arise from gastrointestinal or renal losses (Table 7-25) (99,108). Hypercalcemia of any cause produces a high filtered load of calcium that competes with magnesium for reabsorption. Any kind of diuresis can decrease the tubular reabsorption of magnesium. In patients with short-bowel syndrome, urinary magnesium levels fall before serum levels and are an early indicator of evolving deficiency (109). Although urinary magnesium is not often useful in diagnosing deficiency, the situation may be different in short-bowel syndrome, in which absorption is so limited.

TABLE 7-25. Causes of Magnesium Deficiency

Gastrointestinal	Renal
Malabsorption	Volume expansion
Diarrhea, especially chronic	Osmotic diuresis
Short bowel syndrome	Metabolic acidosis
Enterocutaneous fistulae	Drugs (thiazides, loop diuretics, alcohol, aminoglycosides, cisplatin, amphotericin B, cyclosporine, foscarnet, pentamidine)
Nasogastric suction, long-term	
Primary intestinal hypomagnesemia	
Malnutrition, severe	Phosphate depletion
Pancreatitis, acute	Postobstructive nephropathy
Prematurity	Diuretic phase of acute renal failure
	Renal transplantation
	Hungry bone syndrome
	Hypercalcemia of any cause
	Renal tubular dysfunction

Treatment

The choice of oral or parenteral magnesium depends on the severity of depletion. The extent of depletion cannot be predicted by laboratory findings, but may be as high as 1–2 mmol per kg of body weight (99). However, acute magnesium infusion decreases magnesium absorption in the loop of Henle, so much of the infused parenteral magnesium is excreted. Thus, oral replacement is preferred if the clinical presentation allows. The problem with oral therapy is that most of the salts of magnesium are only poorly soluble.

Parenteral. Moderate or severe deficiency should be treated parenterally, especially if tetany or ventricular arrhythmias are present, with 4 to 8 mmol given as an IV loading dose (8 mmol is contained in 1 g of heptahydrated magnesium sulfate), followed by 25 mmol per day thereafter until the plasma magnesium is above 0.4 mmol per L (104). In patients with normal renal function, up to 20 mmol (2.5 g) can be infused IV over 3 hours in 5% dextrose or 0.9% normal saline solution if deficiency is severe. Magnesium sulfate is incompatible with soluble phosphates, and with alkaline carbonates and bicarbonates, except in dilute solution. For mild deficiency, 1 g can be given intramuscularly (IM) every 6 hours for a total of four doses. Magnesium has been used parenterally in the absence of deficiency in patients with pre-eclampsia. The MAGPIE trial used 32 mmol initially, followed by 8 mmol per hour in women with pre-eclampsia (110). For torsade de pointes the Advanced Cardiac Life Support Guidelines suggest a loading dose of 16 mmol of magnesium given over 15 minutes, followed by 8 mmol per hour (111).

Oral. Magnesium oxide is commonly used, but it is poorly soluble and can act as a cathartic. Magnesium gluconate is preferred because it is more soluble and is available in a palatable liquid form (Table 7-26). Thus, large numbers of tablets can be avoided for long-term therapy. Magnesium chloride is absorbed poorly, less well than magnesium acetate or dietary magnesium (from nuts), and should not be relied on for replacement therapy (112). Magnesium salts can decrease the absorption of some drugs, such as aminoquinolones, digoxin, nitrofurantoin, penicillamine, and tetracyclines. Calcium supplementation of more than 2.6 g per day can lead to a negative magnesium balance. When malabsorption requires supplementation with both calcium and magnesium, they should be given at separate times.

Supplements for Chronic Medical Diseases. Magnesium supplements have been used for a variety of medical conditions in which patients are felt to be at risk for deficiency (e.g., diabetes) or in which improved muscular performance is desired (e.g., heart disease). Observational studies in heart disease have provided only a hint that magnesium may be useful for patients with mitral valve prolapse (39). Of course, patients should consume enough magnesium-rich foods or take supplements if their intake is not adequate.

TABLE 7-26. Oral Magnesium Preparations

Preparation	Anion	Tablet size (mg)	Elemental magnesium content (mg per tablet or per 5 mL)[a]
Mag-200	Oxide	400	241
Mag-Ox 400	Oxide	140	83
Magnesium oxide	Oxide	250, 600	130, 360
Uro-Mag	Gluconate	500	29
Magtrate	Gluconate	500	29
Magonate	Gluconate	5 mL	54
Magonate, Almora	Gluconate	500	27
Chelated magnesium	Amino acids	500	100
Slow-Mag	Chloride	535	64
Mag-Tab SR	Lactate		84
Maginex DS	Mg-L-aspartate-Cl	1,230 mg powder	122

[a] Assumes equal bioavailability, which is not the case.

Double-blinded placebo-controlled trials of magnesium supplements in hypertension have not demonstrated a reproducible effect, perhaps related to differences in sodium intake. If patients are taking loop or thiazide diuretics, some additional magnesium may be needed to replace that lost in the urine, if one assumes that renal function is normal. Magnesium supplements have not consistently improved glycemic control in either type I or type II diabetes (39), although a few randomized trials show benefit without a change in serum magnesium concentration (113). Likewise, evidence does not support magnesium supplements to treat migraine headaches or premenstrual symptoms or to improve exercise tolerance.

Toxicity

The UL for magnesium is 65 mg per day (children 1 to 3 years old), 110 mg per day (children 4 to 8 years old), and 350 mg per day (all adolescents and adults) (43) (Appendix B). Magnesium supplements are usually not toxic if renal function is normal. Soft stools and diarrhea have been reported after ingestion of more than 500 mg of elemental magnesium (114).

Hypermagnesemia. Hypermagnesemia develops when renal excretion is decreased (as in renal failure and eclampsia), in severe diabetic ketoacidosis, and in Addison disease. Blocking of neuromuscular transmission leads to decreased tendon reflexes (at levels >4 mEq per L) and respiratory paralysis and heart block (at levels >10 mEq per L). Infants of mothers with eclampsia treated with magnesium are at risk, as are patients with renal failure receiving magnesium-containing antacids.

Hypermagnesemia does not usually develop until the GFR falls below 13 mL per minute. In renal failure, magnesium excretion relative to the GFR is lower than expected from the plasma level. Thus, plasma levels can rise rapidly. At levels of 3 to 5 mEq per L, symptoms include nausea, vomiting, cutaneous vasodilation, and hypertension. At higher levels (5 to 9 mEq per L), drowsiness, hyporeflexia, and muscular weakness occur, and above 10 mEq per L, respiratory arrest is noted, along with prolongation of the QTc interval and atrioventricular block.

Therapy of Hypermagnesemia. Therapy of hypermagnesemia involves withdrawal of any oral or parenteral magnesium compounds, hemodialysis or peritoneal dialysis, or infusion of calcium to compete with magnesium on the cellular level. Usually, calcium infusion (1 g of calcium gluconate IV) is not required except for those patients who are critically ill.

Phosphorus

Requirement

Ratio of Phosphorus to Calcium. The recommended ratio of calcium to phosphorus in the diet is between 2:1 and 1:2. Because dietary phosphorus is so abundant and deficiency from decreased intake occurs so rarely, the recommended phosphorus intake is similar to that for calcium except in young infants. In the case of infants ingesting cow's milk with a calcium–phosphorus ratio of 1.2:1, the relative increase in phosphorus intake may contribute to hypocalcemia in early life. Thus, the AI for phosphorus is set at 100 mg, in comparison with 210 mg for calcium for the first 6 months of life, but nearly equal for the next 6 months (Table 7-27).

Dietary Reference Intake. Data to establish a requirement for phosphorus are not available because, similar to urinary magnesium excretion, urinary phosphorus excretion does not reflect dietary intake. In general, if the protein intake is adequate, so is the phosphorus intake. About 1 g of phosphorus is needed for each 17 g of nitrogen retained. The DRI exceeds this because of incomplete absorption and obligatory urinary excretion. The efficiency of absorption varies with the source of phosphorus and the ratio of calcium to phosphorus in the diet, so that the recommendation for dietary intake is further confused. The current DRI for adults is 700 mg per day, somewhat below the DRI for calcium (1,000 to 1,200 mg per day); for growing adolescents and pregnant or lactating women, the DRI is 1,250 mg per day, nearly the same as that for calcium (1,300 mg per day).

Food Sources

Phosphorus is a constituent of all cells and is thus present in all foods. The phosphorus content of some foods is listed in Table 7-28. Both organic and inorganic phosphorus (Pi) esters are handled alike by the alkaline phosphatase present in the intestinal tract.

TABLE 7-27. Dietary Reference Intake for Phosphorus

Life stage group	Phosphorus (mg/day)	Life stage group	Phosphorus (mg/day)
Infants		**Females**	
0–6 months	100[a]	9–13 years	1,250
7–12 months	275[a]	14–18 years	1,250
Children		19–>70 years	700
1–3 years	460	**Pregnancy/lactation**	
4–8 years	500	≤18 years	1,250
Males		19–50 years	700
9–18 years	1,250		
19–>70 years	700		

[a] Estimate based on adequate intake (AI). Other values reflect recommended dietary allowance (RDA). Modified from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: National Academies Press, 1997.

Beverages, Including Milk and Soda. The important, relatively low-phosphorus food of animal origin is human milk. In newborns, who cannot respond to the stimulus of low calcium levels by increasing parathyroid hormone output, this is a perfect food. One liter of human milk contains 150 to 175 mg of phosphorus, or 25 mg per 100 kcal. In contrast, each liter of cow's milk provides 1,000 mg of phosphorus, or 150 mg per 100 kcal. This is an excessive load of phosphorus for a newborn and tends to reduce the serum calcium level by increasing the serum phosphorus level. Colas and diet colas contain ~30 to 60 mg of phosphorus per can, and it has been suggested that high phosphorus intake with low calcium intake can contribute to low bone mass and fractures, especially in children (50). However, soft drink intake is linked with lower BMD in girls only and just for non-cola and diet drinks, not the sodas with the highest phosphorus content (115). Thus, the outcome may be related to displacement of other beverages (e.g., milk), and not to phosphorus intake. A dietary calcium:phosphorus intake of ~1.5 to 2.0:1 on a molar basis is a common recommendation, but its clinical value is unproven (50).

Grains and Cereals. A major source of phosphorus in grains and cereals is inositol hexaphosphoric acid, or phytic acid. Calcium, zinc, and magnesium phytates are insoluble and are excreted in the stool. During leavening and baking of bread, some of the phosphorus from phytic acid is converted to orthophosphate by the action of phytases, so that some of the phosphorus is absorbed. However, in countries where unleavened wheat is used, the phytate content of grain products is increased. If the intake of calcium and vitamin D is also limited, calcium deficiency may develop partly as a consequence of excess dietary phytate.

Assessment

Phosphorus is well absorbed from the intestine, and the plasma level is carefully regulated by the tubular reabsorption of phosphate. In addition, the movement of phosphorus across cell membranes is rapid and responds to alterations in metabolic activity (e.g., glucose utilization). Thus, neither plasma phosphate nor urinary excretion of phosphate reflects intake or body stores. Abnormal plasma levels can reflect real changes in body stores, but more often they reflect altered renal or metabolic activity.

Plasma Phosphate. The usual serum assay measures the colored ammonium phosphomolybdate complex. Specimens collected with EDTA or citrate are not acceptable because these compounds interfere with the color reaction of the assay. Hemolysis must be avoided because red cells have a high phosphate content. The normal level is 0.81 to 1.29 mmol per L (25 to 45 mg per L) in adults, 1.2 to 2.23 mmol per L (37 to 69 mg per L) in children,

TABLE 7-28. Phosphorus Content of Food

Food	Portion	Phosphorus (mg)
Grains and cereals		
Bread, white	1 slice	30
Hamburger bun	1 each	44
Cornbread muffins	1 each	128
Rice, cooked	1 cup	74
Bran flakes, 40%	1/2 cup	63
Meat and fish		
Beef, lamb, veal	3 oz	125–300
Beef liver	3 oz	392
Chicken, white meat, roasted	3 oz	183
Fish	3 oz	230–330
Fruits		
Apple, medium	1 each	10
Banana, medium	1 each	22
Cantaloupe	1 cup	27
Orange	1 each	19
Vegetables		
Potato, baked	1 each	115
Tomato	1 each	30
Green peas, frozen	1/2 cup	69
Dairy products		
Milk, whole	1 cup	227
Cheese	1 oz	200–250
Egg, large	1 each	86
Nuts		
Peanuts, almonds, walnuts	1 cup	520–730
Peanut butter	2 tbs	103
Beverages		
Colas	1 can	44–62
Colas, diet	1 can	27–39

and 1.6 to 2.1 mmol per L (50 to 65 mg per L) in infants (34). An assay of fasting serum inorganic phosphate levels is important for meaningful interpretation. The interpretation of serum levels is difficult because many factors influence the phosphorus concentration. The rapid infusion of glucose or insulin can lower levels. In starvation, tissue catabolism releases phosphate, and plasma levels are maintained. When the starving patient is re-fed, it is essential to provide adequate phosphorus because serum levels can fall precipitously. Table 7-29 lists the major causes of altered plasma phosphate concentrations.

Urinary Phosphate. The average phosphorus excretion rate in the United States is 600 to 800 mg per day, reflecting a mean intake of 1,500 mg per day for men and 1,000 mg per day for women 340). With phosphate depletion, urinary excretion falls to nearly zero. Urinary phosphate varies with intake but cannot be used to estimate intake because it is regulated largely by parathyroid hormone. However, in the appropriate setting, a low urinary excretion rate can confirm a clinically suspected low dietary intake. Levels above 1,300 mg per day are considered high and reflect high intake.

Physiology

Absorption. Dietary phosphorus is absorbed as the inorganic form and as a component of phosphoproteins, phosphosugars, and phospholipids. In cow's milk, the phosphorus is 70% inorganic, but in cereals and soft tissues of animals, it is largely organic. All the

TABLE 7-29. Causes of Altered Plasma Phosphate Levels

Condition	Mechanism
Hypophosphatemia	
Increased urinary excretion	Urinary loss, decreased replacement on IV therapy, acute alcoholism, vitamin D deficiency, hypophosphatemic rickets, kidney transplantation, volume expansion, renal tubular defects, metabolic or respiratory alkalosis, hyperparathyroidism (decreased tubular reabsorption of phosphate)
Decreased intestinal absorption	Vitamin D deficiency, dietary phosphorus restriction (severe), antacid abuse (phosphate binding), chronic diarrhea
Phosphate compartmentalization	Rapid shift of phosphate between body compartments, TPN, recovery from diabetic ketoacidosis, respiratory alkalosis, sepsis, refeeding syndrome, hormonal therapy (insulin, glucagon, corticosteroids), carbohydrate infusion (glucose, fructose, lactate)
Hyperphosphatemia	
Increased exogenous load	Feeding cow's milk to premature infants, IV infusion, oral supplements, vitamin D toxicity, phosphate enemas
Increased endogenous load	Hemolysis, lactic acidosis, respiratory acidosis, rhabdomyolysis
Decreased urinary excretion	Renal failure, hypoparathyroidism, acromegaly, vitamin D toxicity, bisphosphonate therapy, magnesium deficiency
False (pseudo) hyperphosphatemia	Hemolysis *in vitro,* hypertriglyceridemia, multiple myeloma

IV, intravenous; TPN, total parenteral nutrition.

phosphorus must be liberated by phosphatases on the enterocyte brush border and in biliary secretions before absorption can take place. Net absorption is 65% to 75% from cow's milk but exceeds 80% from human milk. In adults and older children ingesting a mixed diet, absorption varies from 58% to 70% and is proportional to intake at all levels of ingestion. Alkaline phosphatase is quite resistant to damage in most diseases of the small bowel; thus, phosphate maldigestion is uncommon. Fecal output of phosphorus is not greater than intake—that is, no obligatory loss occurs in the gut. Digestive juices provide about 200 mg per day in adults. However, because two-thirds of luminal phosphorus is absorbed and the kidney can adjust phosphate excretion over a wide range, deficiency of phosphate from malabsorption rarely occurs.

Absorption is predominantly by passive diffusion. At low levels of phosphorus intake, active sodium-dependent transport (via the NPT2b transporter) is controlled by 1,25-dihydroxyvitamin D_3 (116). Because of the negative charge on phosphate and paracellular channels, simple diffusion between cells is unlikely. Efflux of phosphate across the basolateral membrane of the enterocyte is probably passive. Absorption is probably stimulated to some extent by vitamin D and perhaps by parathyroid hormone. Although malabsorption of phosphorus can occur in vitamin D deficiency, sufficient phosphorus is usually absorbed to satisfy daily needs because dietary intake is high and absorption is fairly high, even when somewhat impaired.

Urinary Excretion. Plasma phosphate is derived from input from the intestine and bone. Unlike that of calcium and magnesium, the daily flux of phosphorus to and from bone, the major store of body phosphorus (85%), is quite small. This flux approximates 200 mg per day (3 mg per kg). Plasma levels are regulated mainly via the kidney. There are at least five sodium-dependent phosphate co-transporters (Table 7-30). The type 2 transporter is the major regulator in the renal proximal tubule. The main factor influencing tubular reabsorption of phosphate is parathyroid hormone. However, plasma phosphate levels do not regulate the secretion of parathyroid hormone. It is the calcium level that secondarily regulates phosphate levels. Other hormones—for example, thyroid and growth hormone,

TABLE 7-30. Sodium-dependent Phosphate Co-transporters

Parameter	NPT1	NPT2a	NPT2b	NPT2c	NPT3
Pi affinity	5–10 nM	0.1–.2 mM	0.05 mM	0.1–0.2 mM	0.025 mM
Na^+ affinity	50–60 mM	50–70 mM	33 mM	50 mM	40–50 mM
Localization	Kidney, liver	Kidney, lung	Gut, lung	Kidney	Kidney, others
Regulators	Glucose, insulin, glucagon	[Pi]s, PTH, GH, 1,25-$(OH)_2$ vit D	[Pi]s	[Pi]s	[Pi]s

Adapted from Takeda E, Yamamoto H, Nashiki K, et al. Inorganic phosphate homeostasis and the role of dietary phosphorus. *J Cell Mol Med.* 2004;8:191.
GH, growth hormone; Pi, inorganic phosphate; PTH, parathormone.

estrogens, calcitonin, and vitamin D—all influence plasma phosphate, but much less so than parathyroid hormone does. Finally, phosphorus moves rapidly across cell membranes via NPT1 in response to requirements for intracellular phosphorus and available energy to form high-energy phosphate bonds. During phosphate depletion, the kidney becomes relatively resistant to the phosphaturic effects of parathyroid hormone (104).

Studies of inherited disorders have led to the discovery of two genes that regulate the sodium-dependent phosphate transporters, PHEX and FGF12. PHEX is mutated in X-linked hypophosphatemic rickets, and encodes an endopeptidase expressed in bone and teeth, but not in kidney (116). Mutations may alter the cleavage site of the endopeptidase, leading to accumulation of a "stable" circulating peptide that inhibits renal phosphate reabsorption.

Phosphate Homeostasis. Phosphate homeostasis is mainly regulated by the relationship between absorbed phosphorus, plasma inorganic phosphate, and urinary phosphate. Absorbed phosphorus and urinary phosphorus rise with increased intake. Thus, at any given phosphorus intake, the individual adjusts the plasma phosphate to the level at which phosphorus influx into plasma and excretion into the urine are equal. Twelve percent of serum phosphate is bound to protein. A high oral phosphate load stimulates parathyroid hormone output by reducing calcium and probably magnesium concentration in the ECF. Parathyroid hormone inhibits tubular reabsorption of phosphate and increases urinary excretion of phosphate. When the serum phosphorus level is reduced by decreased intake or absorption, the serum calcium level increases to inhibit parathyroid hormone output and urinary excretion of phosphate falls. The serum calcium level rises in hypophosphatemia because production of 1,25-dihydroxyvitamin D_3 is stimulated by a low phosphate concentration. Simultaneous vitamin D deficiency does not allow these events to take place; instead, a reduction in calcium absorption and the serum calcium level leads to an increased output of parathyroid hormone and increased urinary phosphate excretion.

Function. Phosphorus is important for all cells; 80% to 85% of phorphorus is in the bone. The rest is important for energy production (adenosine triphosphate), phospholipid formation, nucleotide formation, buffering systems, and calcium homeostasis.

Deficiency

Causes. Most patients who manifest clinical evidence of hypophosphatemia have an underlying wasting disease (117, 118). Acute phosphate depletion results from rapid transfer of the ion from extra- to intra-cellular fluid, or from extensive gastrointestinal loss. Chronic phosphate depletion occurs both with high serum calcium (hyperparathyroidism) or normal serum calcium (increased bone avidity in metastatic disease, diuretic use, renal tubular disease, and hyperphosphaturia from other causes). The common wasting diseases include intestinal malabsorption, malnutrition, cancer, and chronic alcoholism. Recovery from severe burns is also associated with hypophosphatemia. Other causes are listed in Table 7-29.

Hypophosphatemia at the onset of ketoacidosis probably indicates severe depletion. Multiple genes have been related to renal phosphate reabsorption, and include phosphate-regulating genes with homologies to endopeptidases on the X chromosome (PHEX), with fibroblast growth factor 23 (FGF-23), and the overproduction of FGF-23 and other proteins (matrix extracellular phosphoglycoprotein, MEPE, and frizzled-related protein 4, FRP-4) that increase in tumor-induced osteomalacia (119).

Clinical Manifestations. Clinical manifestations occur when plasma phosphorus levels fall <0.32 mmol per L (10 mg per L). Proximal myopathy and ileus may be the initial symptoms. Severe depletion can be manifested by hemolytic anemia (Pi <0.5 mg per dL), rhabdomyolysis (Pi <1.0 mg per dL), and a variety of complications in less severe depletion (Pi, 1.0 to 1.5 mg per dL). These include impaired chemotaxis, platelet dysfunction, metabolic encephalopathy, metabolic acidosis, peripheral neuropathy, central nervous system dysfunction including seizures, cardiac failure, osteomalacia, and decreased glucose utilization (120). A decrease in Pi leads to decreased levels of 2,3-diphosphogluconate (2,3-DPG), an altered affinity of oxygen for hemoglobin, and tissue anoxia. Renal loss of phosphate is often responsible for clinical phosphate deficiency. In an adult with a plasma phosphate level of 3.5 mg per dL and a GFR of 125 mL per min, filtered phosphate amounts to 6,300 mg per 24 hour. With an intake of 1,500 mg of phosphorus and 60% intestinal absorption (900 mg), reabsorption of 5,400 mg or 85% of the filtered load is required. In renal tubular disease, loss of phosphate can lead to depletion, evidenced by muscle weakness, malaise, and anorexia. Ingestion of large amounts of aluminum hydroxide or calcium salts can lead to phosphate depletion, even in patients with normal kidneys. Such ingestion causes depletion more rapidly when malabsorption is present.

Treatment

Mild to Moderate Hypophosphatemia. Mild to moderate hypophosphatemia (15 to 25 mg per L) can be managed without supplemental phosphorus by treating the underlying disorder. When levels fall to 0.32 to 0.48 mmol per L (10 to 15 mg per L) or risk factors for phosphorus depletion are present, replacement is advised with oral supplements—either milk or other oral preparations. Usually, a dosage of 1,000 mg per day corrects phosphorus depletion. Cow's milk contains about 1 mg of phosphorus per mL and is an excellent replacement fluid. Oral supplements as tablets of sodium or potassium phosphate can be given at a dosage of 2 to 3 g per day. Neutrophos (250 mg of phosphorus with 7 mEq of sodium and potassium per capsule) or Phospho-Soda (129 mg of phosphorus with 4.8 mEq of sodium per milliliter) is used most commonly. Uro-KP-Neutral and K-Phos Neutral tablets also contain 250 mg of phosphorus and only 1 mEq of potassium with 250 to 300 mg of sodium. The usual dose is two capsules of Neutrophos or 5 mL of Phospho-Soda given two or three times a day. Oral therapy is limited by the production of diarrhea. These supplements should be used with caution if sodium or potassium restriction is required because they contain significant amounts of these cations.

Antacids that contain magnesium, calcium, or aluminum can bind phosphate and prevent its absorption. When hypophosphatemia is caused in this way, it can be corrected simply by stopping the antacids. Sometimes, the binding properties of phosphate itself can be used for treatment. Calcium phosphate binds unconjugated bilirubin and has been used to supplement phototherapy in patients with Crigler-Najjar type I disease (121).

Hypophosphatemia occurs commonly in patients receiving specialized nutrition support, and replacement with phosphate is often recommended for treatment. A weight-related protocol is safe and efficacious, especially in critically ill patients (122). For patients with serum phosphorus of 0.73 to 0.06 mmol per L, treatment consists of 0.32 mmol per kg (low dose) intravenously; with phosphorus of 0.51 to 0.72 mmol per L, 0.64 mmol per kg (moderate dose) is used, and with phosphorus of ≤0.5 mmol per L, 1 mmol per kg is used (high dose). Patients with serum potassium <4 mmol per L receive potassium phosphate, and with higher potassium levels, sodium phosphate is used.

Severe Hypophosphatemia. Severe hypophosphatemia (<0.32 mmol per L, or <1 mg per dL) with symptoms should always be treated with IV phosphorus. One cause of such severe hypophosphatemia is the refeeding syndrome, but other causes include systemic

alkalosis, alcoholism, surgery, sepsis, diabetic ketoacidosis (especially after insulin therapy), cirrhosis, and chronic obstructive pulmonary disease (123). Intravenous therapy carries a risk for hypocalcemia and should be used with caution. Commercial solutions are mixtures of monobasic and dibasic sodium or potassium salts and provide 3 mmol of phosphate per milliliter. To avoid confusion, one should always order in terms of millimoles (mmol) of phosphorus. Initially, the dose should be 0.3 mmol of elemental phosphorus per kilogram of body weight given over 4 to 6 hours in normal saline solution. If the creatinine clearance is below 50 mL per min, this dose should be reduced by half. Other protocols suggest 0.08 mg per kg over 8 hours, or 15 mmol of sodium phosphate over 2 hours (123). After serum phosphate and calcium have been checked, subsequent therapy depends on the response. To avoid hypocalcemia or sodium or potassium overload, the dosage of 0.3 mmol per kg of body weight every 6 to 8 hours should not be exceeded. These values must be viewed only as rough guidelines because severe hypophosphatemia may develop with normal body stores of phosphorus. Because phosphate infusion can cause hypocalcemia, IV phosphate should not be used when hypocalcemia is present. Also, calcium and phosphate should not be used in the same IV infusion to avoid precipitation. When renal insufficiency is present, great caution must be exercised in administering Pi by any route.

Toxicity

Hyperphosphatemia develops in patients with renal insufficiency and a marked decrease in GFR. Secondary hyperparathyroidism can ensue with skeletal demineralization. The UL has been set at 4 g per day for adults up to age 70, and at 3 g for those older than 70 years (43) (Appendix B). Treatment entails a low intake of phosphate and ingestion of phosphate binders—aluminum hydroxide, calcium carbonate, or sevelamer hydrochloride (Renagel). Calcium carbonate is preferred initially because it is more palatable and is a more effective antacid in treating the duodenal inflammation commonly associated with chronic renal failure. It is not possible to eliminate dietary phosphorus completely because it is ubiquitous. However, a low phosphorus intake can be achieved and is important in the successful management of chronic renal disease (see Chapter 13).

Oral phosphate preparations (e.g., Fleet Phospho-soda, Visicol) are now widely used for bowel cleansing prior to colonoscopy (124). Hyperphosphatemia and hypocalcemia have been reported, leading to an FDA alert for increased risk in patients with congestive heart failure, colitis, ileus, and those with limited ability to take adequate liquid during the preparation (125). The FDA suggests checking baseline and post-treatment electrolytes, especially if >45 mL of oral sodium phosphate is used per 24 hours. The FDA has also issued an alert for acute phosphate nephropathy, a form of acute renal failure, associated with the use of oral sodium phosphate preparations used for bowel cleansing (www.accessdata.fda.gov/scripts/cder/drugsatfda/). Individuals at risk of this complication include those with advanced age, with kidney disease, with decreased intravascular volume, and those using medicines that might affect renal perfusion, such as diuretics, ACE inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs).

TRACE MINERALS

Iron

Requirement

Unlike those of other minerals, iron stores are not regulated by increased or decreased excretion. The major control mechanism is intestinal absorption, which increases during iron deficiency.

Daily Losses. In the normal person, iron requirements are determined by the limited and fixed amount of iron excreted. Daily losses are through the gastrointestinal tract, skin, and urine; additional iron is lost from the uterus in women. Fecal iron averages from 6 to 16 mg per day, most of which is unabsorbed dietary iron. Endogenous losses from cells amount to 0.1 to 0.2 mg, and blood loss accounts for 0.3 mg. Biliary secretion is 1 mg per day, but only about 0.20 mg is excreted in the stool. Urinary losses are 0.1 to 0.3 mg per day.

Dermal losses in sweat, hair, and nails range from 0.2 to 0.4 mg per day. Total daily losses range from 0.9 to 1.4 mg in males. Additional menstrual losses in women amount to 0.5 to 1.0 mg per day when averaged over a whole month.

Rate of Absorption. Iron requirements are estimated from the daily losses, and an assumption is based on the amount absorbed from food. The Food and Nutrition Board of the National Research Council and the WHO assume absorption of 10% to 15% provided the percentage of calories from animal sources containing heme iron is high, as it is in industrialized nations.

Recommended Dietary Allowance (RDA). Requirements per kilogram of body weight are highest in infancy (because of low iron stores), during periods of rapid growth, and during menstruation and pregnancy. Table 7-31 outlines the requirements and recommended allowances for iron at various stages. The Standing Committee on the Scientific Evaluation of Dietary Reference Intakes has now assigned an RDA for males of all age groups and for postmenopausal women of 8 mg per day, and for premenopausal women of 18 mg per day (126). During pregnancy, the recommended intake is 27 mg. At birth, the placental supply of iron is replaced by the diet. Even the infant of an iron-deficient mother has normal iron stores at birth. Iron treatment during pregnancy is most beneficial to the mother because the infant has priority for available iron. Milk is a poor source of iron, but the AI for infants 0 to 6 months of age is based on the daily amount in ingested milk (~ 0.35 mg per L). Because it is assumed that milk intake and requirements are correlated with body size, the AI may not be adequate for all infants, especially those with a lower intake. In the first 6 to 8 weeks of life, the hemoglobin level falls to 10 mg per dL because increased erythropoiesis is required for oxygen delivery to tissues. Extramedullary hematopoiesis also decreases in this period. During the second 6 to 8 weeks of life, erythropoiesis increases and the hemoglobin level rises to 12.5 mg per dL. In the third 6 to 8 weeks after birth, the dependency on dietary iron increases secondary to growth. The RDA for infants 7 to 12 months of age assumes that by 6 months, feedings complementary to milk are in place. It is at this time during infancy that extra iron is most needed, so that iron deficiency usually occurs at ages 6 to 24 months rather than earlier. Premature infants have decreased stores at birth and use their reserves faster during the growth spurt at 3 to 6 months of age. During adolescence, the hemoglobin level rises 0.5 to 1.0 mg per dL per year. For this reason, adolescents require 50 to 100 mg of iron per year, or a total of about 300 mg during adolescence.

TABLE 7-31. Dietary Reference Intakes of Iron for Individuals

Life stage group	Iron (mg/day)	Life stage group	Iron (mg/day)
Infants		**Females**	
0–6 months	0.27[a]	9–13 years	8
7–12 months	11	14–18 years	15
		19–50 years	18
Children		51–>70 years	8
1–3 years	7		
4–8 years	11	**Pregnancy**	
		14–50 years	27
Males			
9–13 years	8	**Lactation**	
14–18 years	11	14–18 years	10
19–>70 years	8	19–50 years	9

[a] Estimates based on adequate intake (AI). Other values are recommended dietary allowances (RDAs). Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC: National Academies Press, 2002.

Food Sources

Dietary iron is available in a variety of nuts and seeds and in red meat and egg yolks (Table 7-32). About 40% of the iron from these sources is heme iron, absorbed with about 15% to 45% efficiency. This accounts for 7% to 12% of dietary iron in the United States. Milk products, along with potatoes and fresh fruit, are poor in iron. Nonheme iron is absorbed with only about 1% to 15% efficiency. Vegetable iron content varies greatly according to the growing conditions of plants. Many sources of iron, especially inorganic salts and vegetable iron, are not well absorbed without ascorbic acid to reduce ferric to ferrous iron. However, continual ingestion of grams of vitamin C daily can interfere with copper absorption. The sources of nonheme iron often contain unidentified ascorbic acid (e.g., in meat, poultry, and fish) or inhibitors (e.g., tannic acid in tea; phytates in whole grains and legumes; polyphenols in tea, coffee, and red wine; calcium in dairy products or tofu; and zinc in multimineral preparations). Other inhibitors include soy protein, egg, EDTA, and phosphate salts (127). Calcium is often added to bread products and orange juice. EDTA (ethylendiamine-tetraacetic acid) is added to many foods to prevent oxidation and color changes. Organic acids (malic, ascorbic, citric) are found widely in foods and enhance absorption. Amino acids from protein, particularly cysteine and histidine, also enhance absorption. In addition, the use of antacids, histamine$_2$ receptor antagonists, or proton pump inhibitors decreases gastric acid secretion and impairs the absorption of inorganic iron.

Food Preparation. Food preparation is important. Boiling can decrease the iron content of vegetables by 20%, and milling can decrease the iron content of grains by 70% to 80%. The iron content of some foods (e.g., grain products) is enhanced by fortification. Iron-fortified infant formulas and cereals have been widely used, usually with iron sulfate or gluconate. They should contain 4 to 12 mg of iron per liter to prevent deficiency. However, some of the iron salts used for fortification (ferric orthophosphate and pyrophosphate) are absorbed less well than other forms of nonheme iron in the diet. Vegetarians are at risk for iron deficiency because of limited iron availability. Iron fortification is provided for staple cereals such as wheat, rice, and maize, especially in countries in which these grains form a major part of the diet (42). Many well-absorbed iron salts are reactive in foods, causing lipid peroxidation and color change, and thus cannot be used. The United States mandates iron fortification of wheat flour at the level of 44 mg per kg; in the United Kingdom the level is 16.5 mg per kg. Many iron supplements are available commercially in the United States. Approved forms considered safe (GRAS) include ferric salts (phosphate, pyrophosphate), ferrous salts (gluconate, lactate, sulfate), and reduced iron. Forms that are allowed, but are non-GRAS include sodium iron EDTA, iron amino acid chelates, and carbonyl iron (42). Supplement use comprises a considerable portion of iron intake in the United States, according to the NHANES III. It may be necessary to ingest a sufficient excess of supplemental iron (e.g., $>4 \times$ DRI of 8 mg for males) in order to increase body stores (128).

Intake. Average intake in the United States is 15 mg on a 2,500-kcal diet. The iron content of foods is fairly constant, about 6 mg per 1,000 kcal. Heme iron is relatively well absorbed, and the absorption of heme iron is not affected by the composition of the diet. However, heme iron accounts for only 1 to 3 mg per day in the diet. Nonheme iron is less available, and its absorption is influenced by dietary components (e.g., ascorbic acid). Besides the "classical" factors that affect iron absorption noted above, newer food additives (e.g., caseinophosphopeptides, fructo-oligosaccharides) also affect iron bioavailability (129). Baked goods account for 20% of iron intake in the United States, which is usually added in the form of ferric orthophosphate or sodium acid sulfate salts. The amount of iron in fortified cereals may exceed the amount listed in the label by 100%, although its bioavailability may be rather low (130). The USDA Food Consumption Survey (1989–1991) showed that average diets meet or exceed the RDAs for all life stage groups, except 1- to 2-year-old children (91% of RDA) and women ages 12 to 49 years (75% of RDA). It is not surprising that these two groups are most at risk for dietary iron deficiency.

Breast milk contains only 0.3 mg per L and cow's milk 0.5 mg per L. Thus, only about 0.25 to 0.85 mg of iron is supplied by milk. If this is the only food source for no more than 3 months, deficiency will not develop. About 50% of iron in breast milk is absorbed, compared with less than 10% of formula iron. Thus, breast milk can be an important source of iron even though the content is low. Iron is added to other infant foods. Electrolytic iron

TABLE 7-32. Iron Content of Selected Foods

Food	Portion	Iron content (mg)	% of RDI (18 mg for females)[a]
Breads and cereals			
White bread	1 slice	0.7	1–5
Hamburger bun	1 each	0.8	1–5
Saltines	4 each	0.5	1–5
Rice, cooked	1 cup	2.26	10–24
Oatmeal, cooked	1 cup	1.59	5–10
Bran flakes, 40%	1/2 cup	6.2	25–39
Spaghetti noodles, cooked (enriched)	1 cup	1.96	5–10
Bagel, enriched	1	1.2	2–5
Meat and fish			
Beef, lamb, veal	3 oz	2.4–2.6	10–24
Beef liver	3 oz	5.34	25–39
Chicken, white meat roasted	3 oz	0.91	1–5
Fish, cooked	3 oz	0.5–1.0	1–5
Pork, ham	3 oz	0.6–0.8	1–5
Shrimp, boiled	3 oz	2.6	10–24
Sliced meats	1 piece	0.32–0.46	1–5
Vegetables			
Spinach, cooked fresh	1 cup	6.42	25–39
Green beans, frozen	1 cup	1.11	5–12
Peas, frozen	1 cup	2.5	10–24
Potato, baked	1 each	2.75	10–24
Tomato	1 each	0.5	1–5
Dried legumes	1 cup	4–5	10–24
Other vegetables	1 cup	0.8–1.2	5–12
Fruits			
Strawberries	1 cup	0.57	1–5
Apples	1 each	0.25	1–5
Bananas	1 each	0.35	1–5
Orange, small	1 each	0.14	1–5
Apricots, dried	16 halves	2.6	10–24
Dairy products			
Milk, whole	1 cup	0.12	1–5
Cheese	1 oz	0.3	1–5
Eggs, large	1 each	0.72	1–5
Nuts			
Peanuts, pecans, almonds	1 cup	3.3–5.0	25–39
Peanut butter	1 cup	4.3	25–39
Soy products/meat substitutes			
Tofu, raw, regular	~4 oz	6.65	25–39
Veggie burger	~3.4 oz	3.89	10–24
Soy burger	~3.4 oz	1.44	5–10

RDI, recommended dietary intake.
[a] ~5% bioavailable from non-heme sources, but % is variable, so % of RDI is based on total iron content.

is added to dry cereal at 10 times the normal grain content (45 mg per 100 g). This form of iron has a small particle size with a large surface area, but it is not clear how much is absorbed. During the first year of life, it is wise also to provide a meat source of iron to ensure good absorption. Iron deficiency can occur if the iron in enriched foods is poorly absorbed (fortified cereals) and can be avoided if the iron in iron-poor foods is well absorbed (breast milk, vegetables with ascorbic acid). Table 7-32 lists the iron content of selected foods.

Estimated Iron Absorption. An average of 40% of total iron in animal tissues is heme iron; all the rest in the diet is nonheme iron. Thus, in any meal, one calculates the amount of iron from meat, poultry, or fish, multiplies that number by 0.4, and assumes 23% absorption for the heme iron. For the remainder of the iron, 8% absorption is assumed if adequate ascorbic acid (>75 mg per meal) is present. Otherwise, 5% absorption is assumed for an ascorbate intake of 25 to 75 mg, and 3% absorption if less ascorbic acid is ingested (126). On this basis, meals can be categorized according to whether the iron content is of low, medium, or high availability. A low-availability meal provides less than 30 g of meat, poultry, or fish and less than 25 mg of ascorbate. A medium-availability meal provides 30 to 90 g of meat or 25 to 75 mg of ascorbic acid with adequate nonheme iron. A high-availability meal provides more than 90 g of meat or more than 75 mg of ascorbic acid with adequate nonheme iron, or 30 to 90 g of meat plus 25 to 75 mg of ascorbate and nonheme iron.

Estimates of the available iron in average diets change with age. From infancy to adulthood, dietary iron increases from 3 to 18 mg for males and to 11 mg for females. The available dietary iron is 50 μg per kg of body weight in infancy, 72 μg per kg of body weight in childhood, and 45 μg per kg of body weight in adolescence, falling to 39 μg per kg of body weight for adult men and 27 μg per kg of body weight for adult women.

Assessment

Because iron absorption is so inefficient and excretion is not regulated, none of the routinely available tests reflect intake but rather assess body stores. They are all used to determine whether iron deficiency or overload syndromes are present. However, the tests for iron deficiency can be especially difficult to interpret. The separation of iron deficiency from anemia of chronic disease is a troubling aspect of nutritional management. A major problem in diagnosis is that iron deficiency often develops slowly, so that the detection of deficiency depends on the stage of iron depletion (131). Moreover, when chronic inflammation is present, iron cannot be mobilized from stores, and the clinical and laboratory presentation can look very similar to that seen when body stores of iron are deficient. Thus, no single test is sufficient. In addition, the tests vary in sensitivity. Table 7-33 outlines the various tests available, and highlights the distinction between iron deficiency and the anemia of chronic inflammation (132,133).

Hemoglobin. About 60% to 65% of total body iron is in hemoglobin, 4.5% in myoglobin, 10% in nonheme enzymes, and about 30% in storage (ferritin, hemosiderin). Only a small amount (~0.15%) is in transport (transferrin) or in cytochromes and other heme enzymes (0.2%). Because the size of the iron pool is related largely to hemoglobin, the size of the total pool varies with body size (and blood volume) and sex, and males have more hemoglobin than females. Table 7-34 lists the median values and lower limits for hemoglobin and mean corpuscular volume. Other causes of both a low hemoglobin level and a low mean corpuscular volume include anemia of chronic inflammation and heterozygous thalassemia trait. The red cell distribution width is usually high (>14.5%) in iron deficiency and tends to be normal in heterozygous thalassemia, but high values are also associated with other conditions, so that red cell distribution width is a poor diagnostic tool for iron deficiency. However, falling values are an early manifestation of a response to oral iron supplementation.

Serum Iron. Analysis is based on the formation of a colored complex of ferrous iron and dye (43). Hemolysis interferes with the assay, as does EDTA, citrate, or gross lipemia (>1,000 mg per dL). Serum iron is largely bound to transferrin, a β-globulin with a molecular weight of 80 kDa. Two iron molecules are bound per mole of protein. At any time, 4 to 6 mg of transferrin-bound iron is present in plasma, and transferrin in plasma has the capacity to bind 25 to 30 mg. However, 25 mg of iron passes each day from the

TABLE 7-33. Assessment of Functional Body Iron Status

Measurement	Diagnostic use	Reference range (adults)
Functional iron		
Hemoglobin	Assess severity of anemia	13–18 g/dL (M); 12–16 (F)
Red cell indices	Reduced when iron supply or incorporation into Hb is low	MCV 80–94 μm^3; MCH 27–32 g/L
RBC zinc protoporphyrin	↑ Protoporphyrin and ↓ RBC ferritin indicate low iron supply to marrow	<70 μg/dL RBC
RBC ferritin	"	
Serum transferrin receptor	↑ in early iron deficiency when erythropoiesis increases; especially useful when ferritin is normal. Can increase suspicion of anemia of chronic inflammation, when normal or somewhat low, but can be elevated when erythropoiesis is increased by factors other than iron stores	3–40 attograms/cell 4–8.5 mg/L
Tissue iron supply		
Serum iron	Transit compartment, change rapidly	10–30 μmol/L
Serum transferrin	↑ in iron deficiency	47–70 μmol/L
Transferrin saturation	↓ in deficiency if transferrin is high, ↑ in iron overload	16–60%
Iron stores		
Serum ferritin	↓ in deficiency, low normal value is indeterminate in anemia of chronic disease	15–300 μg/L
Response to EPO	If storage iron cannot be used, anemia will respond	NA
Tissue iron	↓ in deficiency, normal in anemia of chronic disease	3–33 μmol/g of dry weight of liver

EPO, erythropoietin; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; RBC, red blood cell.
Adapted from Wormwood M. The laboratory assessment of iron status—an update. *Clin Chim Acta.* 1997;259:3; and Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med.* 2005;352:1011.

reticuloendothelial cells to the plasma, where it is turned over at a rate of 50% hourly. Therefore, the measurement of serum iron is inherently unstable. The daily coefficient of variation can be 30% in the same person. A diurnal variation is seen, with morning values about 30% higher than those in the evening. The value decreases before the menstrual cycle and is increased by the use of oral contraceptives because of progesterone. By the seventh month of pregnancy, the serum iron level reaches a nadir because of dilution and the mobilization of storage iron to the fetus.

The normal serum iron level in newborns is 150 to 250 μg per dL. This falls in the first few days and then rises again to 130 μg per dL by 2 weeks. In the infant who is not given supplemental iron, the level falls to 80 μg per dL by 6 to 12 months and probably reflects iron deficiency. Normal adult levels range from 65 to 200 μg per dL, with values in men slightly higher than those in women. Mean values for males are 100 ± 35 μg per dL (mean ± SD); for females, they are 90 ± 40 μg per dL.

Low iron levels are associated with blood loss, chronic illness and infection, malignancy, and chronic skin disease. The serum iron level is high when outflow from the plasma is decreased, as in aplastic anemia, and when inflow into the plasma is increased, as in

TABLE 7-34. Normal Values for Hemoglobin and Mean Corpuscular Volume

	Hemoglobin (mg/dL)		MCV (μm^3)	
Age (years)	**Median**	**Lower limit**	**Median**	**Lower limit**
0.5–1.9	12.5	11	77	70
2–4	12.5	11	79	73
5–7	13	11.5	81	75
8–11	13.5	12	83	76
12–14 (females)	13.5	12	85	78
12–14 (males)	14	12.5	84	77
15–17 (females)	14	12	86	79
Adults (females)	14.5	12	87	80
Adults (males)	15.5	14	88	80

megaloblastic anemia with inefficient erythropoiesis. Lysis of cells (hemolytic anemia, acute hepatitis) raises the serum iron level. None of these causes is correlated with increases in body iron stores. In hemochromatosis, alcoholic liver disease, and porphyria cutanea tarda, the increase in body stores is reflected in an elevated serum iron level.

Transferrin. Transferrin is made in the liver and has a half-life of 8 days in plasma. The coefficient of variation is only 8%, less than that for iron. Normal levels for males are 350 ± 50 μg per dL; for females, they are 380 ± 70 μg per dL. Each 500 mL of whole blood contains about 250 μg of iron not incorporated into hemoglobin; most of this is bound to transferrin.

In pregnancy, levels of transferrin can rise to 400 μg per dL because of the action of progesterone. In infants, the transferrin level is lower, 250 μg per dL (range, 180 to 320 μg per dL). Thus, in infancy, the serum iron level is higher but the transferrin level is lower than in the adult. Transferrin levels are increased during iron deficiency, also during pregnancy even in the absence of iron deficiency. Transferrin levels are decreased by chronic disease, protein deficiency, and hepatic impairment. The usual interpretation of iron and of transferrin levels is based on combined values and the percentage saturation noted, in addition to the individual values.

Free Erythrocyte Protoporphyrin. When iron is deficient, protoporphyrins cannot be utilized for heme synthesis and gradually increase during 2 to 3 weeks. They are usually, but not always, elevated (134). Free erythrocyte protoporphyrin levels are often elevated early in iron deficiency, often before anemia develops (>1.24 μmol per L of red blood cells). However, levels rise in most disorders associated with inefficient heme synthesis (e.g., anemia of chronic disease, sideroblastic anemias), so that these increases are nonspecific.

Ferritin. Ferritin is the major storage form of iron in the liver, spleen, and bone marrow (135). It also protects cells from high concentrations of free iron, which can be toxic. Each molecule has 24 subunits, at least two of which are immunologically distinct. Each ferritin complex, with a molecular weight of 450 kDa, has a capacity to bind 2,000 iron molecules or release them in the presence of reducing agents. The source of serum ferritin is unknown but is probably the reticuloendothelial cells. Normally, only very small amounts of apoferritin leak into the serum. The distribution of normal ferritin is skewed to the higher values. Males have larger stores of iron, a finding reflected in their serum ferritin levels. Serum levels reflect reticuloendothelial stores, a compartment that is increased in infection or chronic disease.

Serum ferritin levels are proportional to marrow iron and inversely proportional to transferrin levels, suggesting that ferritin levels reflect iron stores. One microgram of ferritin is equivalent to about 8 mg of storage iron, or 120 μg per kg of body weight. Values rise after birth as the destruction of fetal hemoglobin increases stores. Ferritin

TABLE 7-35. Diagnostic Use of the Serum Ferritin Test

Serum ferritin (ng/mL)	Interpretation	Iron-deficiency anemia		Likelihood ratio (present/absent)
		Present (%)	Absent (%)	
<15	Very positive	59	1.1	52
15–34	Moderately positive	22	4.5	4.8
35–64	Nondiagnostic	10	10	1.0
65–94	Moderately negative	3.7	9.5	0.39
>95	Very negative	0.9	75	0.08

Adapted from Sackett DL, Richardson WS, Rosenberg W, et al. *Evidence-based Medicine.* New York: Churchill Livingstone, 1997:124.

levels fall later in childhood as adult hemoglobin is produced. Median concentrations of ferritin are about 40 and 170 ng per mL in young women and men, respectively. In anemic, iron-deficient patients, the mean level is <10 ng per mL (women) and 15 ng per mL (men).

Iron deficiency and decreased stores are associated with levels <15 ng per mL in adult men, and with levels below 10 ng per mL in women. However, these values are present only about half the time (Table 7-35). The value for diagnosis depends on the stage of iron deficiency, with values in later anemic states falling below 10 ng per mL. Iron overload in patients with hemochromatosis or undergoing transfusion is often associated with high ferritin levels. However, acute liver damage or endogenous ferritin production by tumors elevates ferritin levels without an increase in body iron stores. Cell damage in inflammatory diseases is also associated with falsely high ferritin values. When iron deficiency is combined with reticuloendothelial cell destruction in chronic inflammation, serum ferritin levels are normal and do not reflect true body stores.

Serum ferritin levels can be abnormal as soon as a lack of iron is detected in bone marrow, but a cutoff value of less than 15 ng per mL is not sufficiently sensitive (Table 7-35). The likelihood of iron deficiency in patients with values between 15 and 34 ng per mL is still nearly 5%, and iron deficiency can be present even with higher values. Patients with iron deficiency and ferritin values above 15 mmol per L may be at an early stage of deficiency, or they may have a chronic inflammatory condition that raises the level of serum ferritin, an acute-phase reactant protein. In such cases, values of serum ferritin about twice those in Table 7-35 may be of the same diagnostic significance. Because the "gray" area for serum ferritin is so large (between 15 and 100 mmol per L), it is logical to combine serum ferritin with other measures of the severity of disease. Several tests have been used, none with complete success. The most promising is the soluble plasma transferrin receptor, or the ratio of soluble transferrin receptor to the log of serum ferritin (133).

Serum ferritin can be elevated in hereditary hemochromatosis, when transferrin saturation is high, but it can also be elevated when transferrin saturation is normal or only slightly modified (136). The L-ferritin gene is mutated in the hereditary hyperferritinemia cataract syndrome without iron overload presenting with congenital cataracts. The ferroportin I gene is mutated commonly with iron overload predominantly in endothelial cells, and is an important form of dominant hereditary iron overload that may explain the condition known as "African hemochromatosis," and was supposed to be associated with consumption of beer prepared in lead containers. The ceruloplasmin gene is mutated rarely in Japanese families, presenting with late onset of neurologic symptoms with hyperferritinemia and aceruloplasminemia (136).

Soluble Plasma Transferrin Receptor (sTfR). The plasma protein is a truncated form of the membrane receptor (lacking its first 100 amino acids) that is present as a TfR–transferrin complex (137). The TfR number on the cell surface is a reflection of the iron status, increasing as deficiency develops. Marrow erythropoietic activity in erythroblasts, not

reticulocytes, is the most important determinant of sTfR concentrations, so levels are decreased when marrow activity is low (anemia of chronic inflammation) and high when erythropoiesis is stimulated (hemolysis, ineffective erythropoiesis). Normal values average 5.0 ± 1.0 mg per L, but because of the lack of an international standard there is considerable variation from lab to lab. The sTfR levels correlate best with Hb levels among all the other tests of iron status. Iron status influences sTfR, in that iron deficiency elevates serum levels fivefold to eightfold. Iron overload lowers sTfR, but only by ~20%. Thus, the test can be very useful in the patient with iron deficiency with inflammation in whom the serum ferritin levels are normal and sTfR levels are high. The lack of elevation of sTfR suggests anemia of chronic inflammation, but this diagnosis cannot be made with quite the same degree of confidence. This is because sTfR is a marker of erythropoiesis only when iron stores are adequate and available, and is a marker of iron status only when there is tissue iron deficiency. The log transformation of the ferritin value has been suggested as part of a ratio of TfR/log ferritin (TfR–F index) to normalize TfR values in patients with chronic inflammation (137,138). This increases specificity but not sensitivity for the diagnosis of iron deficiency. sTfR can be normal when iron is deficient, if cytokine production suppresses erythropoiesis. Conversely, levels can be high if erythropoiesis is stimulated by factors other than iron status. sTfR is also a marker of erythroid response to recombinant human erythropoietin (rHuEPO), so does not help identify the etiology of the anemia. Finally, sTfR can be elevated in erythroid and nonerythroid malignancies, and in myelofibrosis. It remains to be seen whether this (or any related) measure is robust in repeated studies.

Direct Methods for Assessing Iron Stores. Iron stores can be assessed directly by three means: phlebotomy, marrow staining, and liver biopsy.

Phlebotomy. If 500 mL is removed per week until the hemoglobin remains below 10 mg per dL for 2 weeks without further bleeding, it can be assumed that iron deficiency has been achieved. The red cell deficit can then be calculated from the hemoglobin content (each 1-g decrease of hemoglobin per deciliter corresponds to a total loss of about 100 mg of iron). Addition to the red cell deficit of 2 mg per day for absorbed iron gives an estimate of the mobilizable storage iron. Normal values in the United States range from 600 to 900 mg for males and from 200 to 300 mg for females. This method is used only when iron overload is present and treated by phlebotomy.

Marrow staining. Marrow staining is a qualitative method that distinguishes low iron stores in iron deficiency from other conditions in which stores are normal. In such conditions, low serum measurements of iron deficiency can be caused by chronic disease or a decreased release of iron from the tissues. Marrow staining is not a reliable method for assessing iron overload in hemochromatosis, in which marrow iron is normal.

Liver biopsy. The normal hepatic iron concentration is 70 to 100 μg per g of dry liver weight. In adults, values in hemochromatosis are consistently in excess of 5 g. With values below 70 μg of iron per gram of liver, iron staining is scanty and stores are low.

Response to therapy. The response to therapy is sometimes the best diagnostic approach when iron deficiency occurs in chronic inflammation and test results are indeterminate. Interpretation of the response can be complicated in patients with intestinal disease because oral iron may be poorly absorbed. In some cases, it is appropriate to use IV iron (see below) or erythropoietin (132,133).

The response to recombinant human erythropoietin has revealed a new phenotype of iron deficiency in such patients. Iron stores and serum ferritin levels are often normal or elevated, transferrin saturation is often (but not always) below 20%, and mean red cell indices are normal. Such patients may have adequate storage iron but cannot mobilize it rapidly enough to mount a sustained hemoglobin response. In these cases, IV iron may be needed to achieve a good response and reduce the amount of erythropoietin needed (138).

Summary of Assessment. Iron deficiency is usually sought when anemia is present, although evidence for deficient stores can be found before anemia develops. Iron depletion is progressive, so that the test values diagnostic of deficiency may change during progression from depletion of iron stores without anemia to deficiency with anemia. The best

screening test is the serum ferritin level because the only cause of a low value is a decrease in iron stores (139). Values <15 ng per mL confirm iron deficiency in the presence of anemia, but values between 15 and 100 ng per mL also can indicate deficiency in patients with chronic inflammation. Determinations of serum iron and binding capacity are often ordered at the same time, and if the results are consistent, these help to confirm inadequate iron stores. When iron-binding capacity was elevated, 78% of patients were iron-deficient, but only 26% were deficient when a low transferrin saturation was the parameter used (140). Low serum iron and low binding capacity are the best indicators of anemia associated with chronic inflammation. How to proceed when ferritin values are between 35 and 100 ng per mL is not certain, but the soluble transferrin receptor may be the next best test to perform (133). An elevated red cell distribution width may be helpful in monitoring response to therapy but does not discriminate very well in detecting iron deficiency (141). If confusion still exists, because of the many factors that affect the results of these assays, staining of a bone marrow aspirate can provide a direct measure of iron stores. Histologic staining for iron is only semiquantitative but is good enough to distinguish iron deficiency from disorders of iron metabolism in which tissue iron is normal. Sometimes the iron status is not clear, even after all tests are completed, and the response to therapy must be used.

Screening for Iron Deficiency and Overload. The tests available now for iron deficiency can also be used to screen for hereditary hemochromatosis (142,143). In addition, genotyping can be performed to detect the typical C282Y mutation of the hemochromatosis gene, *HFE*. Table 7-36 summarizes the strategies available for screening populations for

TABLE 7-36. Screening Strategies for Iron Deficiency and Hemochromatosis

Parameter	Phenotypic	Phenotypic/ genotypic	Genotypic/ phenotypic
Iron deficiency			
Initial tests	Hgb, Tfr saturation, ferritin		
Secondary tests	RBC protoporphyrin, sTfR, marrow stain, response to therapy		
Genetic hemochromatosis			
Initial test	Tfr saturation (>50 for men, >45 for women), ferritin (>300 μg/L for men, >200 for women)	Tfr saturation, ferritin	C282Y mutation
Secondary test	Repeat Tfr saturation and ferritin	C282Y mutation	Ferritin, Tfr saturation
Liver biopsy needed	Yes, hepatic iron ≥ 5,000 μg/g dry weight, 3–4+ iron staining	No	No
or phlebotomy needed	> 4 g of iron removed	No	No
Detects all genetic hemochromatosis	No	No	Yes
Detects non-iron overloaded hemochromatosis I	No	No	Yes

Tfr, transferrin; Hgb, hemoglobin; sTfR, soluble transferrin receptor; RBC, red blood cell.
Adapted from Adams PC. Population screening for hemochromatosis. *Hepatology.* 1999;29:1324; and Whitlock EP, Garlitz BA, Harris EL, et al. Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2006;145:209.

iron-related disorders. Transferrin saturation and serum ferritin levels remain the "standard" approach, but genotyping for C282Y homozygosity is often performed, particularly in family members of probands, as the test can identify iron overload even in the absence of clinical disease. Adult genetic hemochromatosis is mostly related to mutations of the HFE gene (C282Y and H63D), but is rarely associated with mutations of the TFR2 gene (136). Juvenile hemochromatosis is rare, and related to mutations in the HJV gene for hemojuvelin and the HAMP gene encoding for hepcidin.

Physiology

Iron exchange functions as a closed system, moving from plasma transferrin to red blood and tissue cells, from red blood cells to macrophages, and from macrophages back to plasma transferrin (aspects of iron metabolism can be viewed at www.irontherapy.org). Iron is involved in many reactions: as a redox cofactor for nonheme enzymes (iron–sulfur protein and metalloflavoproteins); as a required cofactor for nonoxidative enzymes (aconitase, ribonucleotide reductase); as a component of heme enzymes involved in electron transport (cytochromes); and as a major constituent of heme as an oxygen-carrying cofactor (hemoglobin, myoglobin). Iron is absorbed differently depending on whether it is ingested as heme (1.5 to 3 mg per day) or in vegetables and nuts (15 to 20 mg per day). The inorganic or nonheme iron is affected by gastric pH and by other salts in the lumen. Heme iron is not affected by luminal factors and is absorbed intact, bound to a putative "heme receptor" on the brush border or intercalated directly into the membrane. Inside the mucosal cell, hydrolysis by heme oxygenase, a microsomal enzyme, liberates free iron. Iron absorption by this route is very efficient (20% to 40%), depending on the state of total body iron stores. When anemia is present, absorption rates are higher. Iron either enters the body or is deposited as ferritin in the mucosal cell. The signal for iron absorption is probably not mucosal ferritin itself, which is increased when the rate of absorption is low. Mucosal ferritin may provide a mechanism of iron excretion into the lumen when the cell is exfoliated.

Absorption and Body Stores. When the size of the iron body pool is decreased, iron absorption increases (144). As much as 5 mg of iron (20% to 30% of intake) can be absorbed each day. When stores are normal (~4 to 5 g in adults), absorption varies from 1 mg in males to 2 to 3 mg in premenopausal females and matches daily iron losses. Iron overload occurs because excretory capacity is limited. In hemochromatosis, iron absorption is paradoxically elevated. Alcoholics may absorb excess iron from iron complexes in alcoholic beverages and by both paracellular and normal mechanisms.

Factors Affecting Absorption. Iron is absorbed most efficiently in the upper small intestine, especially the duodenum. Gastric acid, hydrogen ions from a reducing agent such as ascorbic acid, or a brush border ferrireductase, Dcytb, is needed to reduce nonheme ferric ions to the ferrous form, which is much better absorbed (145,146). Organic acids (citric, lactic) and amino acids (histidine, lysine, cysteine) form chelates with iron that enhance absorption. Disease or bypass of the proximal small bowel decreases absorption of both heme and nonheme iron. The presence of phytates in grains and of phosphates decreases nonheme iron absorption (147). Inorganic zinc can inhibit the uptake of iron. Humans are unique among mammals in the relatively small amount of dietary iron that is available for absorption and the limited loss of iron from the body.

The major transmembrane iron transporter is natural resistance-associated macrophage protein 2 (nramp2), now called *divalent metal ion transporter 1* (DMT1) (145) (see Table 7-37). DMT1 is related to nramp1, which is involved in host resistance to intracellular pathogen. DMT1 is expressed mostly in the apical brush border of the duodenal epithelium, especially the crypts. Expression is markedly increased in diet-induced iron deficiency, which suggests that it is regulated by iron status. An inverse relationship has been found between DMT1 and serum ferritin in normal persons, but not in patients with hereditary hemochromatosis (148). Absorption of heme iron is independently mediated by the apical protein HCP1 (149,150). There are two heme exporter proteins in the basolateral membrane, BCRP (breast cancer resistance protein) and FLVCR (feline leukemia virus, subgroup C receptor), providing a mechanism whereby heme may cross the enterocyte intact before being exported into the serum.

TABLE 7-37. Molecules Involved in Iron Absorption and Metabolism

Protein (symbol)	Location	Function	Mutation phenotype
Cytochrome b (DCYTVB)	Duodenum, apical	Iron reductase	None
Divalent metal transporter I (DMT1, NRAMP2)	Duodenum, apical	Ferrous iron transporter	Refractory microcytic Anemia
Heme carrier protein 1	Duodenum, apical	heme transporter	None
Ferroportin I (FPN, MTP1)	Duodenum, mΦ, basolateral	Iron transporter	mΦ iron loading, adult onset, mild anemia, type 4 HC
Feline leukemic virus, subgroup C (FLVCR)	Small intestine, basolateral	Heme iron exporter under stress	None
ABCG2/breast cancer resistance protein (BCRP)	Small intestine, basolateral	Heme iron exporter under stress	? Penetrance of erythropoietic protoporphyria
Hephaestin (HEPH)	Small intestine, basolateral	Iron oxidase	Refractory anemia (mice sla strain)
Hemochromatosis (HFE)	Liver mostly	Regulates hepcidin, binds Tfr1 receptor	Type 1 HC, iron overload
Transferrin receptor 2 (TfR2)	Liver mostly	Regulates hepcidin	Type 3 HC
Hemojuvelin (HJV)	Skeletal/cardiac muscle > liver	Regulates hepcidin	Type 2 (juvenile) HC
Hepcidin (HEPC)	Liver	Represses iron export from gut and mΦ	Type 2 (juvenile) HC

Adapted from Anderson GJ, Frazer DM. Recent advances in intestinal iron transport. *Curr Gastroenterol Rep.* 2005;7:365; and Latunda-Dada GO, Simpson RJ, McKie AT. Recent advances in mammalian haem transport. *Trends Biochem Sci*. 2006;31:182.
HC, hemochromatosis; mΦ, macrophage.

Iron Loss. Although the term *iron stores* usually refers to those tissues that contain ferritin and hemosiderin (e.g., liver, spleen), most of the iron in the body is in tissues that require it for function (red blood cells, marrow, muscle). It is also from these functional tissues that iron is lost. Iron can be lost through bleeding because red blood cells contain most of the iron of the body (2,750 mg in 70-kg males and 2,180 mg in females). Bone marrow and muscle contain 610 and 520 mg, respectively, in the two sexes.

Red Blood Cell Production. Only 20 mg (or 0.5% of a total store of 4 g) is needed for new red cell production each day. This iron comes from the marrow. Only about 5 mg of iron is mobilized per day from storage tissues (liver, spleen), and such mobilization does not provide a rapid buffering for when acute iron loss occurs due to bleeding (about 250 mg of hemoglobin iron per 500 mL of blood) (151).

Transcellular Iron Transport. The mechanism by which iron is released from transferrin involves receptor-mediated endocytosis (145) and release in acidic vesicles when iron–transferrin complexes are involved. Once inside the red cell, ferrous iron is incorporated into the protoporphyrin of hemoglobin by a ferrochelatase. When the red cell dies after about 120 days, the iron in hemoglobin is oxidized and methemoglobin is formed. The iron is re-used for hemoglobin synthesis or stored as the ferric ion. High intracellular iron levels down-regulate ferritin synthesis via an iron-responsive element-binding protein (90 kd) that depresses translation (152). The movement of iron across the basolateral membrane is mediated by ferroportin I along with the iron oxidase hephaestin (146,149). The activity of ferroportin I is regulated by the liver β-defensin-like peptide, hepcidin (153). It has antimicrobial activity and regulates intestinal iron absorption and macrophage iron release negatively. Thus, it reduces the amount of iron available to bacteria, and

it affects them directly. Its effect on reducing iron absorption and increasing macrophage stores is a secondary action that has a marked effect on iron homeostasis. The hemojuvelin (HJV), transferrin receptor 2 (TfR2), and the hemochromatosis gene (HFE) are involved in regulating hepcidin synthesis, but the precise pathways are unclear (153). Hepcidin synthesis is down-regulated by low iron concentration, by anemia, and by hypoxia. Hepcidin is correlated inversely with DMT1, Dcytb, and ferroportin I expression, and it causes internalization of ferroportin I, leading to decreased cellular iron efflux. When pro-inflammatory cytokines are elevated, hepcidin synthesis increases. Iron is kept within cells, helping to create the situation seen in anemia of chronic inflammation, when normal iron stores and decreased erythropoiesis are largely driven by inflammatory cytokines.

Oxidation and Transport of Absorbed Iron. The ferroxidase reaction converts ferrous to ferric ion. This conversion is catalyzed by ceruloplasmin in the serum or by its membrane-bound homologue, hephaestin (154). When the reaction occurs in serum, the ferric ion is incorporated into apotransferrin, although the mechanism for this capture is not clear. Another ferroxidase that is different from ceruloplasmin is also found in serum. This circulating form of iron is not toxic, as it is unable to generate free radicals. Iron is brought from storage forms as ferritin in the ferric (Fe^{+++}) form. The release of iron from ferritin occurs via a ferritin reductase system.

Transferrin delivers iron to the cells via two types of plasma membrane transferrin receptors (TfR) (154). Both receptors bind diferric transferrin and deliver the complex via endocytosis in clathrin coated pits into specialized endosomes. Inside the cell iron regulatory proteins (IRPs) bind to iron regulatory elements (IREs) located in the untranslated portions of the TfR mRNA. The hemochromatosis protein HFE is a membrane protein that binds to TfR1 and reduces the affinity of transferrin to its receptor. Transferrins can bind two ferric ions with a high affinity. Although iron is the major metal bound with high affinity at neutral pH, 36 other metals have been shown to bind to one or both of the metal binding sites of transferrin (154).

Deficiency

Iron deficiency is characterized mainly by symptoms of anemia—weakness and pallor. In addition, other signs and symptoms are caused by iron deficiency alone: angular stomatitis, atrophic lingual papillae, and koilonychia. Iron deficiency in children is associated with anorexia, decreased resistance to infection, decreased growth, and reversible protein-losing enteropathy. In the absence of anemia in children, iron deficiency can have deleterious effects on behavior and cognitive functions (155). The tests used to diagnose iron deficiency vary according to the stage of the deficiency. Table 7-38 outlines the predictive value of such tests.

Increased Utilization. Iron deficiency is common in children 6 to 24 months old because of increased need and limited body stores. These patients are at risk for developing impaired intellect, although the degree of impairment is not closely correlated with anemia (156). Thus, treatment with iron until body stores are fully repleted is often justified.

Blood Loss. In premenopausal women, anemia is caused by blood loss during menstruation. Iron deficiency in an adult or adolescent male or a postmenopausal woman frequently signifies blood loss from the body, usually from the gastrointestinal tract. Each unit of blood contains approximately 250 mg of elemental iron.

Inadequate Intake. Iron deficiency is often associated with ingestion of foods in which iron bioavailability is low. It is also associated with other vitamin and mineral deficiencies, most notably with folic acid deficiency in pregnancy and intestinal disease and with zinc deficiency in children that produces anemia, dwarfism, and hypogonadism (157). Iron is no longer included in home total parenteral nutrition (TPN) formulations, so iron deficiency anemia can develop in patients on long term home TPN (158). Small regular amounts of iron (10 to 75 mg on any given day) are recommended according to estimated daily loss.

Malabsorption. Another significant cause of iron deficiency is malabsorption, either in mucosal disease or after bypass of the proximal bowel, as in subtotal gastrectomy with gastrojejunostomy.

TABLE 7-38. Predictive Values of Laboratory Tests in Different Stages of Iron Deficiency

	Stage of iron deficiency[a]			
	I	II	III	IV
Test		(Predictive value, %)		
Bone marrow iron stain	100	100	100	100
Serum ferritin (μg/L)	100	100	100	100
Zinc protoporphyrin (μmol/mol of heme)	0	100	100	100
Transferrin saturation (%)	0	71	78	96
Hemoglobin (g/L)	0	0	100	100
MCV (μm^3)	0	0	22	100
MCH (pg)	0	0	33	100

[a] The prevalence rates of patients presenting in each stage of deficiency are about 24%, 23%, 15%, and 38%, respectively, for stages I through IV.
Adapted from Hastka J, Lassere J-J, Schwarzbeck A, et al. Laboratory tests of iron status: correlation or common sense? *Clin Chem.* 1996;42:5.

Restless Leg Syndrome (RLS). Iron deficiency can occur with or without anemia, especially in elderly patients with this syndrome, a sleep disorder associated with unpleasant leg sensations (159). Brain acquisition of iron appears to be impaired, perhaps by neuromelanin cells (160). Local brain deficiency may be more important than total body stores of iron, however, because cases of RLS have been reported with hemochromatosis (161). An abnormality in brain iron metabolism may explain why the association with iron deficiency is not tight, and also why treatment is not persistently effective. In a randomized, controlled, double-blind trial of RLS patients with end-stage renal disease, regardless of iron status, iron (1,000 mg of IV iron dextran) provided transient relief of symptoms that was gone after 4 weeks (162).

Treatment

Oral Iron. Oral iron is available in a wide variety of preparations as the only nutrient (Table 7-39) or in combination with other vitamins, in doses ranging from 27 to 200 mg of elemental iron per multivitamin/mineral dose. The dose of iron given is not crucial provided that it is adequate because the amount absorbed is not linearly related to the dose ingested. In fact, above doses of 10 mg of elemental iron, the increase in milligrams of iron absorbed is rather limited. However, even at high doses of ingested elemental iron (100 mg), 10% can be absorbed by the anemic patient. The ferrous salt is absorbed about three times better than the ferric salt, and all ferrous salts are absorbed equally well. The side effects of iron preparations (nausea, indigestion, diarrhea, abdominal cramping) limit the amount that can be given. The oral route is preferred in virtually all situations, despite the frequency with which side effects occur. Gastrointestinal side effects may be less common with slow-release forms of oral preparations, but the response varies greatly. Some preparations contain tartrazine, which may cause allergic reactions in susceptible patients. Iron absorption may be decreased by antacids, coffee, tea, eggs, or milk. Iron interferes with the absorption of penicillamine and tetracyclines. Oral iron can be used with only slightly increased intolerance (25%) over control subjects (17%) (163).

Oral iron preparations should be used for 1 to 3 months until the hemoglobin level is restored to normal and then given for 1 to 3 months longer to allow tissue stores to be replenished. Hemoglobin contains only about 60% of body iron. Thus, it is usually necessary to treat during this second period for nearly as much time as is required to restore hemoglobin levels to normal. Because iron is absorbed better when body stores are low, it is absorbed best during the first month of treatment. Absorption during the second period, when tissue stores are being repleted, is less efficient. The iron deficit can be determined

TABLE 7-39. Selected Iron-containing Prescription Products for Oral Use[a]

Product	Formulation	Dose	Other components
		Total mg (elemental mg)	
Ferrous sulfate[b]			
Various brands	Tablet	325 (65)	None listed
Various brands	Elixir (5 mL)	220 (44)	5% Alcohol, sweeteners
Various brands	Drops (0.6 mL)	75 (15)	0.2% Alcohol, stabilizers, sweeteners
Ferrous sulfate exsiccated			
Feratab	Tablet	187 (60)	
Feosol	Tablet	200 (65)[c]	Glucose
Slow FE	Tablet, slow release	160 (50)	Cetostearyl, lactose
Ferrous gluconate			
Various brands	Tablet	325 (36)	None listed
Fergon	Tablet	240 (27)	Sucrose
Ferrous fumarate			
Various brands	Tablet	325 (106)	Polydextrose
Mission brand	Tablet	200 (66)	Sugar
Slow-release iron	Tablet, slow release	150 (50)	Maltodextrin
Nephro-Fer	Tablet	350 (115)	None listed
Feostat	Tablet, chewable	100 (33)	Chocolate flavor
Feostat	Suspension (5 mL)	100 (33)	Preservative, butterscotch flavor
Carbonyl iron			
Feosol	Tablet	(50)	Lactose, sorbitol, PEG
Ircon	Tablet	(66)	None listed
Icar	Suspension (1.25 mL)	(15)	Sorbitol
Polysaccharide-iron complex			
Niferex	Tablet	(50)	Lactose
Various brands	Capsules	(150)	Sucrose
Niferex, Nu-Iron	Elixir (5 mL)	(100)	10% Alcohol, sorbitol
Iron with vitamin C			
Ferrex 150 plus	Capsule	(150)	Polysaccharide iron, 50 mg AA
Vitelle Irospan	Tablet, timed release	(65)	Ferrous sulfate exsiccated, 150 mg AA
Fero-Grad-500	Tablet, timed release	(105)	Ferrous sulfate, 500 mg sodium ascorbate
Hemaspan	Tablet, timed release	(110)	Ferrous fumarate, 200 mg AA, sugar

[a] The content in milligrams is given as the iron salt, with the elemental iron content in parentheses. The percentage of elemental iron provided in salts is ferrous sulfate, 20%; ferrous sulfate exsiccated, 30%; ferrous gluconate, ~12%; ferrous fumarate, 33%. All forms listed are available over the counter. Data from *Drug Facts and Comparisons*. 59th ed., St Louis, MO: Facts & Comparisons, 2005:36.
[b] Available as elixir, 44 mg of iron per teaspoon.
[c] Preparations available with or without vitamin C.

roughly by calculating the amount of iron necessary to replace red blood cell hemoglobin, with 1,000 mg added for an average-sized male adult to replete stores:

$$\text{Iron deficit (mg)} = \text{Body weight (lb)} \times [15 - \text{Hemoglobin (g/dL)} \div 1{,}000]$$

One can use 13 g per dL as the figure for females. If one assumes an overall absorption rate of 10%, the total elemental iron needed can be estimated by multiplying the iron

deficit by 10. The dose tolerated per day, once determined, allows the required duration of therapy to be estimated.

Oral iron causes nausea and epigastric distress, constipation or diarrhea, and darkened stools. It is taken on an empty stomach unless gastrointestinal side effects occur. In that case, it is usually given after meals 2 or 3 times a day. Side effects often dictate the dose that can be tolerated orally. Preparations coated with a wax matrix are available (e.g., Slow Fe, which contains 50 mg of Fe per 160-mg tablet) and may be better tolerated. Children should be given iron in a dose of 3 mg per kg per day. Complex vitamin and iron preparations should not be used for symptomatic iron deficiency because other additives can decrease iron availability (164).

It is important to recognize when laboratory tests are not specific for iron deficiency, and will not respond to oral iron. When iron is low after acute stress, such as surgery, but body stores are normal, iron supplements will not help (165). The anemia of chronic inflammation presents with low hemoglobin and iron, but ferritin is usually low, although it can be elevated from pro-inflammatory cytokines. These patients may need erythropoietin in addition to iron in order to respond (166). Iron therapy is often attempted in women who complain of fatigue but who are not anemic, and most of the time such therapy is unsuccessful. However, one study showed that using full doses of iron (80 mg per day) raised ferritin levels and improved fatigue in women who were not anemic, but had low or borderline ferritin levels (167). Thus, it is important to investigate possible iron deficiency in patients with unexplained fatigue.

Most products contain ample iron to treat iron deficiency, provided that absorption is reasonably normal (Table 7-39). During iron deficiency, net absorption is increased to about 15% to 20% of the ingested dose. Ascorbic acid is included in many preparations, but it is not certain that it enhances absorption to a clinically significant degree. In determining the dose of iron to be given, one should think of the total content of elemental iron, not iron salt. Because the amount of each salt in the tablets varies among manufacturers, one should calculate the elemental iron based on the percentage of iron in each individual salt (Table 7-40).

Parenteral Iron

Indications. When bleeding is recurrent and the rate of loss exceeds the capacity to absorb iron, when malabsorption is the cause of deficiency, or when oral iron cannot be tolerated, parenteral iron may be needed. Iron supplements are not included in standard parenteral nutrition therapy but can be safely given when iron deficiency is present (168). Parenteral iron is often given to dialysis patients with or without erythropoietin to prevent iron deficiency, treat iron deficiency, or enhance the response to erythropoietin when iron has been repleted (169). Suggested guidelines for initiating such therapy in dialysis patients include a serum ferritin level below 100 μg per L, a transferrin saturation below 20%, and the presence of more than 10% hypochromic red cells. A combination of IV iron and erythropoietin has also been used in chronic inflammatory conditions, such as Crohn disease or ulcerative colitis. Most patients with IBD respond to IV iron alone, but erythropoietin or the related darbepoetin-alfa (with a longer half-life) can enhance the response (170). There are three formulations available in the United States: iron dextran, sodium ferric gluconate, and iron sucrose (Table 7-41).

TABLE 7-40. Elemental Iron Content of Therapeutic Iron Preparations

Iron salt	Approximate percentage as elemental iron
Sulfate anhydrous	30
Sulfate, 7·H_2O hydrated	20
Fumarate	33
Gluconate	11.6

TABLE 7-41. Comparison of Intravenous Iron Preparations

Parameter	Iron dextran	Sodium ferric gluconate	Iron sucrose
Trade name	InFeD, Dexferrum	Ferrlecit	Venofer
Formulation	100 mg/2 mL vial	62.5 mg/5 mL vial	100 mg/5 mL vial
Molecular mass	165,000–267,000	350,000	34,000–60,000
Suggested dose	100 mg/day until repleted or total dose infusion	125 mg/dialysis session x 8, may be repeated if needed	100 mg 1–3 times/week x 10, may repeat
Test dose	2.5 mg dose required	Not required	Not required
Administration	Undiluted: not > 50 mg (1 mL)/min Diluted: total dose in 250–1000 mL NS, Infused over 4–6 hours	Undiluted: not > 12.5 mg (1 mL)/min Diluted: in 100 ml NS, infused over 1 hour	Undiluted: not > 20 mg (1 mL)/min Diluted: in 100 mL NS, infused over at least 15 minutes
Hypersensitivity	0.2%–3%	0.005%	0.4%
Anaphylaxis	0.6%–0.7%	0.002%	0.04%
PN compatible	100 mg/L for 18 hours at RT in non-lipid PN	Not studied or recommended	Not studied or recommended
Relative cost	1X	2X	2X

Adapted from Kumpf VJ. Update on parenteral iron therapy. *Nutr Clin Pract.* 2003;18:318; and Silverstein SB, Rodgers GM. Parenteral iron therapy options. *Am J Hematol.* 2004;76:74.
NS, normal saline; PN, parenteral nutrition provision; RT, room temperature.

Dose calculation. The total iron (in milligrams) needed to restore hemoglobin and replace stores is given by the following formula:

$$\text{Replacement iron} = 0.3 \times \text{weight (lbs)} \times (100 - [\text{actual Hgb} \times 100/\text{desired Hgb}])$$

where Hgb = hemoglobin in g/dL; a value of 14.8 is often used for men, and 13.0 for women. This formula is valid for calculating the replacement dose for any of the three forms of parenteral iron.

To calculate the dose in milliliters, divide the result by 50 for iron dextran, by 12.5 for ferric gluconate complex, and by 20 for iron sucrose. This formula is applicable only for patients with chronic iron-deficiency anemia, not for those who require iron replacement after blood loss. When the patient weighs <30 lb, use 80% of the required dose to adjust for a normal hemoglobin value of 12 g per dL in that age group.

Iron dextran (InFeD, DexFerrum). Parenteral iron can be given in the form of iron dextran, a complex of ferric hydroxide [$Fe(OH)_3$] and dextran in normal saline solution containing 50 mg iron per milliliter. The complex is dissociated by the reticuloendothelial system and the iron transferred to transferrin. A normal reticuloendothelial system is needed for iron dextran to be useful.

Intramuscular route. First inject a test dose of 0.5 mL IM. Although anaphylactic reactions usually occur within a few minutes, a waiting period of 1 hour is recommended before the treating dose is administered. Each day's dose should not exceed 0.5 mL (25 mg) for infants weighing less than 10 lb, 1 mL (50 mg) for children less than 20 lb, and 2 mL (100 mg) for all others. Injection should be only into the upper outer quadrant of the buttock, placed deeply with a 2- or 3-inch needle. If the patient is standing, inject into the buttock that is not bearing weight. If the patient is in bed, inject the uppermost buttock. To avoid leakage into subcutaneous tissues, a Z-track method, in which the skin is displaced laterally before injection, is recommended. IM injections can produce brown discoloration at the injection site, sterile abscesses, lymphadenopathy, and local soreness.

Intravenous route. The IV route of administration is preferred for parenteral iron because it is better tolerated than repeated IM injections. The test dose (0.5 mL) is given IV, and a delay of 1 hour should elapse before treatment to avoid missing delayed reactions. IV injections of 2 mL or less can be given slowly (<1 mL per minute), or the full dose can be diluted in 250 or 500 mL of normal saline solution and infused slowly over 2 to 3 hours. Iron dextran is not very compatible with parenteral nutrition (PN) formulations and is best administered separately. If maintenance doses are added, they should be used with nonlipid formulations and added just before infusion. Twenty-five to 50 mg per month (0.5 to 1.0 mL) is usually adequate for patients on chronic PN.

The manufacturer recommends that no more than 2 mL be administered at any one time, but this is not always practical when large deficiencies are present. When great care is used and resuscitation equipment is available, full replacement can be provided with iron dextran. Iron can be provided in low-dose (up to 100 mg per infusion), medium-dose (100 to 400 mg per infusion), or high-dose (500 to 1,000 mg or up to full replacement per infusion) regimens. The total calculated dose of iron replacement can be given safely IV to patients with chronic illness (171) and to patients undergoing dialysis (172). Total dose replacement is more convenient, less expensive, and just as efficacious as divided doses, and it is safe when precautions and observation are adequate.

Anaphylaxis is extremely rare when iron dextran is given in this way. When it occurs, the reaction is usually within the first few minutes after administration and is characterized by respiratory difficulty and cardiovascular collapse. Therefore, iron dextran injections should be administered only to patients with clear indications of iron deficiency who cannot take oral iron. The incidence of all acute hypersensitivity reactions other than anaphylaxis has been estimated to be 0.2% to 3.0% (173). Such reactions include dyspnea, urticaria, itching, arthralgias, myalgias, and fever. Severe (anaphylactic) reactions have been reported at 0.6% to 0.7% with the older IV iron preparation (174). Since the introduction of the other two preparations that produce fewer severe reactions, the use of iron dextran has decreased, making it difficult to assess accurately the incidence of anaphylaxis with the newer iron dextran formulations (175). Local phlebitis, vascular flush with too rapid infusion, and hypotension can occur after IV injection. Because of these risks, all patients should be closely supervised. IV iron should be given cautiously to persons with a history of asthma or significant allergy. Epinephrine (0.5 mL of a 1:1,000 solution) should be available for acute hypersensitivity reactions. All iron preparations can induce reactions to what is thought to be "free iron" if the circulating plasma transferrin saturation is exceeded. When more than 2 mL is given IV at one time, patients can experience fever, malaise, arthralgias, headache, nausea, shivering, and flushing, reminiscent of a serum-sickness-like illness. Despite concerns about iron overload in patients with chronic diseases who require repeated injections of iron, no evidence of this has been found provided iron is used in conjunction with erythropoietin (169).

Sodium ferric gluconate (Ferrlecit) and iron sucrose (Venofer). Neither of these preparations requires a test dose, nor do they carry a warning about hypersensitivity. However, hypersensitivity reactions have been reported with all three parenteral iron preparations, but have been most severe with iron dextran. The other two preparations have been used much less often, limiting any valid comparison of rates of hypersensitivity. There is no known cross sensitivity between preparations. A number of nonallergic adverse reactions have been reported with all IV iron preparations, especially hypotension when the rate of infusion is rapid (169). Myalgia, arthralgia, backache, fever, headache, nausea, vomiting, and dizziness can occur. Although there is a wide experience using large replacement doses of iron dextran, experience with the newer products is limited, and they are usually given daily in smaller doses until full replacement is reached. The recommended dosage for sodium ferric gluconate is 125 mg per day and for iron sucrose 100 mg 1 to 3 times per week. These preparations have been used most extensively for patients on chronic hemodialysis who are receiving erythropoietin.

Response to Iron Therapy. Reticulocytosis may be mild initially and usually peaks at 5 to 10 days after the start of therapy. The reticulocyte count or red cell distribution width need be checked only if there is concern about obtaining a response, and then only until it

is ascertained that an adequate response has occurred. The reticulocyte count should be corrected for the degree of anemia:

$$\text{Corrected reticulocyte count} = \text{measured reticulocyte count} \times \text{Hct}/40$$

The hemoglobin level usually rises gradually over 1 to 2 months. Failure to respond suggests inadequate intake or absorption of iron, an incorrect diagnosis, or the simultaneous development or detection of folate or vitamin B_{12} deficiency. When erythropoietin (epoetins or darbopoetin) are used to treat anemia of chronic inflammation, iron deficiency will develop unless there is available iron, either from transfusions or from iron infusions. Body iron stores of 800 to 1,200 mg should be provided over any given year (~20 to 25 mg per week), if there are no excessive losses. The best way to monitor for iron therapy is with serum ferritin and transferrin iron saturation (138). The National Kidney Foundation guidelines for erythropoietin and iron use in chronic renal failure conclude that more iron supplements will not help if transferrin saturation is >20% and serum ferritin is >100 μg per dL (173). For renal patients a target hemoglobin level of 11 to 12 g per dL is suggested.

Toxicity

Iron overload syndromes are seen when iron absorption exceeds excretion. This can occur when large doses are ingested or when massive transfusions are administered in diseases of red cell destruction in which iron is not lost in excess from the body. Acute ingestion of less than 20 mg of iron is generally nontoxic to adults. Ingestion of 20 to 50 mg per kg produces gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. The UL is set at 45 mg/d (126). Doses above 60 mg per kg are potentially lethal. Shock, intestinal perforation, oliguria, coagulopathy, acidosis, and lethargy may occur. A serum iron level below 350 μg per dL is not associated with toxicity. Levels above 700 μg per dL are often (50%) associated with toxicity. Chronic overload also develops when iron absorption is excessive but intake is not. This situation arises in genetic hemochromatosis, cirrhosis of the liver, and porphyria cutanea tarda. Tissue damage to the liver, pancreas, heart, joints, and endocrine glands may occur.

Diagnosis. Diagnosis of iron overload is best suggested by a high ferritin level and an elevated transferrin saturation and confirmed by liver biopsy.

Phlebotomy. Phlebotomy (500 mL per month) can remove 250 mg of iron at a time and reverse some of the tissue damage, especially to the heart and liver. This is the treatment of choice for hemochromatosis. Secondary iron overload after multiple transfusions (as in thalassemia) can be prevented by the use of desferoxamine, best administered subcutaneously by a pump capable of providing a continuous mini-infusion. The range of doses is 20 to 40 mg per kg per day. Adverse effects include local pain and itching, allergic reactions, blurred vision, diarrhea, and tachycardia. For acute symptomatic iron intoxication (serum Fe >350 μg per dL), desferoxamine should be administered IV at a dose of 10 to 15 mg per kg of body weight.

Zinc

Requirement

The body contains between 1.5 and 2.5 g of zinc, so that it is the second most abundant "trace" mineral in the body, after iron. Turnover of body zinc measured by radioisotope studies is about 6 mg per day in adults. Balance studies show that 12.5 mg of dietary zinc is needed per day to maintain a positive balance. Daily loss is estimated at 2.5 mg, mostly in feces. Absorption averages 30% to 40% but has been estimated at 20% for diets containing the highest amounts of fiber. The Standing Committee on the Scientific Evaluation of Dietary Reference Intakes has set the RDAs at 9 and 13 mg per day for adult women and men, respectively. The RDAs for various age groups are outlined in Table 7-42. Because of the relatively poor absorption of zinc, subjects ingesting a vegetarian diet, especially with high phytate content, may require as much as 50% more than those ingesting animal foods as their major source of zinc (126).

The additional amount of zinc needed for fetal development is estimated to be 0.53 to 0.73 mg per day for the last half of gestation. Because zinc is important for the fetus, a

TABLE 7-42. Dietary Reference Intakes of Zinc

Life stage group	Zinc (mg/day)	Life stage group	Zinc (mg/day)
Infants		**Females**	
0–6 months	2[a]	14–18 years	9
7–12 months	3	19–>70 years	8
Children		**Pregnancy**	
1–3 years	3	14–18 years	13
4–8 years	5	19–50 years	11
9–13 years	8	**Lactation**	
Males		14–18 years	14
14–>70 years	11	19–50 years	12

[a] Estimate based on adequate intake (AI). All others based on recommended dietary allowances (RDAs). Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC: National Academies Press, 2002.

liberal allowance of 3 mg of additional zinc is recommended during pregnancy, with the assumption that many diets do not contain much zinc. The rate of absorption of zinc increases during pregnancy, when the level of ingestion (9 mg per day) was marginal (176). Thus, there may be compensation in absorption during periods of marginal zinc intake. Zinc loss in milk is about 1.2 mg per day and 0.6 mg per day for the first and second 6 months of lactation, respectively (highest in the first month at 2.1 mg per day); the additional recommendation of 4 mg per day during lactation assumes a 20% availability and absorption. Zinc requirements may vary with dietary availability. Assuming that a Western-type diet is ingested with 35% to 40% availability, infants should need 5 mg per day, whereas children ages 1 to 10 years need 10 mg. These amounts may not be enough if a large amount of unrefined cereals containing phytates is ingested or if zinc is lost in sweat or in the intestinal tract.

Food Sources

The average zinc content of diets ingested by adults in the United States has been reported to range from 10 to 15 mg per day or from 6 to 12 mg per day. Whichever figures are correct, the amount of zinc ingested is probably adequate to provide the RDA because clinical zinc deficiency is not common in the United States when the losses of zinc are not excessive.

Zinc content of food varies with the content of the soil in which the food is grown and with the content of the fertilizer used. In general, the available zinc is proportional to protein intake because muscle meats and seafood have the highest content and vegetable sources contain zinc-binding anions. More than half of the zinc in U.S. diets comes from animal foods, and half of that from beef (127). Lacto- and ovo-vegetarian diets with phytate-zinc ratios of 5:15 show only ~33% absorption of zinc, compared with ~50% from meat diets. Despite the low bioavailability of zinc from vegetarian diets, it is still usually adequate to use legumes and whole grains to supply zinc, because their high zinc content more than compensates for less efficient absorption.

In addition, zinc is lost during the process of milling cereals. Breast milk is low in zinc. The risk for zinc deficiency is greater in patients ingesting a lacto-ovo vegetarian diet, but this can be countered by increasing the ingestion of whole grains and legumes (177). An increased rate of growth has been documented in children given modest zinc supplementation in double-blinded, controlled conditions, which suggests a pre-existing growth-limiting state of zinc deficiency (178). These findings led to zinc fortification of cow's milk formulas in the mid-1970s. Table 7-43 lists the zinc content of selected foods.

TABLE 7-43. Zinc Content of Selected Foods

Food	Portion	Zinc content (mg)	Percentage of RDI (11 mg)
Grains			
Bread, white	1 piece	0.173	1–5
Bread, rye	1 piece	0.38	1–5
Spaghetti noodles, cooked	1 cup	0.742	1–5
Product 19 (Kellogg)	1 cup	15	100
Bran flakes	1 cup	5.15	30–40
Meat and fish			
Beef, lamb	3 oz	4–6	25–39
Chicken, breast, roasted	1 each	1.05	5–12
Chicken, thigh	1 each	1.75	10–24
Turkey, dark meat	3 oz	3.80	25–39
Turkey, light meat	3 oz	1.73	10–24
Liver, beef	3 oz	4.2	25–39
Clams	1 each	0.5	1–5
Fish	3 oz	0.41–0.53	1–5
Oysters, eastern	1 cup	226	100
Oysters, Pacific	1 cup	41	100
Vegetables/fruits/nuts			
Vegetables, cooked	1 cup	0.45–0.6	1–5
Peas, green, cooked from fresh	1 cup	1.9	10–24
Lentils, cooked	1 cup	2.52	15–25
Kidney beans, red, cooked	1 cup	1.89	10–24
Fruits, fresh	1 each	0.05–0.09	1
Nuts	1 cup	4.1–4.8	25–39
Peanut butter	2 tbsp	1.06	5–15
Dairy/soy/egg products			
Milk, whole	1 cup	0.93	5–12
Yogurt, low-fat, plain	1 cup	2.02	10–24
Cheese	1 oz	0.7–0.93	5–12
Eggs	1 each	0.55	1–5
Soy milk	1 cup	2.90	20–30
Tofu, raw, firm	0.5 cup	1.98	10–24
Egg substitute	0.5 cup	1.6	10–20
Beverages			
Cola	1.5 cup	0.28	1–5
Orange juice	1 cup	0.128	1–5

RDI, recommended dietary intake.

Zinc Content of Diets. The NHANES III estimated total nutrient intake, including that in beverages and dietary supplements. Mean intakes of zinc were 5.5 mg in infants and up to about 13 mg in adults, with higher values in male adolescents and adults and values 2.5 to 3.5 mg higher in adults than the mean dietary intake (179). This difference represented supplements taken by 20% of the adult population. Slightly more than half of the population was ingesting more than 77% of the RDA. Those most at risk for inadequate zinc intakes were children from 1 to 3 years old, female adolescents from 12 to 19 years old, and elderly persons more than 71 years old. A general hospital diet provides 13 to 14 mg of zinc daily. However, a low-protein diet (40 g) contains only 6 to 7 mg. Full liquid diets are marginal in zinc content (8 to 9 mg), and clear liquid diets

are quite inadequate (0.3 to 0.4 mg). Vegetarian diets may be limited in bioavailable zinc (180).

Assessment

None of the available methods reliably and accurately reflects intake and absorption or body stores. Daily losses can be estimated from fecal zinc, but this determination is not routinely available. The plasma zinc determination is the best screening test, but many factors can alter the level, unassociated with a change in body stores. Thus, it is a poor measure of marginal zinc deficiency (181). If zinc deficiency is suspected clinically, it is best diagnosed by a symptomatic response to zinc replacement.

Plasma. Plasma zinc is relatively insensitive to body status, and several weeks of severe dietary restriction are often needed to see any change in concentration (127). Changes in plasma zinc do not occur until tissue zinc has been reduced. Thus, plasma zinc is a measure of the exchangeable zinc pool, from which an initial loss of zinc produces deficiency (181). Because plasma zinc can decline after a meal, fasting samples should be used. Most of plasma zinc is bound either tightly to α_2-macroglobulins (30% to 40%) or loosely to albumin. In red cells, 60% of the zinc is in hemoglobin and 20% in the enzyme carbonic anhydrase. About 80% of zinc in blood is in red cells—whole blood contains 8.8 μg per mL and plasma contains 0.7 to 1.4 μg per mL (34). Therefore, minor degrees of hemolysis alter plasma zinc levels. Hypoproteinemia and hyperproteinemia, whether caused by chronic illness or inflammation, stress, or altered protein nutrition, affect plasma zinc levels. Drugs (e.g., glucocorticoids, epinephrine) may alter zinc binding to plasma proteins. Although normal plasma levels (115 ± 12 μg per dL) do not rule out deficiency, low levels (<70 μg per dL) indicate deficiency when unaccompanied by hypoproteinemia, acute stress, or the ingestion of drugs that affect zinc levels. Levels <50 μg per mL are associated with an increased risk for the development of symptoms, and patients with levels <30 μg per mL nearly always manifest some aspect of the zinc deficiency syndrome. Marginal zinc deficiency is always difficult to assess with certainty. Table 7-44 outlines a suggested guide to interpretation of plasma zinc levels.

Neutrophil zinc is theoretically a better assessment of body stores, but because it has not been used frequently, it is not known how much better than plasma zinc it is (34). Normal values are 108 ± 11 μg per 1,000 neutrophils. Alkaline phosphatase is a zinc-requiring enzyme, and its activity correlates with plasma zinc levels before and after zinc treatment (182). Low levels can corroborate zinc deficiency.

Urine. Zinc excretion in urine is relatively low and fixed (i.e., it does not respond to changes in zinc stores). Moreover, it can be affected by altered protein binding in plasma. The major change in obligatory zinc loss in response to varying dietary loads occurs by altering endogenous fecal, not urinary, losses (183). Endogenous fecal excretion is about 1 to 2 mg per day when zinc intake is 5 mg per day. Urine is easily contaminated in some instances with stool; the concentration in stool is higher than that in urine, which ranges from 0.3 to 0.6 mg per day. Thus, urinary zinc levels are not helpful in determining zinc status.

TABLE 7-44. A Suggested Guide to Interpretation of Plasma Zinc Concentrations

	[Zn]p	
Interpretation	**(μg/dL)**	**(μmol/L)**
Undesirable	<75	<11.5
Low/borderline	75–85	11.5–13
Acceptable	85–125	13–19
Elevated	>150	>23

Adapted from Malone AM. Supplemental zinc in wound healing: is it beneficial? *Nutr Clin Pract.* 2000;15:253.

Hair and Nails. Hair and nails contain 90 to 280 parts per million and may reflect zinc intake. Levels of <70 parts per million have been associated with poor growth and appetite in children. However, much individual variation is seen because the levels are affected by rate of hair growth and external contamination. Bleaching and cold waving decrease zinc content. Before it is collected, the hair must be washed with water, a nonionic detergent, and EDTA to remove all the easily extractable zinc. It is not clear whether some of the zinc loosely bound to hair is endogenous and should be considered in the total content of the hair. Because collections must be taken with such care, determinations of zinc levels in hair remain a research procedure despite their potential to reflect intake.

Physiology

Most of the 1.4 to 2.3 g of zinc in the body is bound to zinc-containing enzymes. These include carbonic anhydrase, carboxypeptidases A and B, alcohol dehydrogenase, glutamate dehydrogenase, malate dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase, alkaline phosphatase, RNA and DNA polymerase, and reverse transcriptase. Zinc is required for both catalytic and structural functions. Zinc may activate or inhibit enzymes, modify membrane function, and bind to transcription factors (zinc fingers). In addition, studies of experimental zinc deficiency in animals reveal that zinc regulates other proteins not known to require zinc for activity, including intestinal fatty acid binding protein, cholecystokinin, J chain of immunoglobulins, and ubiquinone oxidoreductases (184). Cells require zinc to be distributed into all the cellular compartments that contain these many proteins, thus necessitating a complex series of transport mechanisms (185).

Absorption. About 20% to 30% of ingested zinc is absorbed, particularly in the proximal bowel. Both carrier-mediated and nonsaturable diffusion components have been reported, but the former is more active when zinc intake is low. The mammalian ZIP family of zinc transporters has been well described, but the mechanism of transport is not clear (186). ZIP4 is induced by low dietary zinc in mice, and becomes more localized to the apical membrane. With normal zinc intake, mucosal metallothionein increases, and ZIP5 is located in the basolateral membrane (186), but these effects appear to be secondary, perhaps to buffer intracellular zinc. Low zinc intake causes a fall in pancreatic cells in expression of zinc transporter genes, Znt1 and Znt2, along with reduction in metallothionein and internalization of ZIP5. These changes are thought to represent an attempt to restore zinc homeostasis by increasing absorption and decreasing pancreatic secretion.

Copper binds to metallothionein more avidly than zinc does. Thus, when zinc is used to treat Wilson disease, the presumed mechanism involves induction of metallothionein with decreased transfer of copper to the body (187). Acrodermatitis enteropathica is a rare disorder of zinc deficiency due to impaired zinc absorption. Homozygosity mapping of genes from affected families led to identification of a gene, SLC39A4, designated hZIP4, a member of a larger family of zinc transport proteins. hZIP4 is located in apical membranes, and appears to be the transporter responsible for intestinal absorption of zinc (188). Moreover, zinc deficiency in cultured cells upregulates hZIP4, supporting a role for this protein in controlling dietary zinc absorption (189). However, acrodermatitis is a disease that affects infants but not adults, suggesting that other mechanisms (possibly ZIP1) take over during human development. Another member of the ZIP family, ZIP5, is located basolaterally on the enterocyte, and may supply zinc to the enterocyte from body stores and/or regulate the degree of zinc absorption (185).

Similar to calcium and magnesium, the absorption of zinc is decreased by phosphate and nonphosphate binders in the lumen (190). Phytates are particularly rich in whole grains and soy products. Calcium availability affects the zinc–phytate relationship because calcium forms a complex in foods such as cereals, corn, and rice. Inositol hexaphosphates and pentaphosphates are the compounds that inhibit zinc absorption the most. Release of zinc from the complex can be affected by trace metals (especially copper) and by amino acids. Moreover, the biopotency of phytate is affected by food processing. Thus, the availability of zinc from cereals cannot be predicted (191). Zinc absorption is decreased by a high intake of calcium, phosphate, or both. Zinc oxide, carbonate, and sulfate salts are equally well absorbed by animals, but comparable data are not available in humans. When

inorganic zinc is ingested (as sulfate), its absorption is decreased by inorganic iron in the lumen, especially if taken as a separate supplement (192). If either zinc or iron is present as the organic form (food zinc or heme iron), such competition does not occur. Thus, the absorption of zinc from liquid formulas or mineral supplements may depend on the luminal content of iron (or even calcium and phosphate). Cadmium, increasingly found in foods, also inhibits absorption.

Zinc absorption is promoted by animal proteins and by low-molecular-weight organic compounds, such as sulfur-containing amino acids and hydroxy acids (193). Physiologic states that increase the demand for absorbed zinc, such as infancy, pregnancy, and lactation, may affect zinc absorption. Once absorbed, zinc enters a vascular compartment that rapidly turns over and that equilibrates slowly with two extravascular pools, located primarily in the liver, red blood cells, and kidney (176).

Binding and Cellular Uptake. In plasma, zinc is tightly bound to α_2-macroglobin and transferrin. About 60% to 75% of plasma zinc is loosely bound to albumin. Although this binding was thought to be nonspecific, a potential site requiring five coordinates has been identified, and this site is altered by high fatty acid binding (194). In the liver, zinc is bound in part to the metal-binding protein metallothionein. It is not clear if this represents a storage form of zinc separate from the functional enzymes, which contain most of the zinc in the body.

Within cells there are two families of eukaryotic zinc transporters (185,195). The ZIP family (Zrt- or Irt-like proteins) has been given the systematic name SLC39. These proteins transport zinc and other metals from the extracellular space (or from the lumen of an organelle) into the cytoplasm. This family is well preserved by all phyla. The mechanism of transport is not clear, but may involve a bicarbonate gradient. There are 14 known members of the ZIP family in the human genome. ZIP1 is directed to the plasma membrane of many tissues from a subcellular location, and is the major uptake system in some cells, e.g., prostate. ZIP2 is present only in prostatic and uterine tissue. ZIP3 appears to mediate zinc uptake by mammary epithelial cells and may regulate zinc secretion into milk (195). ZIP4, as noted above, appears to mediate intestinal absorption of zinc in infants, but other mechanisms presumably develop by the time the intestine is fully mature. ZIP14 is involved in uptake of zinc into the liver in response to inflammation.

The second family of zinc transporters is called CDF (cation diffusion facilitator), also known as ZnT, or by the systematic name SLC30. This family supports movement of zinc in the opposite direction to that of the ZIP family proteins, i.e., it transports zinc and other metal ions from the cytoplasm in the lumen of organelles or across the plasma membrane to the outside of the cell. This family contains many members, but the role of four of them (ZnT 1 to 4) has been fairly well characterized. ZnT-1 is the major efflux transporter in the plasma membrane of eukaryotic cells. It may account for reabsorption of zinc in the renal tubule, and in intestinal absorption, as it is located in the duodenum and jejunum, although on the basolateral membrane (195). ZnT-2 is located on endosomal/lysosomal membranes and leads to accumulation of zinc in these structures. ZnT-3 is found only in the brain (in membranes of synaptic vesicles) and testis. Thus, it may facilitate neuronal transmission. ZnT-4 in mammary gland epithelium is responsible for zinc transport into milk, and in basolateral endosomes in the enterocyte may help to regulate transport of zinc across the cell (195).

Excretion. The major route of excretion is in the feces (2 to 3 mg per day). About 7.5 to 14 mg of zinc from body stores (1.5 to 2.0 g per 70-kg person) is secreted daily into the upper intestine. This amount is equal to ingested sources. During passage through the small intestine, an amount equivalent to endogenous loss is usually reabsorbed, but the margin of safety is small. The amount of zinc secreted with each meal is variable, and efficient absorption is required to maintain a normal zinc balance (190). The major normal source of endogenous fecal zinc may be pancreatic juice. Diarrheal fluid may contain more than 11 mg of zinc per liter. Thus, the severity of diarrhea is a good indication of the risk for zinc depletion in patients with gastrointestinal diseases. Urinary excretion is not altered by changes in oral intake, whereas fecal zinc increases in proportion to intake. Another route of excretion is sweat, which has an average concentration of 1.15 mg per L. Thus, during profuse sweating, up to 4 mg can be lost daily. During

menses, about 0.4 to 0.5 mg of zinc is lost with the blood. Seminal emissions contain an average of 0.6 mg of zinc per ejaculum. Urinary losses average 0.5 mg per day but are unregulated. Urinary losses can be increased in nephrosis, sickle cell disease, and cirrhosis, and after therapy with penicillamine. Daily loss in normal persons has been estimated at 2.2 to 2.8 mg.

Immune Function. Zinc deficiency causes a rapid decline in antibody- and cell-mediated immune responses in both humans and animals (196). Low zinc status alters cellular mediators of the innate immune system, affecting macrophage, neutrophil, and natural killer T cell activity (187). These defects contribute to the lymphopenia seen in patients with sickle cell anemia, HIV infection, acrodermatitis enteropathica, and chronic renal and gastrointestinal diseases. T cells and B cells are lost from the bone marrow. Because zinc deficiency often accompanies protein–calorie malnutrition, the cause of these defects may be multifactorial. Even in the healthy elderly person with low serum levels of zinc, Th-1 cytokine production by leukocytes may be diminished (197). Many of the features of zinc deficiency and aging are similar, including a shift toward a Th2 profile, and impaired function of the innate immune system. These similarities have suggested that perhaps marginal zinc deficiency, always difficult to assess, might be quite prevalent among the elderly population (198).

Deficiency

Zinc deficiency in humans is clearly associated with certain clinical syndromes and has been implicated in others (199).

Definite or Likely Syndromes. As a result of the documentation of these syndromes, the clinical manifestations of zinc deficiency are now better defined (Table 7-45). The symptoms are often nonspecific, but in the appropriate clinical setting, zinc deficiency can be suspected. Acrodermatitis enteropathica is a hereditary disorder that begins in early childhood. It is characterized by pustular and eczematous lesions on the skin and by diarrhea. Oral, anal, and genital ulcers also occur. Irritability and cerebellar ataxia may be present. Growth retardation, anorexia, lethargy, and hypogonadism have been reported, especially in young males in Iran and Egypt, where available dietary zinc is low. Acute zinc deficiency has been reported after weeks of total parenteral nutrition, penicillamine therapy, or severe alcoholism. The findings include a rash on the face and limbs; the rash can be pustular, vesicular, bullous, seborrheic, or acneiform. Moist, indolent skin ulcers, when associated with serum zinc levels below 1.0 μg per mL, have been reported to heal with zinc therapy. Alopecia, confusion, apathy, depression, and loss of taste are associated with zinc deficiency in uremia. Symptoms suggestive of zinc deficiency can be found in patients with gastrointestinal diseases who have documented or suspected increased fecal losses.

TABLE 7-45. Clinical Manifestations of Zinc Deficiency

Degree of deficiency	Cause	Manifestations
Moderate	Diet, alcohol, malabsorption, chronic renal disease, sickle cell disease	Growth retardation, hypogonadism (males), skin rashes, poor appetite, lethargy, taste abnormalities, abnormal dark adaptation
Severe	Acrodermatitis enteropathica, TPN, alcoholism, penicillamine therapy, malabsorption, or severe diarrhea	Bullous pustular dermatitis, alopecia, weight loss, neurosensory and psychiatric symptoms, depressed immune function, impaired reproduction

TPN, total parenteral nutrition.
Adapted from Prasad AS. Zinc deficiency in women, infants, and children. *J Am Coll Nutr.* 1996;15:113.

Diarrheal disease in infants leads to low serum levels of zinc (200). The rapid transit exacerbates the zinc malabsorption that occurs in diseases of the intestine. These diseases include malabsorption syndromes, IBD, and other secretory diarrheas. Endogenous losses of up to 20 mg per day have been documented. Malabsorption can lead to a loss of more than 90% of dietary zinc because of decreased transport of zinc across the mucosa and malabsorption of zinc binders, which accumulate in the lumen. Zinc deficiency associated with protein losses occurs in patients with protein-losing enteropathy and nephrotic syndrome, burns, or trauma. Twenty percent of the total body zinc resides in the skin, so that a severe burn is especially likely to cause zinc deficiency. Requirements for zinc are increased in periods of growth and during pregnancy, so that any superimposed increased losses accelerate the development of zinc deficiency. Patients with cirrhosis excrete excess zinc in their urine; testicular dysfunction, anorexia, lethargy, and night blindness responsive to zinc may develop. Sickle cell anemia leads to urinary losses of zinc. Attributed to zinc deficiency are delayed puberty, hypogonadism, small stature, anorexia, decreased body hair, chronic leg ulcers, and hypogeusia. The gonadal function (potency, libido, sperm count) of patients on hemodialysis has been reported to improve after the administration of oral zinc at a dosage of 50 mg per day (199).

Candidate Syndromes. Poor wound healing is said by some authors to respond to zinc sulfate replacement. However, others note no change. Zinc deficiency can be associated with a diminished response of insulin to glucose, but it is not clear whether zinc plays a role in normal glucose homeostasis or in diabetes. Altered taste (dysgeusia) or smell as an isolated finding in nonuremic patients has been said to respond to oral zinc. Other possible causes of an abnormal sense of taste include iron deficiency, candidiasis, psychiatric disorders, and medications (201). The single, double-blinded study of the effect of zinc supplements on taste and smell dysfunction did not support a role for zinc (202). Acute or persistent diarrhea in children less than 5 years old is prolonged by low weight for age and by decreased cell-mediated immunity, both associated with zinc deficiency in developing countries (203). Zinc has been implicated in depression and other mood disorders, because of its putative role in neuronal transmission (204). In addition, its action in oxidative stress suggests a possible role in degenerative disorders, such as cardiovascular disease, and its activity in regulation of bone metabolism suggests a role in osteoporosis. The European ZENITH study (Zinc Effect in Nutrient/Nutrient Interactions and Trends on Health and Ageing) will evaluate the role of zinc in some of these disorders (204).

Treatment

Zinc is available as a component of many multivitamin and mineral preparations. It can better be provided as an individual oral supplement in the form of zinc sulfate or gluconate. The 67-mg zinc sulfate tablet provides 15 mg of elemental zinc, equivalent to the RDA, or roughly the amount contained per kilogram of stool. When estimated needs are greater, the patient can be given the 220-mg tablet, which contains 50 mg of elemental zinc. Treatment should continue until the symptoms prompting the use of zinc resolve. Then a maintenance dose (67 mg of zinc sulfate) can be given daily. Zinc sulfate (1 or 5 mg per mL) or zinc chloride (1 mg per mL) is available for IV administration but must be diluted first in saline solution.

It is difficult to choose a dose for zinc treatment. Zinc is widely available in a Western-type diet. Therefore, if zinc is given in certain disorders (e.g., malabsorption) to prevent the development of deficiency, it is not possible to determine whether the treatment is beneficial. It seems better to reserve treatment for those syndromes that respond to zinc therapy, and for conditions in which zinc has been shown to be beneficial.

Wilson Disease. In addition to a diet low in copper, 25 mg of zinc can be given every 4 hours from 7:00 A.M. to 7:00 P.M. and 50 mg at 11:00 P.M., or 50 mg can be given three times a day to decrease copper absorption.

Macular Degeneration. A single randomized trial of supplementation with β-carotene, vitamins C and E, and zinc suggested a slowing of progression to advanced macular degeneration, but other trials of antioxidant supplements have been small and inconclusive (205). Zinc supplements cannot be recommended at this time.

Decreased Dietary Intake. Supplements are indicated when the estimated intake is less than the RDA. However, long-term use of large doses (100 to 300 mg per day) can lead to copper deficiency and elevated levels of cholesterol (39). The results of studies of the effects of zinc supplements on calcium absorption and vice versa have been mixed, but there is no effect on iron status (206).

Diarrhea in Children less than 5 Years Old. An analysis of seven randomized studies from developing nations showed that mortality was reduced by 15% (acute diarrhea) and by 24% to 42% (continuing or persistent diarrhea) after the addition of 20 mg of elemental zinc, or 3 to 5 mg per kg (203). The greatest effects were seen in male infants less than 1 year old with persistent diarrhea and evidence of wasting or zinc deficiency. It is not clear whether zinc alone or with vitamin A is best, nor whether zinc supplementation will be useful in more developed countries where clinical zinc deficiency is much less common.

Common Cold. Trials of zinc supplementation for upper respiratory infection continue to provide contradictory results. A systematic review of randomized, controlled, double-blinded trials of rhinovirus infection showed no statistical benefit (207). The issue is still debated, although the data are not sufficient to warrant a recommendation of zinc supplementation. Other reviews concluded that zinc gluconate lozenges are useful, but that it is important to begin therapy within 48 hours and to have the patient suck the lozenges every 2 hours while awake (208). Using the delivery conditions outlined above, a prospective trial administered 12.8 mg of zinc acetate and showed a 40% reduction in the duration of cold symptoms (209). Zinc gluconate nasal gel might be preferable, although the data are mixed (210).

Prevention of Illness by Zinc Supplementation. The incidence, prevalence, duration, and severity of diarrhea and pneumonia can be reduced by zinc supplementation of children in the developing world (211,212). Although the data are not certain, it is likely that intake of bioavailable zinc is low in these populations. The problem again is the difficulty in identifying marginal zinc deficiency. Zinc supplementation has also been reported to relieve the diarrhea of acrodermatitis enteropathica, decrease the prevalence of malaria, and improve the neuropsychiatric performance of children at risk for zinc deficiency (213).

Toxicity

Zinc is relatively nontoxic. Because the zinc content of most foods is low, dietary excess is unlikely. Ingestion of more than 150 mg per day can interfere with copper or iron metabolism, but only if intake of these other ions is limited (214). Impaired immune function and an adverse effect on the ratio of low-density-lipoprotein to high-density-lipoprotein cholesterol have also been reported. All these effects have been reported less frequently with doses between 15 and 100 mg per day. However, the UL for adults is 40 mg per day, based on a reduction in erythrocyte copper/zinc superoxide dismutase activity (126). Very high doses (450 mg per day) have induced copper deficiency with sideroblastic anemia (213). Large acute overdoses (>200 mg) can produce nausea, vomiting, rash, dehydration, and gastric ulceration. Tetracycline absorption may be impaired by zinc.

Two spontaneous disorders of zinc overload have reinforced the concept that zinc can be toxic, if enough of the mineral enters the body. Myelopathy and pancytopenia can present with high zinc and low copper levels, in the absence of excessive zinc intake (215). The anemia was reversed with copper supplementation and high copper intake (8 mg per day) partially reversed neurologic signs. More striking is the syndrome in children of hyperzincemia and hypercalprotectinaemia, as the zinc levels reached 77 to 200 μmol per L, or >300 μg per dL (216). Patients presented with recurrent infection, systemic inflammation, anemia, and growth failure. Iron and copper status was normal. Levels of serum calprotectin (a calcium-binding protein) were ~6,000-fold increased over normal (217). Zinc levels fell by half after treatment with cyclosporine A in a single case (218).

Copper

Requirement

Copper is a trace element that is essential for humans and many other animals. Estimates of copper requirements are based on balance studies of fecal and other losses and copper

TABLE 7-46. Dietary Reference Intakes of Copper

Life stage group	Copper (μg/d)	Life stage group	Copper (μg/d)
Infants		**Adults (M/F)**	
0–6 months	200[a]	9–13 years	700
7–12 months	220[a]	14–18 years	890
		19–>70 years	900
Children			
1–3 years	340	**Pregnancy-all ages**	1,000
4–8 years	440	**Lactation-all ages**	1,300

[a] Estimates based on adequate intake (AI). Other values are recommended daily allowances (RDAs). Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC: National Academies Press, 2002.

absorption for various age groups (126,219). Obligatory losses in adults are about 580 μg per day, and absorption averages about 25%. However, when intake is low, excretion falls, so the formerly recommended intake in excess of 35 μg per kg per day to avoid a negative balance is considered too high (220). Current recommendations for dietary reference intakes range from 400 to 900 μg per day for children >4 years to elderly adults (Table 7-46). Premature infants are born with low copper reserves and may require more copper. Milk provides about 120 μg of copper per day. Infant formulas may contain copper in a poorly available form (e.g., bound to insoluble anions), and the copper requirement may be higher (~0.1 mg per kg of body weight daily) when these mixtures are used.

Food Sources

The richest sources of copper, as of zinc, are crustaceans and shellfish (especially oysters and crabs), and also organ meats (221). The next richest sources are nuts and legumes, dried fruits, and cocoa. Poor sources include dairy products, sugar, and honey. Surveys show that most adults in the United States consume 1 mg of copper or less per day. A hospital diet may contain less than 1 mg of copper because it includes few copper-rich foods. Full liquid diets provide less than 0.5 mg and clear liquid diets less than 0.1 mg. Table 7-47 lists the copper content of some common foods.

Assessment

Plasma Copper. Most of the copper in the body (80 mg) is in tissues. Red blood cells contain 60% of blood copper as erythrocuprein, a copper and zinc protein that functions as a superoxide dismutase. In plasma, copper is tightly bound to ceruloplasmin (molecular weight of 160 kDa), which binds 80% of the plasma copper at a ratio of seven copper molecules per molecule of protein. The rest of copper is bound to transcuprein and albumin. The amount of copper exchanged from ceruloplasmin is small compared with the amount absorbed. Therefore, the plasma copper level does not correlate with intake; it only roughly reflects body stores because the plasma compartment comprises such a small percentage of body stores and the turnover of copper within the compartment is slow. Nonetheless, the plasma copper level is a better initial indicator of copper status than is the tissue copper level when deficiency is suspected because tissue copper levels are more stable.

Normal plasma copper levels for males are 0.91 to 1.0 ± 0.12 μg per mL, and for females they are 1.07 to 1.23 ± 0.16 μg per mL. Oral contraceptives increase the range to 2.16 to 3.0 ± 0.7; this is largely an estrogenic effect. Levels peak in pregnancy at 38 weeks and return to normal within 2 weeks postpartum. Plasma total copper levels can increase in acute and chronic infections and decrease in nephrosis, Wilson disease, kwashiorkor, or any condition that causes protein malnutrition. Free serum copper values are more instructive than total copper values because the latter are affected by factors that alter binding capacity. Bound copper is estimated to be three times ceruloplasmin levels (μg per dL)

TABLE 7-47. Copper Content of Foods

High (>0.2 mg/portion)	Moderate (0.1–0.2 mg/portion)	Low (0.1 mg/portion)
Meat and meat substitutes		
Liver and other organ meats, shellfish, variety meats, lamb, pork, duck, tofu, nuts	Dark meat of chicken, fresh fish, turkey	Beef, veal, bologna, beef frankfurters, eggs
Dairy products		
	Dried skim milk powder, sharp cheeses	Butter, margarine, milk, ice cream, most cheeses, cheese spreads
Vegetables		
Lentils, mushrooms, dried beans, pimentos, French fried potatoes, canned tomatoes	Spinach, sweet potato, squash, beets, asparagus, peas (fresh and canned), baked potato	Green beans, broccoli, cabbage, carrots, cauliflower, corn, brussels sprouts, cucumber, lettuce, green pepper, turnip
Bread and cereal		
Wheat germ and bran, English muffins, bran flakes	Whole wheat bread, pasta, sugar or vanilla wafers	White bread, white rice
Miscellaneous		
Curry powder, nuts, chocolate, molasses, cocoa, Ovaltine, licorice, soup mixes, syrup, canned soup	Pickles, ginger, black pepper, frozen pizza, popcorn, potato chips, pretzels, soda	Hard candy, Jell-O, honey, jelly, white sugar, lemonade, catsup, mayonnaise

Adapted from Pennington JT, Calloway DH. Copper content of foods. *J Am Diet Assoc.* 1973;63:143.

because each milligram of ceruloplasmin contains 3.3 μg of copper (222). Free (not bound to ceruloplasmin) copper equals total serum copper minus bound copper. Values below 25 μg per dL are considered within normal range. This calculation is designed to detect elevated levels of free copper, as in Wilson disease, rather than to detect copper deficiency.

Ceruloplasmin. Ceruloplasmin is a protein that is made in the liver. It functions as a ferroxidase, converting ferrous to ferric ion, and thus affects the flow of iron from cell to plasma. With copper deficiency, ceruloplasmin levels fall, to about 30% in severe deficiency. Iron mobilization is decreased, and a hypochromic, microcytic anemia develops. When ceruloplasmin levels are low in Wilson disease, other ferroxidases in plasma appear to be able to mobilize iron. Normal levels are 105 to 500 μg per dL. Estrogens increase the levels, and low levels are seen in patients with Wilson disease (including 10% to 20% of heterozygotes), uremia, and nephrosis and in persons with a low protein intake. Other forms of chronic liver disease associated with a decreased synthesis of plasma protein can produce a low level. In Wilson disease, ceruloplasmin levels are <23 μg per dL (223). This value provides an adequate screening test, but false-normal levels may occur in a small percentage of patients. The free serum copper concentration is probably a better measure in Wilson disease (224).

Hair. A determination of copper in hair entails the same problems as do the determinations for zinc and other trace metals—individual sex- and age-related variations, exogenous contamination, and strict requirements for sample preparation. It cannot be routinely recommended to test body stores.

Urinary Copper. From 0.01 to 0.06 mg is excreted daily in the urine. This amount does not usually vary much according to changes in copper intake and reflects free tissue copper and plasma copper loosely bound to albumin. Thus, it does not reflect body stores. In

Wilson disease, free copper in tissues is increased, and urinary excretion can exceed 1.5 mg per day. However, this value is quite variable and can be within the normal range. Values below 50 μg per day, however, virtually exclude Wilson disease.

Physiology

About one-third of body copper is in the liver, with large amounts in brain, heart, spleen, and kidneys. Newborns have three times the adult level in their liver, but this falls rapidly after birth and is probably related to immature excretory mechanisms. The newborn has ceruloplasmin in liver but low levels in plasma. Most copper is in the cytosol, bound to enzymes or other copper-binding proteins. The enzymes include cytochrome oxidase, amine oxidases, superoxide dismutase, ceruloplasmin, tyrosinase, dopamine-β-dehydrogenase, uricase, lysyl oxidase, and histaminase, among others (222,225). Copper is important for the enzymes mediating the absorption and release of iron from tissues, and thus it is important in hemoglobin production. It is needed for the development and maintenance of blood vessels, tendons, and bones, functioning of the central nervous system, pigmentation of hair, and normal fertility.

Copper Absorption and Organ Distribution. Dietary copper is absorbed from the stomach and small intestine. The mechanism of absorption of dietary copper is not established with certainty. A protein with a high affinity for copper, hCtr1, may transport copper into enterocytes, although it is expressed in a wide range of other tissues (225). The divalent metal transporter, DMT1, has a wide substrate range (copper, iron, manganese, cobalt) and may be involved as well (226). Intracellular transport of copper is better understood. hCtr1 delivers copper by acting as a permease or via endocytosis (227). There is no free copper inside cells, but the metal is bound to various chaperones. It is guided to the copper transporting ATPase, ATP7B, by ATOX1, a metal chaperone (228). The gene for Wilson disease, ATP7B, is located on the long arm of chromosome 13, and has a cysteine-rich metal binding region on the amino terminus that is critical for its intracellular distribution. Most mutations in Wilson disease are point missense mutations. After binding to ATP7B copper is bound to glutathione and metallothionein and other peptides (227). Excess copper is taken up by hepatocytes and excreted from those cells into bile via the apical canalicular membrane. The copper transporting ATPase resides in the *trans*-Golgi where it provides the copper for ceruloplasmin bound for export. When intracellular copper rises, the ATP7B protein is redistributed to endosomal vesicles for delivery to bile. This accounts for the basal rate of copper excretion in Wilson disease and probably prevents severe copper toxicity in neonates.

The Menkes gene protein, MNK (ATP7A), is another membrane-associated P-type adenosine triphosphatase that is required for secretion of copper excretion primarily in enterocytes and the placenta and cells of the central nervous system. The mechanism of excretion is the same as for ATP7B. Mutations of both ATPases in Menkes syndrome and Wilson disease lead to impaired trafficking across the *trans*-Golgi membrane, and thus present with hypoceruloplasminemia. Hephaestin is a multicopper oxidase that is deficient in mice with sex-linked anemia. It is a membrane-bound analogue of ceruloplasmin required for iron (but not copper) export from the intestine. In the plasma, copper binds to albumin and perhaps histidine, and is taken up by hCtr1 on the liver membrane.

Intracellular Copper Metabolism. Once hCtr1 mediates copper uptake, a series of small cytoplasmic copper chaperones (e.g., hCOX17, HAH1, and CCS) distribute copper to various cellular compartments or mediate incorporation into proteins (225). In all tissues but liver, MNK transports copper into the Golgi apparatus for incorporation into secreted proteins. MNK then moves to the plasma membrane, where it may mediate copper efflux. In the liver, the protein that is deficient in Wilson disease, WND, is present in the Golgi and presumably serves a similar function. No chaperone has been isolated for delivering copper to metallothionein.

Metallothionein. Metallothionein, a small protein (molecular weight of 6 kDa) with tightly bound zinc and copper, is found in many tissues. The high level in fetal liver may allow safe storage of increased liver copper. It may be the initial hepatocyte acceptor for albumin-bound copper from the plasma and may play a role in detoxification. Finally, it has been suggested as a mechanism to block enterocyte absorption of copper. Normally,

about 80% of hepatic copper is bound to metallothionein, which is polymerized and insoluble. In Wilson disease, only about half as much copper is in this form, so that free tissue copper levels rise.

Hepatic Copper Content in Disease. In many disorders, especially Wilson disease, hepatic copper is increased—prolonged cholestasis, Indian childhood cirrhosis, copper poisoning, thalassemia, hemochromatosis, and biliary cirrhosis. However, more stainable copper is demonstrated in the liver in these illnesses than in Wilson disease, and metallothionein levels may be normal. For this reason, these conditions may not be associated with the same degree of tissue toxicity, presumably secondary to free copper, as Wilson disease.

Excretion and Absorption. Copper from the liver is mainly excreted into bile. This is the major excretory route for copper from the body, and the rate of excretion is 0.5 to 1.3 mg per day. The amount excreted usually balances that absorbed each day from the upper small intestine. Absorption is relatively inefficient (~30%), allowing biliary excretion to remove excess copper from the body. The form of inorganic copper affects absorption. The carbonate and nitrate forms are better absorbed than the sulfate, chloride, or oxide. Phytates and ascorbic acid decrease absorption. Copper complexed to amino acids may be better absorbed. Other metals (e.g., Ca, Cd, Zn, Fe, Pb, Ag, Mo) decrease absorption (191).

Other Functions. Copper deficiency leads to low serum levels and high tissue levels of iron. This function of copper is carried out by the multicopper ferroxidases, of which ceruloplasmin was the first reported. Ceruloplasmin knockout mice show a severe impairment of iron efflux from reticuloendothelial cells and hepatocytes (229). The multicopper oxidases may bind to iron transport proteins or may be involved primarily in iron export, as is hephaestin. Copper also is necessary to prevent lipid peroxidation, perhaps by playing a role in selenium metabolism. Both humoral and cell-mediated immunity is impaired by copper deficiency in animals.

Deficiency

Dietary deficiency is uncommon but may occur in premature infants or in malnourished patients repleted with low-copper diets (230). Table 7-48 lists the manifestations of copper deficiency in humans.

Premature Infants. When milk is the major food source, both copper and iron intakes are low. The copper content of the body increases markedly just before birth, so prematurity

TABLE 7-48. Signs and Symptoms Associated with Deficiency of Trace Metals

Mineral	Signs and symptoms	
	Infants and children	Adults
Cu	Anemia, neutropenia, osteopenia, vascular aneurysms, kinky hair, hypothermia, impaired CNS development	Anemia, neutropenia
Mn	None reported	Hypercholesterolemia, weight loss, change in hair color (one case reported)
Se	None reported	Glucose intolerance, peripheral neuropathy
Se	Cardiomyopathy, chondrodystrophy	Cardiomyopathy, myositis

CNS, central nervous system.
Adapted from Triplett WS. Clinical aspects of zinc, copper, manganese, chromium, and selenium. *Nutr Int.* 1985;1:60.

is associated with low body stores. Anemia secondary to either iron or copper deficiency can develop. Bone abnormalities have been reported.

Malnutrition. When repletion is high in calories but low in copper content, neutropenia, anemia, diarrhea, and scurvy-like bone changes may occur that are all responsive to copper. Tissue copper levels are often but not always decreased. Osteoporosis has been reported in severe copper deficiency (231).

Menkes Kinky Hair Syndrome. Menkes kinky hair syndrome is an X-linked recessive inherited disorder caused by a defect in copper absorption (MIM #309400) (232). The tissue content of copper is always low. Characteristic features are failure to thrive, mental deterioration, hypothermia, defective keratinization of hair, metaphyseal lesions, degeneration of aortic elastin, and depigmentation of hair. Most children die early in infancy. Copper supplementation is not helpful, but a copper-histidine complex may delay the onset of some symptoms (233).

Cardiovascular Disease. The copper deficiency theory of ischemic heart disease was first proposed in the 1980s, suggested by sudden death in domestic animals with copper deficiency (e.g., "falling disease" of dairy cattle). The evidence is all indirect but nevertheless intriguing. Decreased activity of lysyl oxidase and superoxide dismutase may lead to a failure of collagen and elastin cross-linking (234). Copper deficiency can be associated with low levels of copper in cardiac muscle, increased levels of plasma cholesterol, and electrocardiographic abnormalities. Patients with ischemic heart disease have low cardiac and leukocyte copper concentrations. Short-term copper depletion experiments in humans have produced changes in lipid profiles, electrocardiographic changes, and impaired glucose tolerance (234). The data are not sufficient to recommend replacement therapy at present.

Myeloneuropathy and Anemia. Myeloneuropathy and anemia due to copper malabsorption is being increasingly recognized (235). The clinical presentation resembles that of cobalamin deficiency, with long tract signs and lower extremity weakness. Copper replacement parenterally reverses the neurologic symptoms. Most cases have had gastric resection (236). The duodenum is the primary site of copper absorption in animals, perhaps accounting for the role of gastrectomy in producing the syndrome. A similar syndrome has been reported in a patient taking 15 to 30 times the recommended daily intake of zinc (as gluconate) to prevent the common cold (235).

Therapy

Because copper deficiency is uncommon, supplementation is unnecessary with most diets. Despite this fact, copper is included in many multivitamin and mineral preparations. Copper sulfate, the form usually available, contains 0.4 mg of elemental copper per milligram of the anhydrous salt. A daily addition of about 1.0 to 1.5 mg of copper adequately treats deficiency states. However, if oral treatment is used, three times this amount should be given, or about 3 mg of copper as copper sulfate, to allow for the 30% absorption efficiency. For replacement in cases with myeloneuropathy doses up to 10 mg per day for 1 to 2 months may be necessary to restore the serum copper level to normal (236).

Toxicity

Acute Toxicity. The UL for adults is 10 mg per day based on protection from liver damage, which is the critical toxic effect (126). Ingestion of more than 15 mg of elemental copper causes nausea, vomiting, diarrhea, and abdominal cramps resulting from direct mucosal toxicity (237). At larger doses, hemolysis results from inhibition of glucose-6-phosphate dehydrogenase. Gastrointestinal bleeding, azotemia, and hematuria may occur. When ingestion is potentially fatal, jaundice with acute hepatic necrosis and renal tubular swelling are seen. The treatment for acute overdose usually involves gastric lavage. If the dose ingested is very high, penicillamine (1 g per day in adults) can be added to remove excess copper from the body.

Chronic Toxicity. In Wilson disease, free tissue copper and total liver copper (>250 μg per g net weight of liver) are increased. Other diseases are associated with increases in hepatic copper (chronic active hepatitis, primary biliary cirrhosis) but tissue damage related

to excess copper has not been seen to develop, perhaps because the level of free tissue copper is not increased. The initial treatment for Wilson disease consists of a low-copper diet and chelating therapy (penicillamine or trientine). It may be important to combine the diet with chelation therapy initially to reduce the excess copper stores. Zinc supplements also may be helpful for maintenance therapy (228).

Iodine

Requirement. Iodine is a nonmetallic halogen element required for the synthesis of thyroid hormone. About 1 μg of iodine is required per kilogram to prevent goiter in adults. The RDAs are currently based on balance studies (126). Studies of urinary excretion indicate that more than 50 μg is needed per gram of creatinine per day. Goitrogens in the diet (fluoride or rubidium) affect the requirement by decreasing thyroid uptake of iodine. To allow a margin of safety, the RDA for children aged 9 to 13 and adults is set at 150 μg per day. For infants age 0 to 6 months the recommended AI is set at 110 μg per day, for infants 7 to 12 months at 130 μg per day, and for children ages 1 to 8 at 90 mg per day. Because the iodine content of human milk is 30 to 100 μg per L, another 70 μg per day is needed during pregnancy, and an additional 70 μg per day (290 μg total) is needed during lactation. The AI for infants 0 to 6 months old is 110 μg per day; for infants 7 to 12 months old, it is 130 μg per day, and it is 90 μg per day for children ages 1 to 8 years. The RDA is 120 μg for children 9 to 13 years old and 150 μg per day for adolescents and children of both sexes 14 years of age or older. The RDA during pregnancy is 220 μg per day, and it is 290 μg per day during lactation.

Food Sources. The iodine content of food and water is closely related to the iodine content of the soil. Areas where the iodine content is likely to be low include glaciated and mountainous regions and areas with heavy rainfall. Seafood is an excellent and consistent source of iodine. The iodine content of dairy products, eggs, and meat depends on the iodine content of the animal feed. The water content varies from 0.1 to 2 μg per L in goitrogenic areas to 2 to 15 μg per L in nongoitrogenic areas. Fruits and vegetables in general are low in iodine. Except for seafood, the source is more important than the type of food in determining iodine content. Shellfish or saltwater fish contain about 70 μg per 4 oz. Eggs contain about 4 to 10 μg each, meats about 5 μg per oz, dairy products about 3 to 4 μg per oz, and fruits 1 μg per oz. Breads are low in iodine unless made by the continuous mix process, during which the dough absorbs atmospheric iodine. Some plants contain natural substances that interfere with iodine absorption. These include brussels sprouts and legumes.

Average iodine intake in the United States is 250 and 170 μg per day for males and females, respectively. The usual supplement for dietary iodine in the United States is iodized table salt, which contains 76 μg of iodine per gram of salt. The use of 3.4 g of iodized salt per day on average adds 260 μg of iodine to the daily intake. In noncoastal regions, iodized salt should be used. In coastal regions, atmospheric iodine is much higher and provides an extra source of iodine.

Assessment

The body contains 15 to 20 mg of iodine, 60% to 80% of which is in the thyroid gland. The concentration of inorganic iodine is low, and organic compounds are the usual circulating form (thyroxine, triiodothyronine, diiodotyrosine, and monoiodotyrosine). Measurement of these compounds in blood is a measure of thyroid function, and this measurement correlates with iodine stores in the absence of other thyroid disease. Thyroid-stimulating hormone is regulated by circulating thyroid hormone levels. Because radioimmunoassays and immunochemiluminometric assays for thyroid-stimulating hormone are stable and easily used, this measurement is preferred (34).

The inorganic iodine concentration is only 0.08 to 0.6 μg per dL. About 3 mL of serum is required, and the assay depends on the catalytic effect on the reduction of ceric ion by arsenious acid. Thyroxine (T_4) is present at a level of 7 to 11 μg per dL. About 0.5% to 0.07% of this is not protein-bound. The level of free thyroxine therefore is 5.4 ± 1 ng per dL. Triiodothyronine (T_3) resin uptake is a measure of the protein-binding capacity for triiodothyronine and is not a determination of iodine content. Values of thyroid-stimulating hormone are 0.1 to 5.0 mU per L in euthyroid subjects (34).

TABLE 7-49. Urinary Iodine Excretion as a Measure of Iodine Nutritional Status

Iodine status	Urine concentration (μg/L)	Urine concentration (nmol/L)
Sufficient/optimal	100–200	781–1,580
Deficiency, mild	50–99	391–780
Deficiency, moderate	20–49	160–390
Deficiency, severe	<20	<160
More than adequate	201–300	1,581–2,360
Excessive/toxic	>300	>2,360

Adapted from Stanbury JB, Dunn JT. Iodine and iodine deficiency disorders. In *Present Knowledge in Nutrition*. 8th ed., Bowman BA, Russell RM, eds. International Life Sciences Institute, Washington. 2001:344.

Urinary iodine is the preferred test to detect iodine deficiency (238). Iodine concentration per L or per mole of creatinine is an acceptable substitute for 24-hour urinary collections. A urinary concentration of 788 nmol per L (100 μg per L) correlates with an intake of ~150 μg per day, the RDA for adolescents and adults. Optimal values are 100 to 200 μg per L (781 to 1,580 nmol per L) (Table 7-49) (239).

Physiology

Food contains mostly inorganic iodide, which is reduced in the gut lumen and nearly completely absorbed. Some iodinated compounds (e.g., thyroid hormones, amiodarone) are absorbed intact. Iodide is handled like chloride and passes easily across membranes, unlike other trace minerals (except for fluoride). It is concentrated in the thyroid and salivary glands by the action of the sodium/iodide cotransporter, SLCA5 (NIS), a member of the sodium/glucose cotransport family (240). This transporter also uses Br, NO3, SCN, and ClO4 as substrates. It is present in basolateral membranes of the thyroid, breast, colon, and ovary. It is secreted as inorganic iodine in saliva and milk but only as the organic form from the thyroid, probably via the apically located sodium/iodide cotransporter, AIT, another member of the SLC5 family. The iodide pool is replenished from the diet, saliva, gastric juice, and the breakdown of organic thyroxine derivatives. The thyroid gland, kidneys, and salivary and gastric glands all compete for free iodide. The thyroid must trap about 60 μg of iodide per day to maintain thyroxine levels. Iodide is concentrated by the sodium/iodide cotransporter, a member of the family of cotransporters that use electrochemical sodium gradients to drive coupled uphill transport of sugars, amino acids, vitamins, ions, and water. Iodide is also taken up by stomach, salivary glands, and mammary glands (241). The three pools of body iodide are the circulating inorganic, intrathyroid organic, and circulating organic pools. Iodide is excreted mostly in urine (>50 μg per day), with lesser losses in stool and sweat.

Deficiency

Iodine deficiency is one cause of hypothyroidism. This deficiency in childhood can result in delayed growth. At all ages, it causes decreases in cellular oxidation and the basal metabolic rate and thus weakness, fatigue, and slow mental responses (242). Depending on the degree of deficiency and age at onset, mental changes can vary from mild intellectual impairment to severe retardation. Iodine deficiency is the most common form of preventable brain damage in the world (243). Hypotension and bradycardia, constipation, pretibial edema, and slow deep tendon reflexes are all seen. Thyromegaly often accompanies dietary iodine deficiency. Because iodide is easily absorbed, malabsorption syndromes do not cause deficiency. Because thyroid hormone production is decreased, the gland becomes hypertrophic in an attempt to compensate, and a goiter develops. Iodine requirement increases in pregnancy, and many women still do not maintain an adequate intake without a supplement (244).

Treatment

Iodine is a component of many multivitamin and mineral preparations. However, supplementation with 2 g of iodized salt per day provides the full RDA. In the United States, recent trends show a decline in iodine intake, especially among women of reproductive age (245). More than 90 countries currently iodize their salt products, at concentrations from 30 to 100 μg per g of salt. In countries without easily available iodized salt, iodized oil has been successfully used as a source of supplemental iodine to prevent goiter (246). When radioactive iodine therapy is administered, it may be necessary to place patients with a high intake of iodine on a low-iodine diet for 1 to 2 weeks so that the uptake of the radioactive element will be sufficient.

Toxicity

Excessive Dietary Intake. When intake exceeds 2,000 μg per day, iodide uptake by the thyroid gland is impaired and organic formation falls. These dietary levels can be reached by a large intake of iodine from iodized salt, vitamin and mineral preparations, or iodine-containing coloring dyes and dough conditioners. The margin of safety is great, and toxicity remains unusual at the present level of iodine supplementation. The tolerable upper intake levels (ULs) are 200 μg per day for children 1 to 3 years old, 300 μg per day for children 4 to 8 years old, 600 μg per day for children 9 to 13 years old, 900 μg per day for children 14 to 18 years old, and 1.1 mg per day for adults, based on serum thyroid-stimulating hormone concentrations during different levels of iodine intake (66). High intake in iodized salt, leading to a urinary excretion >300 μg per L can produce hypothyroidism and autoimmune thyroiditis (247).

Excessive Therapeutic Iodine. Iodine-induced thyrotoxicosis may paradoxically result from excessive iodine therapy given to patients with multinodular goiter or quiescent Graves disease. Commonly used iodine-containing medications include expectorants and antithyroid medications. The iodine content of these medications far exceeds the normal dietary allowance, as listed in Table 7-50.

The side effects of potassium iodide include rash, swelling of salivary glands, a metallic taste in the mouth, stomach upset, allergic reactions, and headache. Iodinated glycerols are contraindicated in newborns and nursing mothers because of the possibility of producing hypothyroidism.

Fluorine

Requirement

The protective effect of fluoride on teeth is observed at intakes from 1.5 to 2.5 mg in adolescents. These levels are consistent with the range of fluoride intake in the United States. Therefore, the total AI recommended from food and drinking water is 3 mg per day for adult women and 4 mg per day for men (43). Because fluoride is required for the growth of bone and enamel, these recommendations are based on the prevention of dental caries, not on total body requirements. For children and adolescents, the primary beneficiaries of

TABLE 7-50. Iodine Content of Medications

Drug	Iodine or iodide content per therapeutic dose
Glycerol, iodinated	15 mg iodine per tablet or 30 mg per teaspoon of elixir
Calcidrine syrup	152 mg calcium iodide per teaspoon
Potassium iodide syrup	300 mg potassium iodide per teaspoon
Potassium iodide	
Solution	1 g potassium iodide per milliliter
Tablet	320 mg per tablet
Lugol solution	5% iodine in solution

the prevention of dental caries with fluoride, the AI is 0.7 mg for ages 1 to 3 years, 1.0 mg for ages 4 to 8 years, 2 mg for ages 9 to 13 years, and 3 mg for ages 14 to 18 years. To avoid the danger of mottling of the teeth of infants and children, the UL for infants ages 0 to 6 months is 0.7 mg and 0.9 mg for ages 7 to 12 months. Comparable ULs for children are 1.3 mg for ages 1 to 3 years and 2.2 mg for ages 4 to 8 years. The UL for all others is 10 mg to avoid producing brittle bones.

Food Sources

Type of Food. Like other anionic trace elements (I, Se), the source of the food (where it is grown) is more important than the type. One exception is ocean fish, each gram of which contains 5 to 10 μg of fluoride. Other foods contain less than 0.5 parts per million (ppm). Tea is the other food naturally high in fluoride, containing 100 to 200 μg per g. The content of food can be decreased by cooking, during which water is lost, or increased by commercial processing, during which water is added. Cereals contain 1 to 3 μg per g of dry weight and are a major source of fluoride for infants. The availability of cereals for infants has raised the question of the need for water supplements (248). Daily intake in the United States averages about 0.4 mg from food; with water content added, the average is about 0.9 mg per day for boys.

Water. Water is the other major source of fluoride. Surface water contains about 1 ppm or less; deep water contains 4 to 8 ppm. The fluoride intake in cities with fluoridated water supplies is from 1.7 to 3.4 mg per day, with a mean of 2.6 mg, exclusive of water ingestion. In nonfluoridated areas, fluoride intake from food averages 0.9 mg per day. The difference represents food preparation. Water intake accounts for 1 to 1.5 mg daily in fluoridated areas and 0.1 to 0.6 mg in nonfluoridated areas. Thus, intake varies from 1 to >4 mg per day. Because water supplies most dietary fluoride, either by itself or in foods, it is recommended that water supplies contain at least 1 mg per L, which ensures adequate fluoride intake to decrease the incidence of dental caries. Fluoride-containing dentifrice is ingested (~25%) by children less than 5 years old, who may ingest 0.3 mg fluoride per brushing. Thus, daily intake of young children brushing twice daily could be doubled.

Assessment

Body Stores. Because fluoride is required for the growth of bone and enamel, these recommendations are based on the prevention of dental caries, not total body requirement. Because most of the fluoride is in bone and enamel and not in extraosseous tissues, no practical method is available for assessing body stores. Bone content ranges from 300 to 600 ppm but is not usually measured.

Urine Levels. Urine levels are proportional to intake and average 0.5 to 0.6 ppm. Urine excretion reflects current ingestion or prior exposure to high levels. The efficient renal excretion mechanisms keep blood fluoride at a low narrow range independent of intake.

Physiology

Fluoride is concentrated in bones and teeth, where it is incorporated into the crystalline structure of hydroxyapatite. This results in increased resistance of the teeth to caries, especially in the pre-eruptive phase. Fluoride is completely absorbed (90% in the stomach) and is distributed like chloride in soft tissues. Uptake in bone depends on its growth and vascularity. Aluminum, iron, magnesium, and calcium salts can decrease the rate of absorption. About 80% of dietary fluoride is excreted in the urine each day.

Deficiency

Because fluoride is present in nearly all water supplies, plants, and animals, deficiency does not occur in humans. Fluoride is an essential element for growth in mice and rats but has not been implicated in growth failure in humans.

Treatment

Over 40% of the water supplies in the United States are still not fluoridated (249). For children living in a nonfluoridated area, the daily addition of the AI for the appropriate age is adequate to prevent caries. Treatment in adults may prevent further caries. Each

2.2 mg of sodium fluoride contains 1 mg of fluoride. Sodium fluoride is available in chewable tablets (1 mg), lozenges (1 mg), drops (0.125 mg per drop), and solution (0.2 mg per mL). The use of slow-release fluoride formulations has largely prevented the gastritis that occurred with earlier preparations. Data showing the protective effect of fluoride via water fluoridation is solid, but evidence for caries protection from dietary or supplemental fluoride is lacking (250). Sodium fluoride has been used to treat osteoporosis (up to 60 mg of fluoride per day alternated in 6-month periods with calcium and vitamin D) in an attempt to stimulate the formation of new bone, which is then hardened by fluoride. No convincing evidence has been found that this treatment is beneficial in the prevention of osteoporosis. Currently the FDA does not approve this form of therapy, because long-term safety has not been demonstrated, and the benefits have been limited to a reduction in vertebral fractures alone (249).

Toxicity

Fluoride is toxic when ingested in excess.

Mottled Teeth. Mottled teeth have been found in children ingesting water containing more than 8 ppm. The most common form of fluorosis is hypermineralization of tooth enamel from excessive systemic fluoride during the period of enamel development, but before tooth eruption. This is manifested by chalky white spots on the teeth (mottling). Mottling occurs only in permanent teeth and is usually not significant. Eczema, urticaria, gastric distress, and headache have been reported.

Systemic Fluorosis. With ingestion of 20 to 80 mg per day for years, a syndrome including osteosclerosis, genu valgum, kyphosis, and spine stiffness can occur. Systemic fluorosis has occurred in areas where a high fluoride intake is endemic (some parts of the Indian subcontinent and South Africa). The UL for adults has been set at 10 mg per day (43). The American Dental Association has recommended that no more than 120 mg of fluoride be dispensed at one time, to avoid the chance for severe fluorosis (249).

Manganese

Requirement. Manganese is a trace mineral essential to animals and probably humans. Many problems arise when balance methods are used to estimate trace minimal requirements, and no overt deficiency state exists in humans. Thus, data are insufficient to establish an estimated average requirement (EAR) for manganese, and all the DRIs are based on median AIs. The AI for infants ages 0 to 6 months is 3 μg per day based on total estimated intake from milk. The estimated AIs for other life groups are as follows: 0.6 mg (infants 7 to 12 months old); 1.2 mg (children ages 1 to 3 years); 1.5 mg (children ages 4 to 8 years); 1.9 mg, 2.2 mg, and 2.3 mg (females ages 9 to 13 years, 14 to 18 years, and 19 to 70 years, respectively); 1.6 mg, 1.6 mg, and 1.8 mg (males ages 9 to 13 years, 14 to 18 years, and 19 to >70 years, respectively); 2 mg for pregnancy; and 2.6 mg during lactation. Because the current dietary intake seems adequate, an estimated safe and adequate dietary intake has been set at those levels, 2 to 5 mg for adults (126). Safe intakes are recommended for children and adolescents as follows: 1 to 1.5 mg for ages 1 to 3 years, 1.5 to 2.0 mg for ages 4 to 6 years, and 2 to 3 mg for ages 7 to 10 years. Safe intakes for formula-fed and breast-fed infants are 0.005 mg per day and 0.30 mg per day, respectively (251).

Food Sources

Nuts, dried fruit, cereals and unrefined grains, pineapple, pineapple juice, and tea are very rich in manganese (>1 mg per serving). Legumes, rice, spinach, sweet potatoes, pasta, and whole wheat bread are good sources of manganese (>0.5 mg per serving). Vegetables and fruits contain only moderate amounts, and dairy products, muscle meats, and seafood contain only small concentrations of the mineral. Drinking water contains ~10 μg per L of manganese from most sources (252). Human milk contains 3 to 10 μg per L, but soy formula has a much higher content (200 to 300 μg per L). The average daily intake for adults in the United States is 2.2 mg for women and 2.8 mg for men. Vegetarian diets or diets rich in whole grain products may provide as much as 8 to 10 mg per day. Hospital diets provide about 1 to 2 mg per day, and low-sodium and low-protein diets may supply <1 mg per day. Components of the diet can limit manganese absorption

or increase excretion, including iron, phosphorus, calcium, copper, phytates, fiber, and polyphenols.

Assessment

As with other divalent cations, no measurement accurately assesses body stores. Like copper, manganese is excreted mainly in bile, not urine. Therefore, urine does not provide a good measure of recent intake. Red cells contain 13.6 to 16.9 μg per L, but serum/plasma contains only 0.59 to 1.3 μg per L (34). The usual assay is based on atomic absorption spectrometry, which measures total manganese. Radiochemical neutron activation analysis has also been used. Manganese is present in serum as the trivalent form, bound to β_2-globulin. Because this level does not change with altered intake and because deficiency in humans is not recognized, the usefulness of serum levels is small. Urine values vary little, are quite low, and are not useful in assessing manganese status. Hair content varies more among individuals and with such factors as exogenous contamination, color, and season than with manganese status.

Physiology

Function. The body contains about 12 to 20 mg of manganese. The liver and pancreas have the highest content. A few metalloenzymes (superoxide dismutase, pyruvate carboxylase) and many metal–enzyme complexes (hydrolases, kinases, dicarboxylases, transferases) contain manganese.

Absorption. Absorption occurs in the small bowel but is very inefficient. Absorption efficiency is increased in animals when they are deficient. Like the absorption of other cationic metals, the absorption of manganese depends on its form; carbonate and silicate salts are poorly absorbed. Luminal calcium, phosphate, and iron decrease absorption. The most likely mechanism for iron competition is common use of the divalent metal transporter (DMT-1) (252). Manganese is bound largely to albumin and gamma globulin, but a small amount of trivalent (3+) ion is bound to transferrin. Tissues with high energy demand (brain) and high pigment content (retina, dark skin) contain the highest concentration of manganese. Excretion varies with bile output, which regulates body content. Manganese activates many enzymes but is an absolute requirement for only a few; thus, deficiency states are rare.

Deficiency

In animals, neonatal ataxia, retarded skeletal growth, decreased reproductive function, and defects in lipid metabolism are seen. In humans, one case has been reported with weight loss, hypocholesterolemia, dementia, nausea, vomiting, and altered hair color (253). Manganese deficiency was induced in 39 days in young men and caused a fleeting dermatitis (254). Some epileptics have been reported with low blood levels of manganese. Manganese deficiency has not been reported in humans consuming a natural diet, and supplements are not indicated for healthy subjects. Men on experimental low manganese diets developed a rash on their torsos, and women on diets containing <1 mg of Mn per day developed altered mood during the premenstrual period (252).

Treatment

Manganese is a component of some multivitamin and mineral supplements. Therapy for specific deficiency symptoms is indicated very rarely.

Toxicity

Manganese is relatively nontoxic when ingested, presumably because absorption is low. However, when inhaled as dust, it can produce psychiatric disorders and extrapyramidal signs. Manganese oxide is absorbed across the lungs and is a concern for miners. The UL, set at 11 mg per day, is based on no observable adverse effects on Western-type diets (126). Hypermanganesemia during treatment with total parenteral nutrition (usually 100 to 800 μg per day) can lead to increased signal density in the globus pallidus on magnetic resonance imaging (255). It can be seen in patients with cholestatic liver disease receiving total parenteral nutrition but is not a risk when only the liver disease is present (256). Patients with cholestasis or neurologic symptoms or who are receiving prolonged total parenteral nutrition should be monitored for hypermanganesemia. If present, the infusion of manganese

should be stopped or diminished. It is standard practice to supplement infants receiving total parenteral nutrition with a neonatal trace element solution containing 25 μg per mL of manganese. The *Pediatric Nutrition Handbook,* 5th edition, and the A.S.P.E.N. report of 2004 recommend 1 μg per kg per day for preterm infants, and 3 μg per kg per day for term infants weighing 3 to 10 kg (252).

Chromium

Requirement

Chromium is an essential trace mineral that potentiates the action of insulin in certain conditions. A safe intake of chromium would be based on the content of a varied diet that does not lead to deficiency, but deficiency is not readily identified in humans. Thus, the current dietary intake recommendations are based on the median intake of chromium at various ages (AI). The adequate daily intake ranges are listed in Table 7-51. The lower recommendations for younger ages are based on extrapolations of expected food intake. However, the WHO has recommended lower intakes of 25 μg per day to prevent deficiency and 33 μg per day to maintain tissue stores (257) because earlier estimates were based on less accurate measurements of chromium.

Food Sources

Chromium is widely distributed as chromite in the soil. Plants contain between 100 and 500 μg per kg and foods between 20 and 590 μg/kg (258). The form or availability of chromium in specific foods is generally not known. A balanced diet provides chromium with an average availability of 1% to 2%. Spices (>10 μg per g) and brewer's yeast (>40 μg per g) contain the highest concentrations. Meat products (1 to 2 μg per g), dairy products (1 to 1.5 μg per g), and eggs (1 to 2 μg per g) are good sources. Leafy vegetables contain chromium in a relatively unavailable form. Rice and sugar are poor sources. Estimates of daily intake are complicated by the availability of more soluble chromium compounds (picolinate, nicotinic acid) available over the counter in supplements at doses from 50 to 600 μg (39). The best diet to maximize chromium status is one low in simple sugars and rich in unprocessed foods.

Assessment

Measurement of chromium in tissues is difficult because of the very low levels. Serum levels (2.5 to 5.2 nmol per L) are 10 times lower than tissue concentrations and are not in

TABLE 7-51. Dietary Reference Intakes of Chromium

Life stage group	Chromium (μg/d)	Life stage group	Chromium (μg/d)
Infants		**Females**	
0–6 months	0.029/kg	9–13 years	25
7–12 months	0.611/kg	14–18 years	35
		19–50 years	35
Children		51–>70 years	30
1–3 years	11		
4–8 years	15	**Pregnancy**	
		14–18 years	29
Males		19–50 years	30
9–13 years	21		
14–18 years	24	**Lactation**	
19–50 years	25	14–18 years	44
51–>70 years	20	19–50	45

Estimates based on adequate intake (AI).
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC: National Academies Press, 2002.

equilibrium with the body stores (34). Serum levels increase rapidly as insulin levels increase and decrease with infection. Urine excretion is 1 to 20 nmol per L, but it correlates poorly with intake because absorption is so poor. Graphite furnace atomic absorption spectrometry is the method most often used. Hair levels are better related to body stores but still are affected by exogenous contamination, individual variations, and the other problems that beset this assay in the case of other trace minerals. Normal chromium levels in hair are about 990 ppm at birth; they fall to about 440 ppm after 2 or 3 years of life. The best way to diagnose chromium deficiency is to observe whether symptoms or signs that appear during total parenteral nutrition (hyperglycemia, neuropathy) respond to chromium infusion (248).

Physiology

Chromium is poorly absorbed (~1% to 2%) regardless of the level of intake or body stores. Oxalates and vitamin C increase and phytates and antacids decrease absorption (259). The hexavalent ion is absorbed better than trivalent chromium. Chromium picolinate and organic complexes from brewer's yeast or with nicotinic acid are absorbed better than the chloride salt. Excretion occurs mainly in the urine. A glucose load or insulin injection increases excretion, especially in diabetics. Trivalent chromium is required for normal glucose metabolism in animals, probably acting as a cofactor for insulin. A low-molecular-weight chromium-binding substance (LMWCr) has been identified as an oligopeptide that binds four chromium ions and activates the insulin receptor (258,260).

Deficiency

Deficiency has been noted after prolonged total parenteral nutrition (see Chapter 11). Glucose intolerance and impaired release of free fatty acids have been noted, along with increased circulating levels of insulin, neuropathy, encephalopathy, and hypercholesterolemia and hypertriglyceridemia (261). Deficiency is hard to document because no good method is available to assess body stores. It is generally agreed that chromium is an essential element, but the data are largely supportive and not definitive (262).

Treatment

IV administration of 5 to 10 μg of chromium chloride daily for the first few days, followed by 10 μg weekly, is probably adequate therapy. Chromium has been marketed as a weight loss aid and a muscle builder, and as an aid in glucose assimilation. However, no studies have shown a definite benefit in controlling diabetes or blood lipids, increasing lean body mass or decreasing body fat, improving muscle mass in athletes, or improving osteoporosis (39,262).

Toxicity

The hexavalent salt is more toxic than the trivalent salt in animals and has been associated with the production of lung tumors. No well-recognized toxic syndrome in humans has been reported. Thus, a UL has not been set (126). Randomized, controlled trials of 175 to 1,000 μg of chromium per day given from 6 to 64 weeks have shown no toxic effects (258). The Environmental Protection Agency has assigned a safety factor of 1,000 to chromium because of no observed adverse effect. This translates to a safe upper limit of 1.47 mg per kg per day. Isolated adverse effects have been reported, but their significance is not clear. Renal failure has been associated with chromium picolinate in two cases (258). The Expert Group on Vitamins and Minerals of the UK Joint Food Standards and Safety Group recommended in 2003 that the health supplement industry voluntarily withdraw chromium picolinate-containing products (262). The FDA is considering possible regulation of the sale of this compound, because of continued evidence of some toxicity. Headaches, sleep disturbances, and mood swings have been reported (39).

Selenium

Requirement

Selenium is an essential trace mineral that is a component of the enzyme glutathione peroxidase. Safe selenium requirements for adult Chinese men to prevent deficiency (Keshan disease) have been estimated at 40 μg per day, and two small supplementation studies suggested 70 and 55 μg per day as the intake required to achieve plateau concentrations of

TABLE 7-52. Selenium Dietary Reference Intakes and Tolerable Upper Intake Levels

Life stage group	DRI	UL	Life stage group	DRI	UL
	μg/d			μg/d	
Infants			**Males, Females**		
0–6 months	15[a]	45	9–13 years	40	280
7–12 months	20[a]	60	14–>70 years	55	400
Children			**Pregnancy**		
1–3 years	20	90	≤18–50 years	60	400
4–8 years	30	150	**Lactation**		
			≤18–50 years	70	400

[a] Estimated on adequate intake. All other DRI values represent recommended dietary allowances (RDAs). DRI, dietary reference intakes; UL, upper intake levels.
Adapted from Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Beta-carotene and Other Carotenoids.* Washington, DC: National Academies Press, 2000.

plasma glutathione peroxidase (263). To adjust for differences in weight and individual variation, the DRI for adults has been set at 55 μg per day, between the highest and lowest estimates (Table 7-52). Because selenium can be toxic, the ULs have been set not too far above the DRIs. The UL of 400 μg per day for adults is close to the reference dose of 5 μg per kg per day set by the Environmental Protection Agency.

Food Sources

Selenium is present in foods as selenomethionine or selenocysteine. Plant content varies with the soil content. Unlike in the United States, there are few selenium-rich food sources in the European diet. The development of deficiency syndromes in livestock in European countries led to measures to increase selenium intake, such as top dressing of pasture land with fertilizers to which selenium has been added, which may increase the soil content. Still, selenium intakes in many parts of Europe are lower than in the United States (264,265). Wheat is a good source of selenium in North America but not in Europe. Much of the selenium in grains is lost in the milling process. The selenium content of animal foods is affected by the selenium content of the animal feed. The best sources of selenium are Brazil nuts and kidney, neither a routine food. Moderately good sources include fish, shellfish, other organ meats, muscle meats, and whole grains. Fruits and vegetables are poor sources. Selenium intakes in the United States average 108 μg per day, with a range of 83 to 129 μg per day. In Europe, comparable values are lower, ranging from 29 to 70 μg per day (264). Food sources supply selenomethionine and selenocysteine, which are incorporated into proteins in place of methionine, but they must be catabolized to an inorganic precursor to form selenophosphate, the precursor for selenocysteine, the active form in selenoproteins. Supplements also provide selenomethionine; however, sometimes the more available selenate and selenite are provided, although they carry the risk for acute toxicity when taken in excess.

Assessment

Serum levels respond to changes in the diet but can be falsely lowered by any cause of hypoproteinemia. About half of the selenium in serum is incorporated into protein in selenoprotein P. After digestion of serum to remove organic material, a selenium complex is measured fluorometrically (34). Normal serum levels are 0.132 to 0.139 μg per mL. Selenium deficiency is defined as a plasma level ≤0.85 μg per mL (265). Red cells contain higher amounts (0.23 to 0.36 μg per mL of cells), and hemolysis can alter the serum levels. Low

serum levels are not associated with decreased cellular selenium and thus do not reflect body stores. Blood levels range from 3.14 to 3.32 μmol per L. Biologically active selenium can be estimated by measuring glutathione peroxidase in red cells (266). The correlation between these variables (enzyme and serum levels) has been inconsistent. This inconsistency has been resolved by the discovery that another protein, selenoprotein P, contains more than 60% of serum selenium in the rat. Hair content correlates with body stores in animals, but the determination is subject to the same problems of contamination and individual variation that arise in measuring the hair content of other trace metals.

Physiology

Liver and kidney contain the most selenium, with muscle, skin, and nails having the next highest concentrations. Inorganic selenium is poorly absorbed; organic (food) selenium is assimilated best into the body. The absorption rate is not regulated and is highest in the duodenum, varying from 60% to 80% in humans. Feces and urine are the usual excretory routes. Selenium is present in bile in low concentrations. It forms complexes with heavy metals and protects against cadmium and mercury toxicity. Selenium provides a system for intracellular redox regulation. The best-known example of this is its role as a cofactor of glutathione peroxidase, which reduces hydrogen peroxide and protects membranes from oxidative damage. Glutathione peroxidase is now known to be a family of at least six various selenoproteins, in different cellular locations, both intra- and extra-cellular (265). Some peroxidases are localized only to specific tissues (e.g., sperm, gastrointestinal mucosa). Selenium also plays a role in electron transfer functions and affects drug-metabolizing enzymes. Selenium is included as the selenoamino acid, selenocysteine, in more than 35 proteins, including thioredoxin reductase and the iodothyronine deiodinases that produce active thyroid hormone (264). The exact functional significance of this amino acid is not clear. Other selenoproteins include selenoprotein P (protecting endothelial cells against peroxynitrite), selenoprotein W (an antioxidant for cardiac and striated muscle), selenoprotein 18kDa (preserving kidney selenium), and selenoprotein N (associated with muscle dystrophy) (265,267). A number of selenoproteins still have no known function.

Deficiency

Definite. Only a few descriptions of a disorder in humans caused by dietary selenium deficiency have been published, even in areas where selenium deficiency in livestock is widespread. A cardiomyopathy that affected children was described in China (Keshan disease); it can be eliminated with oral selenium (268). Plasma and red cell selenium levels can fall during total parenteral nutrition without causing symptoms for 1 month (269). Common symptoms in these patients have been those of cardiomyopathy and myositis (265). A chondrodystrophy (Kashin-Beck disease) also occurs in selenium-deficient areas of China (270). Other causative factors are felt to be involved in both these conditions.

Possible. Deficiency of selenium is associated with loss of immunocompetency, and supplementation improves laboratory parameters of immune function; however, no clinical syndrome is associated with these changes (39). Deficiency has been linked to infection with some viruses, including HIV and coxsackievirus (264). Selenium is important for reproduction in animals, but the data on humans is inconclusive. Low selenium levels have been associated with depression, and high dietary levels of selenium seem to be associated with fewer such symptoms. Epidemiologic studies linking selenium deficiency to heart disease provide conflicting results. Evidence does not support a role for selenium in improving exercise function (39). Controlled interventions with supplements are needed to determine what role, if any, selenium has in these conditions. Perhaps the largest body of data on associated disorders comes from cancer prevention, particularly cancer of the prostate (265). An inverse relationship has been reported between plasma selenium concentration and risk of colorectal adenomas (271).

Treatment

Deficiency. If dietary deficiency occurs, 100 to 200 μg daily should be adequate therapy. Areas in the United States rich in selenium are the Great Plains and Rocky Mountain states, especially the Dakotas and Wyoming. If dietary selenium (in the form of seleno-amino

acids) is not considered adequate, a multivitamin/mineral tablet supplying 55 to 70 μg of selenium can be used. Organic forms (selenocysteine and selenocystine) have been used in recent years, but earlier preparations contained inorganic salts, such as selenite, selenium dioxide, and selenate. Sodium selenite is the most efficacious IV form.

Gastrointestinal Diseases. In severe malabsorption, a low serum level of selenium was almost always noted (272). Epidemiologic evidence has been found that higher plasma levels of selenium are associated with a decreased prevalence of intrahepatic cholestasis of pregnancy (273).

TABLE 7-53. Drugs that Alter Status of Minerals

↓[Na]s

Acetazolamide, carbamazepine, cyclophosphamide, chlorpropamide, furosemide, heparin, hydrochlorothiazide, morphine, oxytocin, pentamidine, selective serotonin reuptake inhibitors (SSRIs), spironolactone

↑[Na]s

Colchicine, ethacrynic acid, foscarnet, furosemide, hypertonic sodium salts, lithium, phenytoin, vinblastine

↑[K]s

Acetazolamide, amiloride, amphotericin B, ampicillin and derivatives, aspirin, beta-blockers, carboplatin, carmustine, corticosteroids, cytarabine, diuretics, intravenous dextrose, didanosine, dobutamine, dosorubicin, fluconazole, foscarnet, ganciclovir, gentamicin, insulin, itraconazole, levodopa, lithium, metolazone, nifedipine, ondansetron, pamidronate, phosphates, polymyxin B, rifampin, risperidone, salmeterol, sargramostim, sirolimus, sodium salts, sorbitol, SSRIs, tacrolimus, terbutaline, tobramycin, torsemide, vincristine

↑[K]s

Amiloride, beta-blockers, captopril and related drugs, cotrimoxazole, cyclosporine, heparin, NSAIDs, pentamidine, potassium salts, spironolactone, tacrolimus, triamterene

↓[Mg]s

Albuterol, amphotericin B, carboplatin, cholestyramine, cisplatin, corticosteroids, cyclosporine, didanosine, digoxin, diuretics, estrogen, ethanol, foscarnet, gentamicin, insulin, laxatives, oral contraceptives, penicillamine, pentamidine, phosphates, sargramostim, tacrolimus, tobramycin, torsemide, zoledronic acid

↑[Mg]s

Lithium, magnesium salts

↓[PO_4]s

Acetazolamide, Al-Mg antacids, bisphosphonates, calcitonin, calcium salts, carmustine, cefotan, cholestyramine, cisplatin, digoxin, ethanol, foscarnet, magnesium, osmotic diuretics, sevelamer, sirolimus/tacrolimus, zoledronic acid

↑[PO_4]s

Phosphate salts

↓[Ca]s

Antacids, bleomycin, calcitonin, carboplatin, cholestyramine, cisplatin, codeine, corticosteroids, cyclosporine, diuretics, doxorubicin, estrogens, fluoride, 5-fluorouracil, foscarnet, H_2 receptor antagonists, interferon, isoniazid, ketoconazole, macrolide antibiotics, magnesium, pentamidine, phenytoin, phosphates, rituximab, sargramostim, triamterene

↑[Ca]s

Calcium salts, ganciclovir, lithium, thiazide diuretics, tamoxifen, theophylline

Adapted from Boullata JI, Influence of medication on nutritional status. In *Preventive Nutrition*. 3rd ed. Bendich A, Deckelbaum RJ, Sommer A. Totowa, NJ: Humana Press, 2006:833.

Cancer Chemoprevention. Supplements of selenium given to patients in many regions with selenium-poor soil and foods have been shown to prevent liver and esophageal cancer in China, oral cancer in India, and colon cancer in Italy (274). However, the quality of many of these studies is uncertain, as studies used either mixed or single supplements, the form of selenium was often unknown, and the statistics were often not well described. The evidence for prevention of prostate cancer shows that apparent benefit is limited to those with low basal plasma selenium, and/or those who smoke (275). The Nutritional Prevention of Cancer trial showed a lower rate of cancers of the skin, prostate, colon, and lung in those receiving 200 μg per day of selenium, but the greatest benefit was found in patients with the lowest basal selenium levels (276). This study has been extended as the Prevention of Cancer by Intervention with Selenium (PRECISE) treating with 200 μg or 400 μg per day for 5 years, to see if the results of the original study can be validated.

Toxicity. A UL for selenium intake has been set at 400 μg per day, and clinical toxicity resulting from much higher intakes in overly potent tablets (>20 mg per tablet) has been reported (263). Nausea, vomiting, fatigue, hair loss, diarrhea, irritability, paresthesias, and abdominal cramps have been reported. Ingestion of 5 mg per day in the diet in Enshi County, China, led to loss of hair and nails, skin lesions, tooth decay, and nervous system abnormalities (277). Toxic symptoms are found with blood selenium levels above 13.3 μmol per L, but urinary measurements are probably a better indicator of toxicity. Urinary levels should be <100 μg per L to avoid selenium toxicity (34).

DRUGS THAT AFFECT MINERAL STATUS

A number of drugs cause minerals to be lost from the body in either urine or feces. The use of such drugs may cause or intensify a deficiency of a given mineral. Table 7-53 lists some of these drugs and the changes in serum levels of the minerals affected. The use of laxatives can lead to sodium and water depletion and dehydration, usually with no change in the serum sodium level. Potassium is secreted from the colon under these conditions, and hypokalemia results. Sodium depletion presents clinically when diuretics are used in the absence of sodium overload syndrome. Diuretics can exacerbate hypomagnesemia but usually do not cause it when body stores are normal. Some drugs cause changes in body stores without altering serum concentrations of the mineral. For example, glucocorticoids are associated with osteopenia, which is not a result of decreased calcium stores alone; abnormal vitamin D metabolism is probably also involved. Other drugs can alter serum concentrations without altering body stores. For example, Neutrophos treatment can cause hypocalcemia without a decrease in body calcium stores.

References

1. Remer T. Influence of diet on acid-base balance. *Semin Dial.* 2000;13:221.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate.* Washington DC: National Academies Press, 2005.
3. Elgart HN. Assessment of fluids and electrolytes. *AACN Clin Issues.* 2004;15:607.
4. Zalepuga R, Di Palma JA. Metals. *Pract Gastroenterol.* 2002;25:14.
5. Manton WI, Angle CR, Krogstrand KL. Origin of lead in the United States diet. *Environ Sci Technol.* 2005;39:8995.
6. McCarron DA. The dietary guidelines for sodium: should we shake it up? Yes! *Am J Clin Nutr.* 2000;71:1013.
7. Craddick SR, Elmer PJ, Obarzanek E, et al. The DASH diet and blood pressure. *Curr Atheroscler Rep.* 2003;5:484.
8. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med.* 2001;344:3.
9. He FJ, Markandu ND, Sagnella GA, et al. Plasma sodium: ignored and underestimated. *Hypertension.* 2005;45:98.
10. Alderman MH. Dietary sodium and cardiovascular health in hypertensive patients: the case against universal sodium restriction. *J Am Soc Nephrol.* 2004;15:S47.
11. Hooper L, Bartlett C, Davey SG, Ebrahim S. Advice to reduce dietary salt for prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2004;(1):CD003656.

12. He JF, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev.* 2004;(3):CD004937.
13. Krousel-Wood MA, Muntner P, He J, Whelton PK. Primary prevention of essential hypertension. *Med Clin North Am.* 2004;88:223.
14. Sawka MN, Montain SJ. Fluid and electrolyte balance: effects on thermoregulation and exercise in the heat. in *Present Knowledge in Nutrition.* 8th ed. Bowman BA, Russell RM, eds., Washington DC: ILSI Press, 2001:115.
15. McGee S, Abernethy WB, Simel DL. Is this patient hypovolemic? *JAMA.* 1999;281:1022.
16. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology.* 1996;46:1470.
17. Streeten DH. Variations in the clinical manifestations of orthostatic hypotension. *Mayo Clin Proc.* 1995; 70:713.
18. Martin MG, Wright EM. Disorders of epithelial transport in the small intestine. In *Textbook of Gastroenterology*, 5th ed. Yamada T, Alpers DH, Kaplowitz N, et al. (eds.), Oxford, UK: Blackwell Publishing, Ltd., 2007:2088.
19. Eisenhut M. Changes in ion transport in inflammatory diseases. *J Inflamm (Lond).* 2006;3:5.
20. Zachos NC, Tse M, Donowitz M. Molecular physiology of intestinal Na^+/H^+ exchange. *Annu Rev Physiol.* 2005;67:411.
21. Marcet B, Boeynaems JM. Relationships between cystic fibrosis transmembrane conductance regulator, extracellular nucleotides and cystic fibrosis. *Pharmacol Therap.* 2006;112:719.
22. Miller C. ClC chloride channels viewed through a transporter lens. *Nature.* 2006;440:484.
23. Puljak L, Kilic G. Emerging roles of chloride channels in human diseases. *Biochim Biophys Acta.* 2006;1762:404.
24. Alpers SL. Molecular physiology of SLC4 anion exchangers. *Exp Physiol.* 2006;91:153.
25. Mount DB, Romero MF. The SLC26 gene family of multifunctional anion exchangers. *Pflugers Arch.* 2004;447:710.
26. Anonymous. Lubiprostone: RU 0211, SPI 0211. *Drugs RD.* 2005;6:245.
27. Adrogue HJ, Madias N. Hyponatremia. *N Engl J Med.* 2000;342:1581.
28. Sentongo TA. The use of oral rehydration solutions in children and adults. *Curr Gastroenterol Rep.* 2004;6:307.
29. Alpers DH. Oral rehydration solutions for adults: an underutilized resource. *Curr Opin Gastroenterol.* 1998;14:143.
30. Hahn S, Kim S, Garner P. Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhea in children. *Cochrane Database Syst Rev.* 2002;(1):CD002847.
31. Ramakrishna RB, Venkataraman S, Srinivasan P, et al. Amylase-resistant starch plus oral rehydration solution for cholera. *N Engl J Med.* 2000;342:308.
32. Matarese LE, O'Keefe SJ, Kandil HM, et al. Short bowel syndrome: clinical guidelines for nutrition management. *Nutr Clin Pract.* 2005;20:493.
33. Adrogue HJ, Madias NE. Hypernatremia. *N Engl J Med.* 2000;342:1493.
34. Sauberlich HE. *Laboratory Tests for the Assessment of Nutritional Status.* 2nd ed. Boca Raton, FL: CRC Press, 1999.
35. Halperin ML, Kamel KS. Potassium. *Lancet.* 1998;352:135.
36. Warth R, Barhanin J. Function of K^+ channels in the intestinal epithelium. *J Memb Biol.* 2003;193:67.
37. Gennari FJ. Hypokalemia. *N Engl J Med.* 1998;339:451.
38. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA.* 1997;277:1624.
39. Fragakis AS. *The Health Professional's Guide to Popular Dietary Supplements.* 2nd ed. Hoboken NJ: John Wiley & Sons, Inc., 2002.
40. Evans KJ, Greenberg A. Hyperkalemia: a review. *J Intensive Care Med.* 2005;20:272.
41. Heaney RP. Osteoporosis: Protein, minerals, vitamins, and other micronutrients. In *Preventive Nutrition: The Comprehensive Guide for Health Professionals.* 3rd ed. Bendich A, Deckelbaum RJ, Sommer A (eds.), Totowa, NJ: Humana Press, 2005:433.
42. Fairweather-Tait, SJ, Teucher B. Iron and calcium bioavailability of fortified foods and dietary supplements. *Nutr Rev.* 2002;60:360.
43. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: National Academies Press, 1997.
44. Kerstetter JE, O'Brien KO, Insogna KL. Low protein intake: the impact on calcium and bone homeostasis in humans. *J Nutr.* 2003;133:855S.
45. Nordin C. Calcium requirement is a sliding scale. *Am J Clin Nutr.* 2000;71:1381.
46. Food and Drug Administration. Food labeling: health claims, calcium and osteoporosis. *Fed Regist.* 1993;58:2665.
47. National Institutes of Health. Optimal calcium intake. *NIH Consensus Statement.* 1994;12:1.
48. Miller GD, Heaney RP, Specker BL. Year 2000 dietary guidelines: new thoughts for a new millennium. There should be a dietary guideline for calcium; should there be a dietary guideline for calcium intake? No. *Am J Clin Nutr.* 2000;71:657.

49. Lanou AJ, Berkow SE, Barnard ND. Calcium, dairy products, and bone health in children and young adults: a reevaluation of the evidence. *Pediatrics*. 2005;115:736.
50. Abrams SA, Atkinson SA. Calcium, magnesium, phophorus and vitamin D fortification of complementary foods. *J Nutr.* 2003;133:2994S.
51. Smith GR, Collinson PO, Kiely PD. Diagnosing hypovitaminosis D: serum measurements of calcium, phosphate, and alkaline phosphatase are unreliable, even in the presence of secondary hyperparathyroidism. *J Rheumatol.* 2005;32:684.
52. Alexeera L, Burkhardt P, Christiansen C, et al. Assessment of fracture risk and application of screening for postmenopausal osteoporosis. *World Health Organization Technical Report Series 843*. Geneva: World Health Organization, 1994.
53. Baddiyra R, Awada H, Okais J, et al. An audit of bone densitometry practices with reverence to ISCD, IOF, and NOF guidelines. *Osteoporos Int*. 2006;17:1111.
54. Raisz LG. Screening for osteoporosis. *N Engl J Med*. 2005;353:164.
55. Moayyeri A, Soltani A, Bahrami H, et al. Preferred skeletal site for osteoporosis screening in high-risk populations. *Public Health*. 2006 Jul 24;120:863.
56. Hodgson SF, Johnston CC. AACE clinical practice guidelines for the prevention and treatment of postmenopausal osteoporosis. *Endocr Pract*. 1996;2:155.
57. Kanis J, Devogelaer J, Gennari C. Practical guide for the use of bone mineral measurements in the assessment of treatment of osteoporosis: a position paper of the European Foundation for Osteoporosis and Bone Disease. *Osteoporos Int*. 1996;6:256.
58. Bonnick SL. *Bone Densitometry in Clinical Practice: Application and Interpretation.* Totowa, NJ: Humana Press, 1998.
59. Bone mass measurement act (BMMA). *Fed Regist*. 1998;63:34324.
60. Bronner F, Pansu D. Nutritional aspects of calcium absorption. *J Nutr.* 1999;129:9.
61. Lewiecki EM, Watts NB, McClung MR, et al. Official positions of the International Society for Clinical Densitometry. *J Clin Endocrinol Metab*. 2004;89:3651.
62. Hans D, Downs RW Jr, Duboeuf F, et al. Skeletal sites for osteoporosis diagnosis: the 2005 ISCD official positions. *J Clin Densitom*. 2006;9:15.
63. De Laet C, Kanis JA, Oden A, et al. Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporosis Int*. 2005;16:1330.
64. Dargent-Molina P. Bone density measurement in older women: who and why? *Joint Bone Spine*. 2004;71:264.
65. Faibish D, Ott SM, Boskey AL. Mineral changes in osteoporosis: a review. *Clin Orthop Relat Res*. 2006;443:28.
66. Schonau E. The peak bone mass concept: is it still relevant? *Pediatr Nephrol*. 2004;19:825.
67. Kleerekoper M, Nelson DA. BMD testing appropriate for all menopausal women? *Int J Fertil Womens Med*. 2005;50:61.
68. Shepherd JA, Lu Y, Wilson K, et al. Cross-calibration and minimum precision standards for dual-energy x-ray absorptiometry: the 2005 ISCD official positions. *J Clin Densitom*. 2006;9:31.
69. Bachrach LK. Measuring bone mass in children: can we really do it? *Horm Res*. 2006;65 (suppl 2):11.
70. Dennison E, Cole Z, Cooper C. Diagnosis and epidemiology of osteoporosis. *Curr Opin Rheumatol*. 2005;17:456.
71. Ramasamy I. Recent advances in physiological calcium homeostasis. *Clin Chem Lab Med*. 2006;44:237.
72. McLarnon SJ, Riccardi D. Physiological and pharmacological agonists of the extracellular Ca^{2+}-sensing receptor. *Eur J Pharmacol*. 2002;447:271.
73. Deroisy A, Zartarian M, Meurmans L, et al. Acute changes in serum calcium and parathyroid hormone circulating levels induced by the oral intake of five currently available calcium salts in healthy male volunteers. *Clin Rheumatol*. 1997;16:249.
74. Recker RR. Calcium absorption and achlorhydria. *N Engl J Med*. 1985;313:70.
75. Hoenderop JGJ, Bindels RJM. Epithelial Ca^{2+} and Mg^{2+} channels in health and disease. *J Am Soc Nephrol*. 2005;16:15.
76. Anonymous. Calcium deficiency. *Lancet*. 1985;1:1431
77. Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *J Clin Invest*. 2005;115:3318.
78. Coates PS, Fernstrom JD, Fernstrom MH, et al. Gastric bypass surgery for morbid obesity leads to an increase in bone turnover and a decrease in bone mass. *J Clin Endocrinol Metab*. 2004;89:1061.
79. Dickerson RN, Morgan LG, Caughen AD, et al. Treatment of acute hypocalcemia in critically ill multiple-trauma patients. *JPEN J Parenter Enteral Nutr.* 2005;29:436.
80. Thacher TD, Fischer PR, Pettifor JM, et al. A comparison of calcium, vitamin D, or both for nutritional rickets in Nigerian children. *N Engl J Med*. 1999;341:563.
81. Kalkwarf HJ, Specker BL, Bianchi DC, et al. The effect of calcium supplementation on bone density during lactation and after weaning. *N Engl J Med*. 1997; 337:523.
82. Scott EM, Gaywood I, Scott BB. British Society of Gastroenterology: Guidelines for osteoporosis in coeliac disease and inflammatory bowel disease. *Gut*. 2000; 46(Suppl 1):1.
83. Compston JE. Management of bone disease in patients on long-term glucocorticoid therapy. *Gut*. 1999;44:770.

84. Andreassen H, Rungby J, Dahlerup F, et al. Inflammatory bowel disease and osteoporosis. *Scand J Gastroenterol.* 1997;32:1247.
85. Storm D, Eslin R, Porter ES, et al. Calcium supplementation prevents seasonal bone loss and changes in biochemical markers of bone turnover in elderly New England women: a randomized placebo-controlled trial. *J Clin Endocrinol Metab.* 1998;83:3817.
86. Nieves JW, Komar L, Cosman F, et al. Calcium potentiates the effect of estrogen and calcitonin on bone mass: a review and analysis. *Am J Clin Nutr.* 1998;67:18.
87. Recker RR, Davies KM, Dowd RM, et al. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women: a randomized, controlled trial. *Ann Intern Med.* 1999;130:897.
88. Porthouse J, Cockayne S, King C, et al. Randomized controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ.* 2005;330:1003.
89. Grant AM, Avenell A, Campbell MK and the RECORD trial group. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomized Evaluation of Calcium OR vitamin D, RECORD): a randomized placebo-controlled trial. *Lancet.* 2005;365:1671.
90. Allender PS, Cutler JA, Follman D, et al. Dietary calcium supplementation on blood pressure: a meta-analysis of randomized clinical trials. *Ann Intern Med.* 1996;124:825.
91. Bucher HC, Cook RJ, Gfuyatt GH, et al. Effects of dietary calcium supplementation on blood pressure. A meta-analysis of randomized controlled trials. *JAMA.* 1996;275:1016.
92. Bostick RM. Human studies of calcium supplementation and colorectal epithelial cell proliferation. *Cancer Epidemiol Biomarkers Prev.* 1997;6:971.
93. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med.* 1999;341:101.
94. Rhys-Jacobs S, Starkey P, Bernstein D, et al. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group. *Am J Obstet Gynecol.* 1998;179:444.
95. Anonymous. Drugs for prevention and treatment of postmenopausal osteoporosis. *Med Lett.* 2002;1:13.
96. Heaney RP. Calcium supplements: practical considerations. *Osteoporos Int.* 1991;1:65.
97. Durlach J, Pages N, Bac P, et al. New data on the importance of gestational Mg deficiency. *Magnes Res.* 2004;17:116.
98. Karppanen H, Karppanen P, Mervaala E. Why and how to implement sodium, potassium, calcium, and magnesium changes in food items and diets? *J Human Hypertens.* 2005;19:S10.
99. Tong GM, Rude RK. Magnesium deficiency in critical illness. *J Intensive Care Med.* 2005;20:3.
100. Simon DB, Lu Y, Choate KA, et al. Paracellin-1, a renal tight junction protein required for paracellular Mg2+ resorption. *Science.* 1999;285:103.
101. Chubanov V, Gudermann T, Schlingmann KP. Essential role for TRPM6 in epithelial magnesium transport and body magnesium homeostasis. *Pfllugers Arch-Eur J Physiol.* 2005;451:228.
102. Schweigel M, Martens H. Magnesium transport in the gastrointestinal tract. *Front Biosci.* 2000;5:D666.
103. Levine BS, Coburn JW. Magnesium, the mimic/antagonist to calcium. *N Engl J Med.* 1984;310;1253.
104. Weisinger JR. Magnesium and phosphorus. *Lancet.* 1998;352:391.
105. Graber ML, Schulman G. Hypomagnesemic hypocalcemia independent of parathyroid hormone. *Ann Intern Med.* 1986;104:804.
106. Reinhart RA. Magnesium metabolism: A review with special reference to the relationship between intracellular content and serum levels. *Arch Intern Med.* 1988;148:2415.
107. Kudenchuk PJ. Advanced cardiac life support antiarrhythmic drugs. *Cardiol Clin.* 2002;20:79.
108. Mouw DR, Latessa RA, Sullo EJ. What are the causes of hypomagnesemia? *J Family Pract.* 2005;54:174.
109. Fleming CR, George L, Stoner GL, et al. The importance of urinary magnesium values in patients with gut failure. *Mayo Clin Proc.* 1996;71:21.
110. Duley L, Farrell B, Spark P, et al. MAGPIE Trial Collaboration Group. Do women with pre-eclampsia and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomized placebo controlled trial. *Lancet.* 2002;359:1877.
111. Cummins RO, Hazinski MF, Baskett PJ, et al, The American Heart Association and the International Liaison Committee on Resuscitation. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2000;102(Suppl):1.
112. Fine KD, Santa Ana CA, Porter JL, et al. Intestinal absorption of magnesium from food and supplements. *J Clin Invest.* 1991;88:396.
113. Rodriguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care.* 2003;26:1147.
114. Shils ME. Magnesium. In: Shils ME, Olson JA, Shike M, et al., eds. *Modern Nutrition in Health and Disease,* 10th ed. Philadelphia: Lea & Febiger, 1999:169.
115. McGartland C, Robson PJ, Murray L, et al. Carbonated soft drink consumption and bone mineral density in adolescence: the Northern Ireland Young Hearts Project. *J Bone Miner Res.* 2003;18:1563.
116. Takeda E, Yamamoto H, Nashiki K, et al. Inorganic phosphate homeostasis and the role of dietary phosphorus. *J Cell Mol Med.* 2004;8:191.

117. Knochel JP. The clinical status of hypophosphatemia: an update. *N Engl J Med*. 1985;313:447.
118. LaRoche M. Phosphate, the renal tubule, and the musculoskeletal system. *Joint Bone Spine*. 2001;68:211.
119. Brame LA, White KE, Econs MJ. Renal phosphate wasting disorders: clinical features and pathogenesis. *Semin Nephrol*. 2004;24:39.
120. Knochel JP. The pathophysiology and clinical characteristics of severe hypophosphatemia. *Arch Intern Med*. 1977;137:203.
121. van der Veere CN, Jansen PLM, Sinaasappel M, et al. Oral calcium phosphate: a new therapy for Crigler-Najjar disease? *Gastroenterology*. 1997;112:455.
122. Brown KA, Dickerson RN, Morgan LM, et al. A new graduated dosing regimen for phosphorus replacement in patients receiving nutrition support. *JPEN J Parenter Enteral Nutr*. 2006;30:209.
123. Marinella MA. The refeeding syndrome and hypophosphatemia. *Nutr Rev*. 2003;61:320.
124. Brown AR, DiPalma JA. Bowel preparations for gastrointestinal procedures. *Curr Gastroenterol Rep*. 2004;6:395.
125. Schwetz BA. Review: oral sodium phosphate. *JAMA*. 2001;286:2660.
126. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academies Press, 2002.
127. Hunt JR. Bioavailability of iron, zinc, and other trace minerals from vegetarian diets. *Am J Clin Nutr*. 2003;78(Suppl):633S.
128. Michels Blanck H, Cogswell ME, Gillespie C, Reyes M. Iron supplement use and iron status among US adults: results from the third National Health and Nutrition Examination Survey. *Am J Clin Nutr*. 2005;82:1024.
129. Lopez MA, Martos FC. Iron availability: an updated review. *Int J Food Sci Nutr*. 2004;55:597.
130. Whittaker P, Tufaro PR, Rader JI. Iron and folate in fortified cereals. *J Am Coll Nutr*. 2001;20:247.
131. Hastka J, Lasserre J-J, Schwarzbeck A, et al. Laboratory tests of iron status: correlation or common sense? *Clin Chem*. 1996;42:5.
132. Wormwood M. The laboratory assessment of iron status—an update. *Clin Chim Acta*. 1997;259:3.
133. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352:1011.
134. Finch CA, Cook JD. Iron deficiency. *Am J Clin Nutr*. 1984;39:471.
135. Sackett DL, Richardson WS, Rosenberg W, et al. *Evidence-based Medicine*. New York: Churchill Livingstone, 1997:124.
136. Aguilar-Martinez P, Schved JF, Brissot P. The evaluation of hyperferritinemia: an updated strategy based on advances in detecting genetic abnormalities. *Am J Gastroenterol*. 2005;100:1185.
137. Beguin Y. Soluble transferring receptor for the evaluation of erythropoiesis and iron status. *Clin Chim Acta*. 2003;329:9.
138. Eschbach JW. Iron requirements in erythropoietin therapy. *Best Pract Res Clin Haematol*. 2005;18:347.
139. Guyatt GH, Oxman AD, Ali M, et al. Laboratory diagnosis of iron-deficiency anemia: an overview. *J Gen Intern Med*. 1992;7:145.
140. Psaty BM, Tierney WM, Martin DK, et al. The value of serum iron studies as a test for iron-deficiency anemia in a county hospital. *J Gen Intern Med*. 1989;2:160.
141. Thompson WG, Meola T, Lipkin M Jr, et al. Red cell distribution width, mean corpuscular volume, and transferrin saturation in the diagnosis of iron deficiency. *Arch Intern Med*. 1988;148:2128.
142. Adams PC. Population screening for hemochromatosis. *Hepatology*. 1999;29:1324.
143. Whitlock EP, Garlitz BA, Harris EL, et al. Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2006;145:209.
144. Cook JD. Adaptation in iron metabolism. *Am J Clin Nutr*. 1990;51:301.
145. Andrews NC, Fleming MD, Gunshin H. Iron transport across biologic membranes. *Nutr Rev*. 1999;57:114.
146. Anderson GJ, Frazer DM. Recent advances in intestinal iron transport. *Curr Gastroenterol Rep*. 2005;7:365.
147. van Dokkum W. Significance of iron bioavailability for iron recommendations. *Biol Trace Elem Res*. 1992;35:1.
148. Zoller H, Pietrangelo A, Vogel W, et al. Duodenal metal-transporter (DMT-1, NRAMP-2) expression in patients with hereditary hemochromatosis. *Lancet*. 1999;353:2120.
149. Andrews NC, Schmidt PJ. Iron homeostasis. *Annu Rev Physiol*. 2007;69:1.
150. Latunda-Dada GO, Simpson RJ, McKie AT. Recent advances in mammalian haem transport. *Trends Biochem Sci*. 2006;31:182.
151. Finch CA, Huebers W. Perspectives in iron metabolism. *N Engl J Med*. 1982; 306:1520.
152. Theil EC. The iron responsive element (IRE) family of mRNA regulators: regulation of iron transport and uptake compared in animals, plants, and microorganisms. *Met Ions Biol Syst*. 1998;35:403.
153. Ganz T, Nemeth E. Regulation of iron acquisition and iron distribution in mammals. *Biochim Biophys Acta*. 2006;1763:690.
154. Sargent PJ, Farnaud S, Evan RW. Structure/function overview of proteins involved in iron storage and transport. *Curr Medicinal Chem*. 2005;12:2683.

155. Lozoff B, Jimenez E, Hagen J, et al. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics.* 2000;105:E51.
156. Gordon N. Iron deficiency and intellect. *Brain & Development.* 2003;25:3.
157. Andrews NC. Disorders of iron metabolism. *N Engl J Med.* 1999;341:1986.
158. Khaodhiar L, Keane-Ellison M, Tawa NE, et al. Iron deficiency anemia in patients receiving home total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2002;26:114.
159. O'Keefe ST. Secondary causes of restless leg syndrome in older people. *Age Aging.* 2005;34:349.
160. Connor JR, Boyer PJ, Menzies SL, et al. Neuropathological examination suggests impaired brain iron acquisition in restless leg syndrome. *Neurology.* 2003;61:304.
161. Haba-Rubio J, Staner L, Petiau C, et al. Restless legs syndrome and low brain iron levels in patients with haemochromatosis. *J Neurol Neurosurg Psychiatry.* 2005;76:1009.
162. Sloand JA, Shelly MA, Feigin A, et al. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. *Am J Kidney.* Dis 2004;43:663.
163. De Silva AD, Mylanoki M, Rampton DS. Oral iron therapy in inflammatory bowel disease: usage, tolerance, and efficacy. *Inflamm Bowel Dis.* 2003;9:316.
164. Seligman PA, Caskey JH, Frazier JL, et al. Measurements of iron absorption from prenatal vitamin–mineral supplements. *Obstet Gynecol.* 1983;61:356.
165. Van Iperen CE, Kraaijenhagen RJ, Biesma DH, et al. In early period after surgery, iron cannot be utilized due to the inflammatory process. *Br J Surg.* 1998;85:41.
166. Ganz T. Molecular pathogenesis of anemia of chronic disease. *Pediatr Blood Cancer.* 2006;46:554.
167. Verdon F, Burnard B, Stubi CL, et al. Iron supplementation for unexplained fatigue in non-anemic women: double-blind randomized placebo controlled trial. *BMJ.* 2003;326:1124.
168. Burns DL, Mascioli EA, Bistrian BR. Effect of iron-supplemented total parenteral nutrition in patients with iron deficiency anemia. *Nutrition.* 1996;12:411.
169. Kumpf VJ. Update on parenteral iron therapy. *Nutr Clin Pract.* 2003;18:318.
170. Koutroubakis IE, Karmiris K, Makreas S, et al. Effectiveness of darbepoetin-alfa in combination with intravenous iron sucrose in patients with inflammatory bowel disease and refractory anemia: a pilot study. *Eur J Gastroenterol Hepatol.* 2006;18:421.
171. Auerbach M, Witt D, Toler W, et al. Clinical use of the total dose intravenous infusion of iron dextran. *J Lab Clin Med.* 1988;111:566.
172. Auerbach M, Winchester J, Wahab A, et al. A randomized trial of three iron dextran infusion methods for anemia in EPO-treated dialysis patients. *Am J Kidney Dis.* 1998;31:81.
173. National Kidney Foundation. Clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis.* 2000;35(6 Suppl 2):S1.
174. Silverstein SB, Rodgers GM. Parenteral iron therapy options. *Am J Hematol.* 2004;76:74.
175. Bailie GR, Clark JA, Lane CE, Lane PL. Hypersensitivity reactions and deaths associated with intravenous iron preparations. *Nephrol Dial Transplant.* 2005;20:1443.
176. Donangelo CM, Zapata CL, Woodhouse LR, et al. Zinc absorption and kinetics during pregnancy and lactation in Brazilian women. *Am J Clin Nutr.* 2005;82:118.
177. Hunt JR, Matthys LA, Johnson LK. Zinc absorption, mineral balance, and blood lipids in women consuming lactoovovegetarian and omnivorous diets for 8 weeks. *Am J Clin Nutr.* 1998;67:421.
178. Brown KH, Peerson JM, Allen LH. Effect of zinc supplementation on children's growth: a meta-analysis of intervention trials. In: Sandstrom B, Walter P, eds. *Role of Trace Elements for Health Promotion and Disease Prevention.* Davis, CA: University of California, 1998:76.
179. Briefel RR, Bialostosky K, Kennedy-Stephenson J, et al. Zinc intake of the U.S. population: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. *J Nutr.* 2000;130:1367S.
180. Freeland-Graves J. Mineral adequacy of vegetarian diets. *Am J Clin Nutr.* 1988;48:859.
181. King JE. Assessment of zinc status. *J Nutr.* 1990;120(Suppl 11):1474.
182. Wiesman K, Hoyer H. Serum alkaline phosphatase and serum zinc levels in the diagnosis and exclusion of zinc deficiency in man. *Am J Clin Nutr.* 1985;41:1214.
183. Wood RJ. Assessment of marginal zinc status in humans. *J Nutr.* 2000;130: 1350S.
184. Blanchard RK, Cousins RJ. Regulation of intestinal gene expression by dietary zinc: induction of uroguanylin mRNA by zinc deficiency. *J Nutr.* 2000;130:1393S.
185. Eide DJ. Zinc transporters and the cellular trafficking of zinc. *Biochim Biophys Acta.* 2006;1763:711.
186. Cousins RJ, Liuzzi JP, Lichten LA. Mammalian zinc transport, trafficking, and signals. *J Biol Chem.* 2006;281:24085.
187. Cousins RJ. Zinc. In Ziegler EK, Filer LJ. *Present Knowledge in Nutrition,* 7th ed. Washington DC: ILSI, 1996:293.
188. Wang K, Zhou B, Kuo YM, et al. A novel member of a zinc transporter family is defective in acrodermatitis enteropathica. *Am J Hum Genet.* 2002;71:66.
189. Kim RE, Wang F, Dufner-Beattie J, et al. Zn^{2+}-stimulated endocytosis of the mZIP4 zinc transporter regulates its location at the plasma membrane. *J Biol Chem.* 2004;279:4523.
190. Krebs NF. Overview of zinc absorption and excretion in the human gastrointestinal tract. *J Nutr.* 2000;130:1374S.
191. Mills CF. Dietary interactions involving the trace elements. *Annu Rev Nutr.* 1985;5:173.

192. Whittaker P. Iron and zinc interactions in humans. *Am J Clin Nutr.* 1998;68:442S.
193. Lonnerdal B. Dietary factors influencing zinc absorption. *J Nutr.* 2000;130:1378S.
194. Stewart AJ, Blindauer CA, Berezenko S, et al. Interdomain zinc site on human albumin. *Proc Natl Acad Sci USA*. 2003;100:3701.
195. Gaither LA, Eide DJ. Eurkaryotic zinc transporters and their regulation. *BioMetals*. 2001;14:251.
196. Fraker PJ, King LE, Laakko T, et al. The dynamic link between the integrity of the immune system and zinc status. *J Nutr.* 2000;130:1399S.
197. Rink L, Kirchner H. Zinc-altered immune function and cytokine production. *J Nutr.* 2000;130:1407S.
198. Haase H, Mocchegiani E, Rink L. Correlation between zinc status and immune function in the elderly. *Biogerontology.* 2006;7:421.
199. Prasad AS. Zinc deficiency in women, infants, and children. *J Am Coll Nutr.* 1996;15:113.
200. Wapnir RA. Zinc deficiency: malnutrition and the gastrointestinal tract. *J Nutr.* 2000;130:1388S.
201. Osaki T, Ohshima M, Tomita Y, et al. Clinical and physiological investigations in patients with taste abnormality. *J Oral Pathol Med*. 1996;25:38.
202. Henkin RI, Schecter PJ, Friedewald WT, et al. A double blind study of the effects of zinc sulfate on taste and smell dysfunction. *Am J Med Sci.* 1976;272:285.
203. Bhutta ZA, Bird SM, Black RE, et al. Therapeutic effects of oral zinc in acute and persistent diarrhea in children in developing countries: pooled analysis of randomized controlled trials. *Am J Clin Nutr.* 2000;72:1516.
204. Meunier N, O'Connor JM, Maiani G, et al. Importance of zinc in the elderly: the ZENITH study. *Eur J Clin Nutr.* 2005;59(Suppl2):S1.
205. Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. *Cochrane Database Syst Rev.* 2006;(2):CD000254.
206. Fischer Walker C, Kordas K, Stoltzfus RJ, Black RE. Interactive effects of iron and zinc on biochemical and functional outcomes in supplementation trials. *Am J Clin Nutr.* 2005;82:5.
207. Marshall I. Zinc for the common cold. *Cochrane Database Syst Rev.* 2000;(2):CD001364.
208. Marshall S. Zinc gluconate and the common cold. Review of randomized controlled trials. *Can Fam Physician.* 1998;44:1037.
209. Prasad AS, Fitzgerald JT, Bao B, et al. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2000;13:245.
210. Hulisz D. Efficacy of zinc against common cold viruses: an overview. *J Am Pharm Assoc*. 2004;24:255.
211. Bhutta ZA, Black RE, Brown KH, et al. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. *J Pediatrics*. 1999;135:689.
212. Brooks WA, Santosham M, Naheed A, et al. Effect of weekly zinc supplements on incidence of pneumonia and diarrhea in children younger than 2 years in an urban, low-income population in Bangladesh: randomized controlled trial. *Lancet*. 2005;366:999.
213. Hambridge M. Human zinc deficiency. *J Nutr.* 2000;130:1344S.
214. Fosmire GJ. Zinc toxicity. *Am J Clin Nutr* 1990;51:225.
215. Hedera P, Fink JK, Bockenstedt PL, Brewer GJ. Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin: further support for existence of a new zinc overload syndrome. *Arch Neurol.* 2003;60:1303.
216. Sampson B, Fagerhol MK, Sunderkotter C, et al. Hyperzincaemia and hypercalprotectinaemia: a new disorder of zinc metabolism. *Lancet*. 2002;360:1742.
217. Fessatou S, Fagerhol MK, Roth J, et al. Severe anemia and neutropenia associated with hyperzincemia and hypercalprotectinemia. *J Pediatr Hematol Oncol.* 2005;27:477.
218. Sugiura T, Goto K, Ito K, et al. Effects of cyclosporine A in hyperzincaemia and hypercalprotectinaemia. *Acta Paediatrica*. 2006;95:857.
219. Klevay LM, Medeiros DM. Deliberations and evaluations of the approaches, endpoints and paradigms for dietary recommendations about copper. *J Nutr.* 1996; 126:2419S.
220. Hughes J, Buttriss J. An update on copper: contributions of MAFF-funded research. *Nutrition Bulletin.* 2000;25:271.
221. Pennington JT, Calloway DH. Copper content of foods. *J Am Diet Assoc*. 1973;63:143.
222. Linder MC, Hazegh-Azam M. Copper biochemistry and molecular biology. *Am J Clin Nutr.* 1996;63:797S.
223. Brewer GJ, Yuzbasiyan-Gurkan V. Wilson disease. *Medicine*. 1992;71:139.
224. Stremmel W, Meyerrose KW, Niederau C, et al. Wilson disease: clinical presentation, treatment, and survival. *Ann Intern Med*. 1991;115:720.
225. Mercer JF, Llanos RM. Molecular and cellular aspects of copper transport in developing mammals. *J Nutr.* 2003;133:1418S.
226. Gunshin H, Mackenzie B, Berger UV, et al. Cloning and characterization of a mammalian proton-coupled metal-ion transporter. *Nature*. 1997;388:482.
227. Prohaska JR, Gybina AA. Intracellular copper transport in mammals. *J Nutr.* 2004;134:1003.
228. Schilsky ML. Wilson disease: new insights into pathogenesis, diagnosis, and future therapy. *Curr Gastroenterol Rep*. 2005;7:26.

229. Eisenstein RS. Discovery of the ceruloplasmin homologue hephaestin: new insight into the copper/iron connection. *Nutr Rev.* 2000;58:22.
230. Triplett WS. Clinical aspects of zinc, copper, manganese, chromium, and selenium. *Nutr Int.* 1985;1:60.
231. Danks DM. Copper deficiency in humans. *Annu Rev Nutr.* 1988;8:235.
232. Shim H, Harris ZL. Genetic defects in copper metabolism. *J Nutr.* 2003;133:1527S.
233. Turner Z, Horn N, Tonnesen T, et al. Early copper-histidine treatment for Menkes disease. *Nature Genet.* 1996;12:11.
234. Klevay LM. Cardiovascular disease from copper deficiency—a history. *J Nutr.* 2000;130:489S.
235. Kumar N, Low PA. Myeloneuropathy and anemia due to copper malabsorption. *J Neurol.* 2004;251:747.
236. Tan JC, Burns DL, Royden Jones H. Severe ataxia, myelopathy, and peripheral neuropathy due to acquired copper deficiency in a patient with history of gastrectomy. *JPEN J Parenter Enteral Nutr.* 2006;30:446.
237. Bremner I. Manifestations of copper excess. *Am J Clin Nutr.* 1998;67(Suppl 5):S1069.
238. Zimmermann MB. Assessing iodine status and monitoring progress of iodized salt programs. *J Nutr.* 2004;134:1673.
239. Stanbury JB, Dunn JT. Iodine and iodine deficiency disorders. International Life Sciences Institute, Washington. In *Present Knowledge in Nutrition*, 8th ed., Bowman BA, Russell RM, eds. 2001:344.
240. Wright EM, Turk E. The sodium/glucose cotransport family SLC5. *Pflugers Arch-Eur J Physiol.* 2004;447:510.
241. Daniels GH, Haber DA. Will radioiodine be useful in treatment of breast cancer? *Nat Med.* 2000;6:859.
242. Kavishe F. Iodine deficiency disorders. In: Sadler MJ, Strain JJ, Caballero B, eds. *Encyclopedia of Human Nutrition.* London: Academic Press, 1998:1136.
243. Hetzel BS. Iodine and neuropsychological development. *J Nutr.* 2000;130:493S.
244. Zimmermann M, Delange F. Iodine supplementation of pregnant women in Europe: a review and recommendations. *Eur J Clin Nutr.* 2004;58:979.
245. Lee K, Bradley R, Dwyer J, et al. Too much versus too little: the implications of current iodine intake in the United States. *Nutr Rev.* 1999;57:177.
246. Angermayr L, Clar C. Iodine supplementation for prevention iodine deficiency disorders in children. *Cochrane Database Syst Rev.* 2004;(2):CD003819.
247. Yeng W, Shan Z, Teng X, et al. Effect of iodine intake on thyroid diseases in China. *N Engl J Med.* 2006; 354:2783.
248. Rao GS. Dietary intake and bioavailability of fluoride. *Annu Rev Nutr.* 1984; 9:115.
249. Anonymous. Position of the American Diatetic Association: the impact of fluoride on health. *J Am Diet Assoc.* 2000;100:1208.
250. Sanders TAB. Diet and general health: dietary counselling. *Caries Res.* 2004;38(suppl 1):3.
251. Freeland-Graves JH, Turnlund JR. Deliberations and evaluations of the approaches, endpoints and paradigms for manganese and molybdenum dietary recommendations. *J Nutr.* 1996;126:2435S.
252. Aschner JL, Aschner M. Nutritional aspects of mananese homeostasis. *Mol Aspects Med.* 2005;26:353.
253. Burch RE, Sullivan JR. Diagnosis of zinc, copper, and manganese abnormalities in man. *Med Clin North Am.* 1976;60:655.
254. Friedman BJ, Freeland-Graves JH, Bales CW, et al. Manganese balance and clinical observations in young men fed a manganese-deficient diet. *J Nutr.* 1987;117:113.
255. Fitzgerald K, Mikalunas V, Rubin H, et al. Hypermanganesemia in patients receiving total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1999;23:333.
256. Wardle CA, Forbes A, Roberts NB, et al. Hypermanganesemia in long-term intravenous nutrition and chronic liver disease. *JPEN J Parenter Enteral Nutr.* 1999;23:350.
257. Anderson RA. Nutritional factors influencing the glucose/insulin system: chromium. *J Am Coll Nutr.* 1997;16:404.
258. Jeejeebhoy KN. The role of chromium in nutrition and therapeutics and as a potential toxin. *Nutr Rev.* 1999;57:329.
259. Ducros V. Chromium metabolism. A literature review. *Biol Trace Elem Res.* 1992;32:68.
260. Vincent JB. Quest for the molecular mechanism of chromium action and its relationship to diabetes. *Nutr Rev.* 2000;58:67.
261. Anderson RA. Chromium metabolism and its role in disease processes in man. *Clin Physiol Biochem.* 1986;4:31.
262. Vincent JB. Recent advances in the nutritional biochemistry of trivalent chromium. *Proc Nutr Soc.* 2004;63:41.
263. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Beta-carotene and Other Carotenoids.* Washington, DC: National Academies Press, 2000.
264. Rayman MP. The importance of selenium to human health. *Lancet.* 2000;356:233.
265. Hardy G, Hardy I. Selenium: the Se-XY nutraceutical. *Nutrition.* 2004;20:590.
266. Diplock AT. Indexes of selenium status in human populations. *Am J Clin Nutr.* 1993;57:256S.
267. Beckett GJ, Arthur JR. Selenium and endocrine systems. *J Endocrinol.* 2005;184:455.
268. Epidemiologic studies on the etiologic relationship of selenium and Keshan disease. *China Med J.* 1979; 92:477.

269. Jacobson S, Plantin LO. Concentration of selenium in plasma and erythrocytes during total parenteral nutrition in Crohn's disease. *Gut.* 1985;26:50.
270. Moreno-Reyes R, Suetens C, Mathieu F, et al. Kashin-Beck osteoarthropathy in rural Tibet in relation to selenium and iodine status. *N Engl J Med.* 1998;339:1112.
271. Jacobs ET, Jiang R, Alberts DS, et al. Selenium and colorectal adenoma: results of a pooled analysis. *J Natl Cancer Inst.* 2004;96:1669.
272. Rannem T, Ladefoged K, Hylander E, et al. Selenium depletion in patients with gastrointestinal diseases: are there any predictive factors? *Scand J Gastroenterol.* 1998;33:1057.
273. Reyes H, Baez ME, Gonzalez MC, et al. Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals in Chile. *J Hepatol.* 2000;32:542.
274. Combs GF, Jr. Current evidence and research needs to support a health claim for selenium and cancer prevention. *J Nutr.* 2005;135:343.
275. Moyad MA. Selenium and vitamin E supplements for prostate cancer: evidence or embellishment? *Urology.* 2002;59(Suppl 4A):9.
276. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. *JAMA.* 1996;276:1957.
277. Yang GQ, Wang SZ, Zhou RH, et al. Endemic selenium intoxication of humans in China. *Am J Clin Nutr.* 1983;37:872.

ALTERNATIVE NUTRITIONAL THERAPY 8

Alternative nutritional therapy includes the use of a wide variety of dietary supplements: herbal products, vitamins, minerals, amino acids, and biochemical intermediates such as carnitine and creatine (1). Dietary supplements are consumed widely in the United States and elsewhere; in the United States alone, more than $13 billion is spent on dietary supplements each year.

For some dietary supplements, good scientific data are available to support safety and efficacy, whereas for others, no such data exist. Few large, controlled clinical trials have assessed the safety and efficacy of dietary supplements. In contrast, large, controlled trials are required by law for the approval of prescription drugs. For this reason, far less information is available to assess the safety and efficacy of dietary supplements than to assess prescription drugs. To address this lack of data, the National Institutes of Health Office of Dietary Supplements (ODS) has developed a website that serves as a clearing house for peer-reviewed information on dietary supplements, http://ods.od.nih.gov/publications/publications.html.

REGULATION OF DIETARY SUPPLEMENTS

The Food and Drug Administration (FDA) requires that prescription drugs have been proved safe and effective for their labeled use before they are marketed; however, no such requirement applies to dietary supplements provided they are not marketed as a treatment for a specific disease. Dietary supplements are regulated under the Dietary Supplement Health and Education Act of 1994 (DSHEA). These regulations, which are largely favorable to the manufacturers of dietary supplements, were enacted by Congress in response to an effort by the FDA to remove some herbal products from the market. The negative public response to this effort caused the government to relax the regulations on dietary supplements.

Under the DSHEA, the labels of dietary supplements can include "statements of nutritional support," but not claims of their efficacy in the treatment of specific diseases. Statements of nutritional support may describe the ability of a supplement to affect the

function or structure of an organ, or promote general well-being. Thus, the label of a dietary supplement can claim that the supplement "improves memory," "supports cardiovascular health," or "enhances mental well-being," but it cannot claim that the supplement is effective in the treatment of Alzheimer disease, coronary artery disease, or depression. The standards for the evidence required as a basis for the statements of nutritional support are quite lax.

Drug manufacturers are required by the FDA to prove that their products are safe before they can be marketed. The manufacturers of dietary supplements are not required to demonstrate safety; instead, the FDA has the burden of demonstrating that a dietary supplement is unsafe before it can restrict or ban the product. Moreover, it is difficult for the FDA to demonstrate safety problems with dietary supplements because no uniform system is in place for reporting adverse events.

The FDA does require that the labels of dietary supplements include an "information panel," similar to the "nutrition facts" panel required on food labels. The information panel must describe the part of the plant used, the suggested serving size, and the amount of specific nutrients included (e.g., vitamins and minerals). For herbal products in particular, such labeling is not informative because herbs contain many different compounds, the levels of which vary according to the soil and climate conditions where the herbs are grown. Moreover, for many herbs, the specific active ingredient is unknown and therefore the amount present in a product cannot be stated.

The manufacture of prescription pharmaceuticals is carefully regulated to ensure that standards of purity and dosing are maintained. Herbal remedies are exempt from this regulation, and there is considerable variation in the composition of herbal products among manufacturers and among lots. There are also discrepancies between label information and actual content. In addition to problems with inconsistency of composition, there are problems with contamination. Herbal remedies have been contaminated with drugs, toxic metals, pesticides, fumigating agents, microbial toxins, microorganisms, and other botanicals (2).

In Germany, where herbal products are widely used, a government agency, the German Federal Institute for Drugs and Medicinal Devices, formed a commission to evaluate the safety and efficacy of a large number of herbal remedies. The report of that commission was translated into English and published as *The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines* (Blumenthal M, ed. Austin, Texas: American Botanical Council, 1998). This publication is a comprehensive and objective guide to the efficacy and safety of herbal medicines.

DIETARY SUPPLEMENTS

In this chapter, we review a few of the hundreds of alternative nutritional products that are available commercially (Table 8-1). Vitamins (the B vitamins and vitamins A, C, and E) and minerals (potassium, calcium, magnesium, zinc) are covered in Chapters 6 and 7. The nutritional products presented in this chapter were chosen because of wide use (e.g., *ginkgo biloba*, *Echinacea*), good evidence of efficacy (e.g., fish oil, phytosterols), or significant safety issues (e.g., ma huang). A larger range of dietary supplements is reviewed in *The Health Professional's Guide to Popular Dietary Supplements,* 3rd edition. Fragakis, AS and Thomson, D. Chicago: American Dietetic Association, 2007).

Acidophilus/Lactobacillus Acidophilus

Lactobacillus acidophilus is a lactic acid bacterium normally found in the human gastrointestinal tract. Lactic acid bacteria convert carbohydrates to lactic acid. Lactobacilli are found in yogurt, where they produce lactase, which hydrolyzes lactose to glucose and galactose. The addition of lactobacilli to milk (acidophilus milk) results in the hydrolysis of lactose. This is one of a group of additives referred to as *probiotics.*

Claims and Supporting Evidence

Decreases Lactose Intolerance. If *Lactobacillus* is added to milk, up to 50% of the milk lactose is hydrolyzed. In most affected persons, lactose intolerance is the result of a

TABLE 8-1. Summary of Selected Alternative Medicines

Supplement	Proposed mechanisms	Disease claims	Safety issues
Lactobacillus acidophilus	Re-establish flora	Antibiotic diarrhea (B) Lactose intolerance (A)	None
Chondroitin/ glucosamine	Inhibits cartilage degradation, increases synthesis	Arthritis (A)	None
Creatine	Role in energy storage	High-intensity exercise (C)	Muscle cramping, dehydration; avoid with renal disease
Echinacea	Immune stimulant	Common cold (C)	Allergy, hepatic toxicity
Fish oil	Eicosanoid synthesis Plt aggregation (TXA_2) Blood flow, edema (PGE_2) Chemotaxis (LTB_4)	TG, plt aggregation (A) Improves symptoms in RA (A) IBD treatment (A)	Bleeding time
γ-Linolenic acid (GLA)	Blocks eicosanoid synthesis, provides GLA	RA (A) PMS (C)	Drug interactions, potentiates hepatotoxicity
Ginkgo biloba	Flavonoids improve memory, blood flow	Alzheimer (A) Peripheral vascular disease (A)	Potentiates antiplatelet agents
Ginseng	Saponins	Improves exercise (C) Enhances cognition (C)	CNS excitation, hypertension, nervousness, drug interactions, hypoglycemia
Ma huang	Sympathomimetic	Bronchodilator (B) Weight loss (B)	Stroke, MI, death, tremors, dizziness, urinary retention
γ-Oryzanol	Phytosterols, ↓ cholesterol absorption	Serum cholesterol (B)	None
Saw palmetto	5-α-Reductase activity	BPH symptoms (A) Prostate enlargement (C)	Hepatic toxicity (1 case)
Soy protein	Isoflavonoids are weak estrogens	Menopause (A) Serum cholesterol (A)	Very large amount needed for effect
St. John's wort	5-HT levels	Depression (A)	Photosensitivity, allergy, fatigue, dyspepsia, sleep disturbance, drug interactions

CNS, central nervous system; IBD, inflammatory bowel disease; LTB_4, leukotriene B_4; MI, myocardial infarction; plt, platelet; PGE_2, prostaglandin E_2; PMS, premenstrual syndrome; RA, rheumatoid arthritis; TG, triglycerides; TXA_2, thromboxane A_2; 5-HT, serotonin.
Support for claims: A, placebo-controlled, randomized trials support; B, inadequate support; C, negative studies.

decreased amount rather than a complete absence of intestinal epithelial lactase, and symptoms are related both to the amount of lactose ingested and to the degree of intestinal lactase activity. By reducing the amount of lactose in milk, treatment with lactobacilli increases the quantity of milk that a lactose-intolerant person can ingest without symptoms. However, even with the use of lactobacilli, most lactose-intolerant persons will have symptoms if they consume a sufficiently large amount of milk.

Decreases Antibiotic-associated Diarrhea. *L. acidophilus* reduces the number of days of diarrhea in children with rotavirus infections (3) but there is no evidence that it prevents infectious diarrhea. *L. acidophilus* is also helpful in the prevention of antibiotic-associated diarrhea (4). A meta-analysis of probiotics in antibiotic-associated diarrhea concluded that although the current data were promising, there was insufficient data for a recommendation to treat all antibiotic-associated diarrhea with probiotics (5).

Dosing

L. acidophilus, in addition to occurring naturally in yogurt, is available in tablets, capsules, and powders. It is often sold in combination with other *Lactobacillus* species and with Bifidobacterium. Typical dosing for *L. acidophilus* is 1 billion to 10 billion live bacteria per day.

Safety Issues

There are no safety issues.

Chondroitin Sulfate and Glucosamine

Chondroitin sulfate and glucosamine are sold separately but are more commonly sold in combination. Both of these agents are produced endogenously in joints. Chondroitin sulfate, a glycosaminoglycan that is formed from repeating disaccharides of galactosamine sulfate and glucuronic acid, is found in articular cartilage, where it is secreted by chondrocytes. It inhibits the enzymes that degrade cartilage and holds water in cartilage, thereby increasing its elasticity. Glucosamine is an aminosugar found in cartilage, tendons, and synovial fluid; it stimulates the synthesis of proteoglycans and glycosaminoglycans.

Claims and Supporting Evidence of Efficacy in the Treatment of Arthritis

In a 6-month, double-blinded, placebo-controlled trial of 93 patients with osteoarthritis of the knee, those who received glucosamine (2,000 mg per day) and chondroitin sulfate (1,600 mg per day) had both a lower arthritis score and a lower requirement for pain medication (6). A meta-analysis of 17 studies of chondroitin sulfate and glucosamine in osteoarthritis concluded that they are effective in improving outcomes, but the magnitude of their effect is unclear because of inconsistencies in the study methods and dependence on industry support for execution of the studies (7). A meta-analysis of placebo-controlled trials of chondroitin alone for osteoarthritis indicated that the symptomatic benefit of chondroitin alone was minimal or non-existent (8). A meta-analysis of placebo-controlled studies of glucosamine alone for osteoarthritis indicated that the glucosamine product made by Rotta was superior to placebo in the treatment of pain and functional impairment whereas non-Rotta products were not superior to placebo (9).

Dosing

Typical dosing for chondroitin sulfate is 1,200 mg per day; for glucosamine it is 1,500 mg per day.

Safety Issues

There are no safety issues.

Creatine

Creatine is synthesized from arginine, glycine, and methionine in a two-step process. It is synthesized endogenously in skeletal muscle and other organs, and dietary creatine is not required. Exogenous creatine is taken up into muscle and increases muscle levels of creatine. Creatine and phosphocreatine are involved in the storage and transmission of phosphate bond energy; phosphocreatine is an important reservoir of chemical energy in muscle. It has been suggested that increased amounts of phosphocreatine can shorten the recovery time of muscle adenosine triphosphate levels after exercise.

Claims and Supporting Evidence that Creatine Enhances Performance in High-intensity Exercise

A large number of blinded, placebo-controlled studies of the effect of creatine on athletic performance has been performed (10,11). In a typical study, 32 swimmers were timed in sprints and then received placebo- or creatine (20 g per day) for a week. No difference in performance was observed between the placebo- and creatine-treated groups after a week of therapy (12). A review of creatine supplementation and exercise performance concluded that creatine supplementation has not consistently proved to enhance exercise performance (13).

Dosing

Creatine is available in pills and powders as creatine monohydrate. Many formulations combine creatine with carnitine and amino acids. Typical dosing is a loading dose of 20 g per day for 5 or 6 days followed by a maintenance dose of 2 g per day.

Safety Issues

Creatine holds water in muscle; increases in intramuscular water may contribute to muscle cramping and dehydration. Creatine should not be given to patients with renal disease. Some athletes consume doses of creatine that are higher than recommended; whether excessive doses lead to additional adverse events is unclear.

Echinacea

Three of the nine species of the genus *Echinacea* are commonly found in herbal preparations. The most commonly used is *Echinacea purpurea,* the purple coneflower. Both the above-ground parts and the root have been used as herbal medicines. *Echinacea* has been used to treat or prevent the common cold and influenza and as a stimulant to the immune system. In one *in vitro* study, *Echinacea* stimulated the production of interleukins-1, -6, and -10 and tumor necrosis factor-α by human macrophages (14); whether an *in vivo* counterpart of this effect exists is unknown.

Claims and Supporting Evidence that Echinacea Prevents or Treats the Common Cold and Influenza

The efficacy of *Echinacea* in reducing the viral load was tested in 437 healthy adults exposed to rhinovirus. No differences were seen in the rate of infection, the severity of symptoms, or viral titers (15).

Dosing

Echinacea is available as the root or the herb; some formulations contain both. Commercial products include tinctures, tablets, capsules, lozenges, and teas. Typical daily dosing is 300 to 900 mg of dried extract, but dosing is difficult to analyze because of the wide range of formulations available.

Safety

Allergic reactions and asthma have been reported with *Echinacea*. Hepatotoxicity has been seen after prolonged use; *Echinacea* should be used cautiously by persons taking potentially hepatotoxic drugs. One anaphylactic reaction to an *Echinacea* extract has been reported.

Fish Oil

Fish oil contains large amounts of highly unsaturated fatty acids, including docosahexaenoic acid (DHA), which has six double bonds, and eicosapentaenoic acid (EPA), which has five. In these fatty acids, the last double bond is located three carbons from the end (ω-3), whereas in the polyunsaturated fatty acids from plants, the last double bond is typically located six carbons from the end (ω-6). EPA and DHA can serve as substrates for cyclo-oxygenase, the rate-limiting step in prostaglandin production, and for lipoxygenase, the rate-limiting step in leukotriene production. The metabolic products of EPA and DHA derived through these pathways are less biologically active than the metabolites of arachidonic acid, the more typical substrate for these enzymes. Thus, one effect of fish oil is to diminish the production of conventional eicosanoids, including thromboxane A_2, prostaglandin E_2, and leukotriene B_4. By blocking the synthesis of thromboxane A_2, fish oil inhibits platelet aggregation and so acts as an antithrombotic agent. By blocking the synthesis of prostaglandin E_2, fish oil reduces the increased blood flow and edema associated with inflammation. Finally, by reducing the synthesis of leukotriene B_4, fish oil reduces the neutrophil infiltration associated with inflammation.

Claims and Supporting Evidence

Beneficial Effects in Heart Disease. Fish oil supplementation beneficially affects persons with cardiovascular disease by at least three mechanisms. It reduces plasma triglycerides by about 30% (16) and reduces blood pressure by a small but statistically

significant amount (17). Fish oil also has antithrombotic properties; it reduces platelet aggregation by decreasing thromboxane production. A meta-analysis of 10 large (a total of 14,727 subjects) randomized trials of fish oil versus placebo revealed decreases of both total mortality and myocardial infarction-related mortality in those receiving fish oil (mean exposure 37 months) (18). The FDA has approved a limited health claim for ω-3 fatty acids regarding coronary heart disease (19). The American Heart Association endorses the benefits of fish oil in heart disease and recommends 1g per day of ω-3 supplements in those with coronary heart disease and 2 to 4 g per day in those with hypertriglyceridemia (20).

Treatment of Chronic Inflammatory Diseases, Including Rheumatoid Arthritis and Inflammatory Bowel Disease. Eicosanoids have been identified as mediators of the inflammatory response in chronic inflammatory diseases, so it is not surprising that an agent that reduces eicosanoid production may be of therapeutic value in these diseases. After prolonged treatment (>3 months) with fish oil, joint tenderness and morning stiffness were decreased in patients with rheumatoid arthritis (21). Fish oil has also proved useful in the therapy of acute disease and in maintaining remission in inflammatory bowel disease (22,23).

Dosing

Fish oil is available in gelatin capsules and as liquid oil. Supplements typically contain 180 to 300 mg of EPA and 120 to 200 mg of DHA. Dosing in either cardiovascular or chronic inflammatory disease studies is 4 to 5.4 g per day (total of EPA and DHA). Most trials of fish oil in either cardiovascular or inflammatory disease lasted at least 3 months. Thus, the benefits of fish oil were largely seen when high doses were taken for a long period of time.

Safety

The FDA has declared fish oil to be generally recognized as safe (GRAS) at doses up to 3 g per day. The major toxic effect is a prolonged bleeding time secondary to inhibition of platelet aggregation. Fish oil should be used cautiously by patients who have bleeding disorders or are taking anticoagulants. Patients taking large amounts of fish oil complain that they acquire a fishy odor.

γ-Linolenic Acid (Evening Primrose Oil, Borage Oil, Black Currant Oil)

γ-Linolenic acid (GLA) is a fatty acid that is endogenously synthesized in humans (24,25). Linolenic acid is converted to GLA by δ-6-desaturase. GLA is also available from the diet. Evening primrose oil (8% GLA), borage oil (23% GLA), and black currant oil (15% GLA) are especially rich dietary sources. GLA can be metabolized to a biologically inactive prostaglandin (prostaglandin E_1) and to a lipoxygenase product, 15-*S*-hydroxy-8,11,13-eicosatrienoic acid, that blocks the synthesis of biologically active arachidonic acid metabolites. In certain disease states, including diabetes and hypercholesterolemia, the conversion of linoleic acid to GLA by δ-6-desaturase may be impaired. In addition, impaired synthesis of GLA has been associated with advanced age, alcoholism, and a variety of vitamin and mineral deficiencies. It has been suggested that supplying dietary GLA may compensate for impaired endogenous conversion of linoleic acid to GLA.

Claims and Supporting Evidence

Treatment of Rheumatoid Arthritis. In a 24-week, double-blinded study, 37 patients with rheumatoid arthritis received placebo or GLA (1,400 mg per day) in borage oil. In the patients who received GLA, disease activity decreased during the 24 weeks, whereas in those receiving placebo, it did not change or increased (26).

Treatment of Premenstrual Syndrome (PMS). It is possible that serum levels of certain fatty acids are altered in PMS. Levels of arachidonic acid and dihomo-γ-linolenic acid (DGLA), a metabolite of GLA, are decreased in PMS. However, a series of trials in which evening primrose oil was given to patients with PMS failed to reveal compelling evidence of a clinical benefit (27).

Dosing

Evening primrose oil, borage oil, and black currant oil are all available in capsules or as liquid oil. The rate of endogenous synthesis of GLA in normal humans is 250 to 1,000 mg per day. Typical dosing of GLA is 500 to 3,000 mg per day.

Safety

Drug interactions with anticonvulsants and tricyclic antidepressants may occur. Patients taking potentially hepatotoxic drugs should not use GLA.

Ginkgo biloba

Ginkgo biloba, an extract of the leaves of the ginkgo tree, is used to improve memory and increase peripheral blood flow. It is one of the top selling herbs in the United States. Ginkgo leaves contain flavonoids, sesquiterpenes, and terpenes called *ginkgolides*. Which of these is the active ingredient is unknown, although flavonoids are scavengers of free radicals and ginkgolides may be platelet-activating factor antagonists.

Claims and Supporting Evidence

Improves Memory. In a double-blinded, placebo-controlled study of older persons with mild to moderate memory impairment, ginkgo biloba extract (120 mg per day) improved results on some but not all tests of memory (28).

Alzheimer Disease. In a 52-week, double-blinded, placebo-controlled trial of 309 patients with Alzheimer disease or multi-infarct dementia, the condition of patients receiving *Ginkgo biloba* extract (120 mg per day) stabilized on the Alzheimer Disease Assessment Scale, whereas the condition of those on placebo deteriorated (29). A Cochrane Database Systematic Review of the efficacy of *Ginkgo biloba* suggested improved clinical global improvement scores using low doses (less than 200 mg per day) for 12 weeks (30). A direct comparison between placebo, a German *Ginkgo biloba* product (eGb761), and a second-generation cholinesterase inhibitor (donepezil) in patients with Alzheimer disease demonstrated that both ginkgo and donepezil were better than placebo but there was no difference between ginkgo and donepezil (31).

Peripheral Vascular Disease. In a 24-week, double-blinded, placebo-controlled trial of 111 patients with peripheral vascular disease, superior, pain-free walking and maximal walking distance were noted in those who received *Ginkgo biloba* extract (120 mg per day) (32).

Dosing

Ginkgo biloba extract is available as a tincture, tablets, and capsules. Typical dosing is 40 to 80 mg, 3 times a day.

Safety

Ginkgo is thought to be a platelet-activating factor antagonist and may potentiate the effects of antiplatelet drugs and anticoagulants.

Ginseng

The term **ginseng** includes American ginseng *(Panax quinquefolius)* and Asian ginseng *(P. ginseng* and *P. japonicus)*. Siberian ginseng *(Eleutherococcus senticosus)* is not a true ginseng but is promoted and sold as ginseng. *Panax* ginseng is the species most widely available in the United States and also the most widely studied. The plant part used is the root. Air-dried root is "white ginseng"; steam-treated root is "red ginseng." Saponins (ginsenosides) are thought to be the active ingredients, although their mechanism of action is unknown.

Claims and Supporting Evidence

Enhances Exercise Performance. In a 3-week, double-blinded, placebo-controlled trial of 28 normal volunteers, exercise time, work load, plasma lactate, and hematocrit did not differ between those who received *Panax* ginseng (200 mg per day) and those who received placebo (33). A review of studies of ginseng and exercise performance concluded that compelling evidence that ginseng improves exercise performance is lacking (34).

Enhances Cognitive Function. In an 8-week, double-blinded, placebo-controlled trial of 60 elderly patients, no difference in cognitive function was noted between those receiving *Panax* ginseng extract (40 mg per day) and those receiving placebo.

Enhances Sexual Function. No blinded studies of the effect of ginseng on sexual function have been performed.

Dosing

The Asian, American, and Siberian forms of ginseng are available as tablets, capsules, powders, teas, and tinctures. Most commercial products contain 100 to 400 mg of extract (equivalent to 0.5 to 2.0 g of root). The levels of ginsenosides vary widely among different commercial products.

Safety

High doses of ginseng are associated with central nervous system excitation, hypertension, sleeplessness, and nervousness. Drug interactions may occur with corticosteroids, estrogens, and digitalis preparations. *Panax* ginseng produces hypoglycemic effects, perhaps by accelerating hepatic lipogenesis, and should be used cautiously in patients with diabetes.

L-Carnitine

L-Carnitine is a short-chain carboxylic acid formed from lysine and methionine. It serves as a carrier molecule for the transport of fatty acids across the mitochondrial membrane into the mitochondria, where they undergo oxidation. Carnitine is found primarily in skeletal and cardiac muscle, which contains large numbers of mitochondria. Humans can synthesize carnitine from lysine and methionine. The major dietary source of carnitine is meat. Carnitine is sold as L-carnitine, propionyl-L-carnitine and L-acetylcarnitine in capsules or tablets.

Claims and Supporting Evidence

Benefits in Heart Disease. In one study, patients with angina were randomized to propionyl-L-carnitine or placebo. The incidence of angina and the consumption of nitroglycerin were not affected by carnitine (35). In another study, patients with claudication were given propionyl-L-carnitine or placebo for 6 months; a small improvement in walking distance was noted in those who received carnitine (36). This study is difficult to interpret because of a high dropout rate.

Improvements in Exercise Performance. It has been suggested that carnitine may improve exercise performance by enhancing fatty acid oxidation and decreasing lactic acid production. When carnitine was given to athletes immediately before exercise, serum carnitine levels increased, but no improvements in respiratory exchange ratios, muscle lactate accumulation, plasma lactate levels, or exercise performance were noted (37,38).

Dosing

Carnitine is available in capsules or tablets as L-carnitine, propionyl-L-carnitine, and L-acetylcarnitine. Dosing is 2 to 4 g per day in 2 or 3 divided doses.

Safety

Very high doses can cause diarrhea and nausea.

Ma Huang *(Ephedra sinica)*

Ma huang, the dried root of the herb *E. sinica*, has been used in Chinese medicine for centuries. It contains the alkaloids ephedrine and pseudoephedrine and is used as a bronchodilator in asthma, a nasal decongestant, and an aid to weight loss. Ephedrine, which is used to treat asthma, is a sympathomimetic agent that can induce tachycardia, raise blood pressure, and cause urinary retention and restlessness. Pseudoephedrine is found in many over-the-counter cold medicines.

Claims and Supporting Evidence

Bronchodilation and Nasal Decongestion. Ephedrine is an effective bronchodilator, and pseudoephedrine is an effective nasal decongestant. The ephedrine and pseudoephedrine

in ma huang provide no advantage over the same substances in prescription drugs and over-the-counter medications. Because of the inability to quantify the alkaloid content of ma huang, both underdosing and overdosing (with toxicity) are possible; the use of prescription drugs or over-the-counter medications poses no such risks.

Weight Loss. Ephedrine, frequently in combination with caffeine, has been used in a number of weight loss programs. When ephedrine and caffeine are combined with a low-calorie diet, a marginally greater weight loss is achieved than with a low-calorie diet alone, but at the expense of a high incidence of insomnia, tremors, and dizziness (39).

Dosing

Ma huang is available as teas, tinctures, capsules, and tablets. The alkaloid content of commercial ma huang products varies from 0.3 to 56 mg. In comparison, prescription asthma medications contain 24 mg of ephedrine, and over-the-counter cold preparations contain 60 to 120 mg of pseudoephedrine.

Safety

Ma huang has been associated with stroke, myocardial infarction, and death (40). More common side effects include tremors, insomnia, and urinary retention. The risk for adverse events associated with ma huang is increased when it is given to patients with pre-existing hypertension, coronary artery disease, thyroid disease, and benign prostatic hypertrophy (BPH). The FDA recommends that everyone avoid ma huang.

Phytosterols (γ-oryzanol)

Plants contain sterols that are structurally similar to cholesterol but are poorly absorbed from the gastrointestinal tract. These plant sterols (which include sitosterol, sitostanol, and campesterol) are collectively called *phytosterols*. Vegetable oils contain significant levels of phytosterols. In general, vegetable oils containing large amounts of polyunsaturated fatty acids (e.g., corn oil) have more phytosterols than oils containing smaller amounts of polyunsaturated fatty acids (e.g., palm oil, coconut oil). Purification and processing can remove phytosterols from vegetable oils. γ-Oryzanol, which is prepared commercially from rice bran oil, is a mixture of ferulic acid esters of phytosterols. Sitosterol esters are available as an additive to margarine (Benacol).

Claims and Supporting Evidence that Phytosterols Lower Serum Cholesterol

The evidence that phytosterols lower serum cholesterol levels is excellent (41,42). The mechanism of this effect is not definitely known, but it may be that phytosterols diminish cholesterol absorption from the intestine. The poor absorption of phytosterols from the intestine supports the suggestion that they act in the intestinal lumen to impair cholesterol absorption. No blinded studies of the effects of γ-oryzanol on serum cholesterol levels have been performed.

Dosing

γ-Oryzanol is available in tablets and capsules in doses of 100 to 500 mg per day. Sitosterol esters are available as an additive to margarine (Benacol).

Safety Issues

There are no safety issues.

Saw Palmetto

Saw palmetto berry is the ripe dried fruit of *Serenoa repens,* a dwarf palm tree that grows in the southern United States. Commercial preparations are extracts containing phytosterols and polysaccharides from these berries. Saw palmetto has been used to treat BPH. Some evidence indicates that it inhibits 5-α-reductase, the enzyme that converts testosterone to dihydrotestosterone, a steroid that promotes prostate growth.

Claims and Supporting Evidence that Saw Palmetto is an Effective Treatment for BPH

Saw palmetto is promoted as an agent that reduces symptoms associated with BPH. A series of double-blinded, randomized, placebo-controlled trials have demonstrated decreases

in nocturia, increases in peak urine flow, and decreases in residual volume in patients with BPH who receive saw palmetto (43). Although the evidence that saw palmetto relieves the symptoms of BPH is reasonably good, no evidence has been found that it reduces an enlarged prostate or prevents prostatic cancer.

Dosing

Saw palmetto, prepared as whole berries or as a lipophilic extract, is available as capsules, tablets, and tinctures. Typical dosing is 1 to 2 g of berries or 160 to 320 mg of lipophilic extract per day. A number of commercially available formulations provide subtherapeutic doses.

Safety

A single case of hepatic toxicity has been ascribed to saw palmetto.

Soy Protein and Isoflavones

Plant products with estrogen-like effects are called *phytoestrogens*. Isoflavones, which are found primarily in soy products, are weak estrogens. The major isoflavones in soy proteins are genestein, daidzein, and glycetein. Because of their estrogenic effects, soy products containing isoflavones have been used to relieve hot flashes and other menopausal symptoms. It has been suggested that phytoestrogens relieve menopausal symptoms without causing the adverse effects seen with hormone replacement therapy, particularly the increased risk for breast cancer. Soy protein also lowers serum cholesterol; whether or not the effects of soy proteins on serum cholesterol are mediated through isoflavones is not known.

Claims and Supporting Evidence

Relieves Menopausal Symptoms. In a 12-week trial, postmenopausal women received placebo or 40 g of soy protein isolate containing 76 mg of isoflavones. In the women who received soy, hot flashes were reduced by 45%, whereas in those receiving placebo, they were reduced by 30% (44). This is clearly a large amount of soy protein, and the consumption of this amount of soy protein would require a major change in dietary habits. Despite this positive report, a review of 21 trials of soy proteins on hot flashes and night sweats failed to demonstrate any benefit (45).

Reduces Serum Cholesterol. A meta-analysis evaluated the results of 38 controlled trials of the effects of soy protein (average intake of 47 g per day) on serum cholesterol. Soy protein was associated with decreases in total cholesterol (9.3%), low-density-lipoprotein (LDL) cholesterol (12.9%), and triglycerides (10.5%) (46). In all of these trials, large amounts of soy protein were consumed, amounts so large that major reductions of other dietary components would be needed to accommodate the increase in soy protein. The FDA allows commercial products containing at least 6.25 g of soy protein to carry a label claiming a role for soy protein in reducing the risk for coronary artery disease when combined with a diet low in cholesterol and saturated fat.

Dosing

Soy proteins are available as soy flour, soy milk, soy protein isolates, natto (fermented soy beans), tofu, and textured soy protein. These preparations contain 1 to 10 mg of isoflavones per gram of protein. The dosage of isoflavones used to treat menopausal symptoms is 76 mg per day or more. Genestein supplements are also available.

Safety Issues

There are no safety issues.

St. John's Wort

St. John's wort, the dried, above-ground parts of *Hypericum perforatum*, has been used extensively to treat depression and as a mood elevator. Several mechanisms of action have been proposed, including increases of serotonin levels and monoamine oxidase activity, but little evidence is available to support any specific mechanism.

Claims and Supporting Evidence that St. John's Wort Is an Effective Treatment for Depression

St. John's wort appears to be better than placebo in the short-term management of mild to moderate depression (47,48,49). However, 8-week studies in major depression did not reveal any advantage over placebo (50,51). In one of these studies a conventional antidepressant, sertaline, was used as an active comparator and was found to be superior to both placebo and St. John's wort (51).

Dosing

St. John's wort is available as tablets, capsules, tinctures, powders, and teas. Typical daily dosing is 900 mg of standardized extract.

Safety

St. John's wort may induce photosensitivity; allergic reactions with hives and skin rash have occurred. Common side effects include fatigue, dyspepsia, and sleep disturbances. Pretreatment with St. John's wort reduces the area under the curve for a number of drugs including digoxin, amitriptyline, midazolam, and the active metabolite of simvastatin (1).

References

1. De Smet PAGM. Herbal remedies. *N Engl J Med.* 2002;347:2046.
2. De Smet PAGM. Toxicological outlook on the quality assurance of herbal remedies. In: De Smet PAGM, Keller K, Hansel R, Chandler RF, eds. *Adverse Effects of Herbal Drugs*. Vol Berlin, Germany:Springer-Verlag, 1992:1–72.
3. deRoos NM, Katan MB, Effects of probiotic bacteria on diarrhea. Lipid metabolism, and carcinogenesis: a review of papers published between 1988 and 1998. *Am J Clin Nutr.* 2000;71:405.
4. D'Souza AL, Rajkuma C, Cooke J, et al. Probiotics in prevention of antibiotic associated diarrea: meta-analysis. *BMJ*. 2002;324:1361.
5. Johnston BC, Supina AL, Ospina M, Vohra S. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev.* 2007; (2) CD004827.
6. Das AK, Eitel J, Hammad T. Efficacy of new class of agents (glucosamine hydrochloride and chondroitin sulfate) in the treatment of osteoarthritis of the knee. *Abstracts of American Association of Hip and Knee Surgeons,* 8th Annual Meeting, Dallas, Texas, November 6–8, 1998.
7. McAlindon TE, LaValley MP, Gulin JP, et al. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA*. 2000;283:1469.
8. Reichenbach S, Sterchi R, Scherer M, et al. Meta-analysis: Chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med*. 2007;146:580.
9. Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev.* 2005(2) CD002946.
10. Volek JS, Rawson ES. Scientific basis and practical aspects of creatine supplementation for athletes. *Nutrition*. 2004;20:609.
11. Kreider RB. Effects of creatine supplementation on performance and training adaptations. *Mol Cell Biochem*. 2003;244:89.
12. Burke LM, Pyne DB, Telford RD. Effect of oral creatine supplementation on single-effort sprint performance in elite swimmers. *Int J Sport Nutr.* 1996;6:222.
13. Williams MH, Branch JD. Creatine supplementation and exercise performance: an update. *J Am Coll Nutr.* 1998;17:216.
14. Burger RA, Tores AR, Warren RP, et al. *Echinacea*-induced cytokine production by human macrophages. *Int J Immunopharmacol.* 1997;19:371.
15. Turner RB, Bayer R, Woelkart K, et al. An evaluation of *Echinacea angustifolia* in experimental rhinovirus infections. *N Engl J Med*. 2005;353:341.
16. Harris WS, Ginsberg HN, Arunakul N, et al. Safety and efficacy of Omacor in severe hypertriglyceridemia. *J Cardiovasc Risk*. 1997;4:385.
17. Morris MC, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. *Circulation.* 1993;88:523.
18. Yzebe D, Lievre M. Fish oils in the care of coronary heart disease patients: a meta-analysis of randomized controlled trials. *Fundam Clin Pharmacol.* 2004;18:581.
19. Food and Drug Administration. Center for Food Safety and Applied Nutrition, Office of Premarket Approval. EAFUS: a food additive database. Available at http://vm.cfsan.fda.gov/~dms/eafus.html. Accessed October 20, 2007.
20. Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation.* 2002;106:2747.
21. Fortin PR, Lew RA, Liang MH, et al. Validation of a meta-analysis: the effects of fish oil in rheumatoid arthritis. *J Clin Epidemiol.* 1995;48:1379.

22. Stenson WF, Cort D, Rodgers J, et al. Dietary supplementation with fish oil in ulcerative colitis. *Ann Intern Med*. 1992;116:609.
23. Belluzzi A, Brignola C, Campieri M, et al. Effect of an enteric-coated fish-oil preparation on relapse in Crohn's disease. *N Engl J Med*. 1996;334:1557.
24. Fan YY, Chapkin RS. Importance of dietary gamma-linolenic acid in human health and nutrition. *J Nutr*. 1998;128:1411.
25. Horrobin DF. Nutritional and medical importance of gamma-linolenic acid. *Prog Lipid Res*. 1992;31:163.
26. Leventhal LJ, Boyce EG, Surier RB. Treatment of rheumatoid arthritis with gamma-linolenic acid. *Ann Intern Med*. 1993;119:867.
27. Budeiri D, Li Wan Po A, Dornan JC. Is evening primrose oil of value in the treatment of premenstrual syndrome? *Control Clin Trials*. 1996;17:60.
28. Rai GS, Shovlin C, Wesnes KA. A double-blinded, placebo-controlled study of Ginkgo biloba extract ("tanakan") in elderly outpatients with mild to moderate memory impairment. *Curr Med Res Opin*. 1991;12:350.
29. Le Bars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blinded, randomized trial of an extract of Ginkgo biloba for dementia. *JAMA*. 1997;278:1327.
30. Birks J, Grimley EV, van Dongen M. Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2002;(4):CD003120.
31. Mazza M, Capuano A, Bria P, Mazza S. Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. *Eur J Neurol*. 2006;13:981–985.
32. Peters H, Kieser M, Holscher U. Demonstration of the efficacy of Ginkgo biloba special extract EGb 761 on intermittent claudication—a placebo-controlled, double-blinded multicenter trial. *Vasa*. 1998;27:106.
33. Allen JD, McLung J, Nelson AG, et al. Ginseng supplementation does not enhance healthy young adults' peak aerobic exercise performance. *J Am Coll Nutr*. 1998;17:462.
34. Bahrke MS, Morgan WP. Evaluation of the ergogenic properties of ginseng. *Sports Med*. 1994;18:229.
35. Bartels GL, Remme WJ, den Hartog RF, et al. Additional antiischemic effects of long-term L-propionylcarnitine in anginal patients treated with conventional antianginal therapy. *Cardiovasc Drugs Ther*. 1995;9:749.
36. Brevetti G, Perna S, Sabba C, et al. Effect of propionyl-L-carnitine on quality of life in intermittent claudication. *Am J Cardiol*. 1977;79:777.
37. Laakmann G, Schule C, Baghai T, et al. St. John's wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. *Pharmacopsychiatry*. 1998;31[Suppl 1]:54.
38. Brass EP, Hoppel CL, Hiatt WR. Effect of intravenous L-carnitine on carnitine homeostasis and fuel metabolism during exercise in humans. *Clin Pharmacol Ther*. 1994;55:681.
39. Astrup A, Breum L, Toubro S, et al. The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine, and placebo in obese subjects on an energy-restricted diet: A double-blinded trial. *Int J Obes Relat Metab Disord*. 1992;16:269.
40. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med*. 2000;343:1833.
41. Yoshino G, Kazumi T, Amano M, et al. Effects of gamma-oryzanol and probucol on hyperlipidemia. *Curr Ther Res*. 1989;45:975.
42. Rong N, Ausman LM, Nicolosi RJ. Oryzanol decreases cholesterol absorption and aortic fatty streaks in hamsters. *Lipids*. 1997;32:303.
43. Wilt TJ, Ishani A, Stark G, et al. Saw palmetto extracts for treatment of benign prostatic hyperplasia: a systematic review. *JAMA*. 1998;280:1604.
44. Albertazzi P, Pansini F, Bonaccorsi G, et al. The effect of dietary soy supplementation on hot flushes. *Obstet Gynecol*. 1998;91:6.
45. Balk E, Chung M, Chew P, et al. Effects of soy on health outcomes. *Evid Rep Technol Assess (Full Rep)*. 2005;126:1.
46. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med*. 1995;333:276.
47. Williams JW Jr, Mulrow CD, Chiquette E, et al. A systematic review of newer pharmacotherapies for depression in adults: evidence report summary. *Ann Intern Med*. 2000;132:743.
48. Whiskey E, Werneke U, Taylor D. A systematic review and meta-analysis of *Hypericum perforatum* in depression: a comprehensive clinical review. *Int Clin Psychopharmacol*. 2001;16:239.
49. Mischoulon D. Update and critique of natural remedies as antidepressant treatments. *Psychiatr Clin N Am*. 2007:30:51.
50. Shelton RC, Keller MB, Gelenberg A, et al. Effectiveness of St. John's wort in major depression: a randomized controlled trial. *JAMA*. 2001;285:1976.
51. Hypericum Depression Trial Study Group. Effect of Hypericum perfortatum (St. John's wort) in major depressive disorder; a randomized controlled trial. *JAMA*. 2002;287:1807.

Therapeutic Nutrition

III

NUTRITIONAL SUPPORT DECISION MAKING

9

DEFINITION OF NUTRITIONAL SUPPORT

Feeding is not considered medical therapy under ordinary circumstances. When patients are unable to meet their daily requirements by consuming a normal diet or when assessment documents deficiencies, then nutritional planning becomes a part of medical therapeutics. Nutritional support is the planning of patient specific nutritional therapy. The Nutrition Care Process as outlined by the American Dietetic Association (ADA) is one way to approach nutritional therapy (1). In hospitalized patients the goals of the Nutrition Care Process are to provide the appropriate macro- and micronutrients to replete existing deficiencies, minimize the patient's metabolic response to stress, aid in the prevention of oxidative cellular injury, support wound healing, and maximize the patient's immune function. This process consists of four parts, including nutrition screening, assessment, intervention, and monitoring.

SUCCESSFUL NUTRITION SCREENING

A successful nutrition screening tool should be easy to use by non-nutritional professionals and adequately identify malnourished patients or those at nutritional risk who require further assessment. Specific nutrient deficiencies or a protein energy deficit can lead to malnutrition. While vitamins and minerals are more easily replaced (see Chapters 6 and 7), this may not cure the underlying problem. For example, intravenous (IV) potassium supplementation may correct low serum levels, but does not address the causative factor (e.g., hyperemesis gravidarum). Primary protein energy malnutrition caused by inadequate intake is often reversible with nutritional therapy. The Joint Commission on Accreditation of Hospitals Organization requires hospitals to complete nutrition screening on all patients within 48 hours of admission. The advancement of the electronic patient medical record has enabled many institutions to surpass this requirement. Admission questionnaires, including nutritional questions completed by admitting or nursing personnel who generate

TABLE 9-1. Example of Nutrition Screening Questions to Include in Admission Survey

1. How is your appetite?
2. Current home diet?
3. Do you take diet or nutritional supplements? If yes what are they?
4. Do you understand your diet?
5. Do you follow your diet?
6. Have you had any recent weight loss or gain over the past 3 months? If yes, how much?
7. Do you have any food intolerances?
8. Are you pregnant or lactating?

When screening a patient for nutritional risk, the above information may be combined with other data pulled from the admission survey such as: admission weight, usual weight, admission height, reason for admission, normal elimination, last bowel movement, and ability to prepare own meals to aid in the determination of the patient's present nutritional status.

nutrition consults based on the patient's responses, are frequently utilized to meet this requirement (Table 9-1).

NUTRITION ASSESSMENT

Nutrition assessment identifies patients with malnutrition or those at risk of developing malnutrition; this is often referred to as a patient's "nutritional risk." The prevalence of hospital malnutrition has been documented at 20% to 50% (2,4–6). The economic, morbidity, and mortality impacts increase as the severity of the malnutrition increases (3,7). One group (3) classified the degree of malnutrition and determined the association with 1-year mortality in hospitalized patients (Figure 9-1). In general, patients who have lost greater than 10% of their body weight over the past 6 months or have a decreased body mass index (BMI), especially in combination with chronic disease or increased metabolic

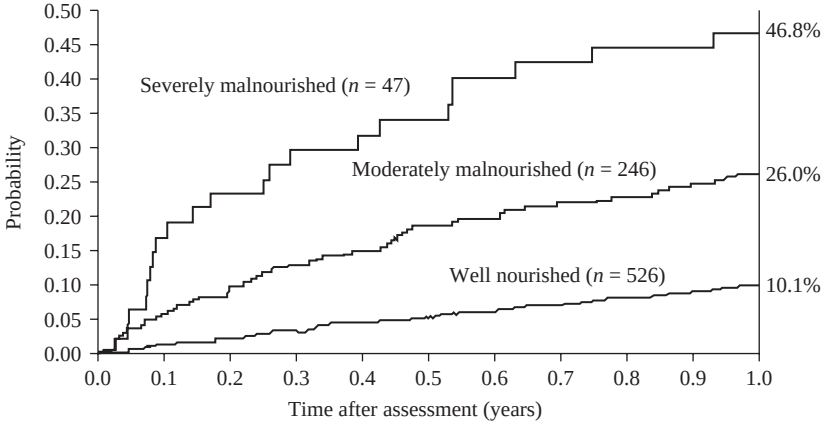


FIGURE 9-1. Malnutrition associated mortality. Incidence of mortality to 1 year. ($P < 0.0005$) between 3 categories (2). Adapted from Middleton MH, Nazarento G, Nivison-Smith I. Prevalence of malnutrition and 12-month incidence of mortality in two Sydney teaching hospitals. *Intern Med J.* 2001:31:455.

TABLE 9-2. Medical and Nutritional History Components

Diet/medication history	■ Recent intake/intolerances/appetite changes ■ Swallowing/chewing difficulties ■ Diet restrictions ■ Supplement usage—herbal, dietary, vitamins, minerals ■ Present home medications ■ Over-the-counter medications
Medical/surgical history	■ Pre-existing conditions ■ Past surgeries ■ Present anatomy (bowel resections/ostomies)
Social/functional/family history	■ Use of alcohol, tobacco, IV drugs ■ Present employment, living arrangements, social support ■ Functional status—ability to perform ADLs, exercise patterns ■ Family medical history ■ Religion, education, cultural factors
Gastrointestinal history	■ Recent nausea/vomiting ■ Normal bowel habits ■ Changes/increase in diarrhea, constipation, steatorrhea, bloating, flatus
Anthropometrics	■ Height ■ Usual body weight ■ Ideal body weight ■ Calculated BMI ■ Recent weight changes
Laboratory assessment	■ Comprehensive metabolic profile ■ Serum magnesium ■ Serum phosphorus ■ Serum triglyceride ■ CBC ■ Hemoglobin A1C, routine blood glucose levels ■ Other labs as indicated: TSH, PTH, CRP, vitamin/mineral studies

ADL, activities of daily living; BMI, body mass index; CBC, complete blood count; CRP, C-reactive protein; IV, intravenous; PTH, parathyroid hormone; TSH, thyroid stimulating hormone.

requirements, are at increased nutritional risk. A complete nutrition assessment should be completed to identify which patients will benefit from nutritional therapy. Optimally, the nutrition assessment should include medical and nutritional histories, a nutrition focused physical examination, and a review of the appropriate laboratory studies (see Tables 9-2 and 9-3).

In the past, hepatic proteins were thought to be associated with a patient's nutritional status. Although a low serum albumin is correlated with an increased incidence of morbidity and mortality (8), it is illness or injury, not malnutrition, which is responsible for the decreased albumin levels in sick patients (9). Even during chronic malnutrition, such as in the anorexic patient, little change in seen in the plasma albumin concentration (10–12). Further information regarding nutritional assessment tools is presented in Table 5-19 in Chapter 5.

NUTRITION INTERVENTION OR SUPPORT

Nutrition intervention or nutrition support may be achieved through several avenues (Figure 9-2). Prior to beginning nutritional support the following questions should be addressed.

TABLE 9-3. Nutrition Focused Physical Assessment

Vital signs	■ Temperature ■ Blood pressure ■ Pulse ■ Respiration—work of breathing, abnormal breath sounds
Oral cavity	■ Dry or inflamed mucosa ■ Cracked lips ■ Magenta tongue ■ Smooth, slick tongue ■ Excess caries, missing teeth ■ Bleeding gums ■ White patches/sores ■ Purple sores ■ Tumors
Skin	■ Color ■ Turgor ■ Sores/pressure ulcers ■ Rashes ■ Moisture/dryness ■ Temperature
Face/hair/eyes	■ Night blindness ■ Bitot spots (eyes) ■ Temporal wasting ■ Asymmetry ■ Drooling ■ Easily pluckable hair ■ Thinning hair ■ Moon face ■ Neck vein distention
Nails	■ Spoon shaped ■ Pale, mottled
Abdomen	■ Presence of distention ■ Percuss for tympany ■ Presence of scars, wounds, ostomies, feeding access
Other	■ Inspect temporalis, deltoid, and quadriceps for muscle wasting ■ Presence of edema in extremities, sacral area ■ Swollen joints ■ Bow legs

What Is the Patient's Current Degree of Nutritional Status?

Many of the decisions regarding the urgency of instituting nutritional support, especially the intensive forms of support (i.e., tube feeding and total parenteral nutrition), revolve around the answer to this question. Clinical, anthropometric, and laboratory data are used to formulate a general opinion regarding the degree of depletion; the difficulties of arriving at a meaningful nutritional assessment are described in Chapter 5. By using current techniques, the physician can divide patients into three main clinical groups: (a) those with mild macro- or micronutrient deficiencies, (b) those with moderate to severe deficiencies, and (c) those without deficiencies. Micronutrient deficiencies should be repleted as outlined in Chapters 6 and 7. For patients with moderate or severe protein/calorie deficiencies, nutrition support should be initiated as soon as possible, even perioperatively. A review of prospective randomized controlled trials of perioperative parenteral or enteral nutrition found a significant reduction in postoperative complications in patients diagnosed with severe malnutrition who received preoperative nutrition support. No clear benefit of perioperative nutrition was noted in patients moderately or well nourished (13).

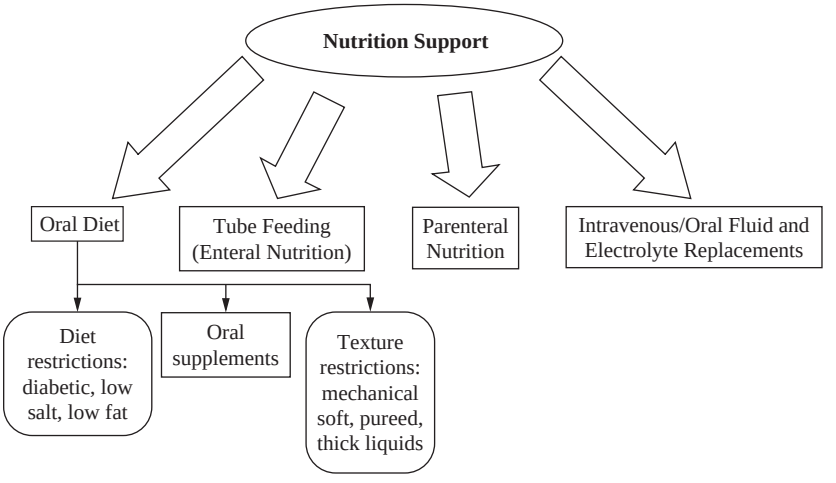


FIGURE 9-2. Avenues of nutrition support.

What Is the Anticipated Length of Time that Nutritional Support Will Be Required?

This will help to address both need and timing for nutrition support (see Figure 9-3). See Chapters 10 and 11 for more information on enteral and parenteral nutrition support and access. Anticipating the length of time that energy and protein requirements will not be satisfied by normal diets (i.e., the cumulative result of negative balance) helps determine the

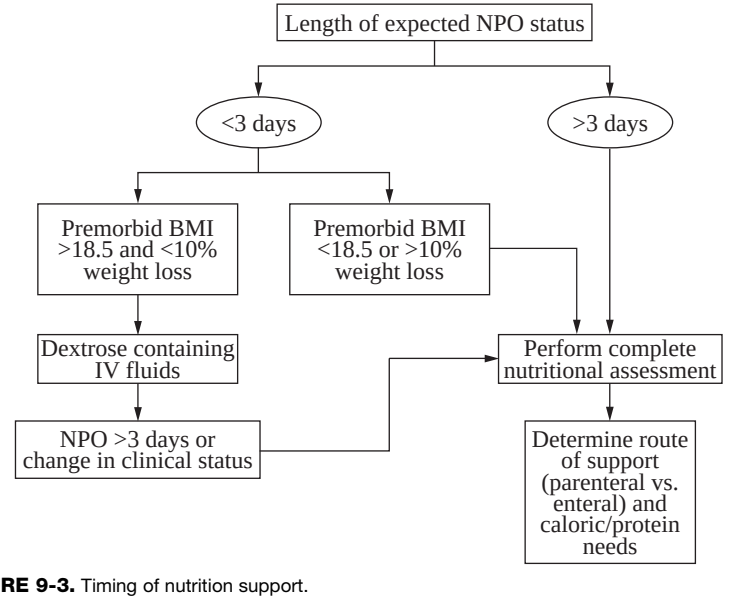


FIGURE 9-3. Timing of nutrition support.

TABLE 9-4. Estimated Cumulative Effect of Negative Balance

Estimated balance (kcal/d)	Cumulative weight loss during illness (illness length in days)											
	2	4	6	8	10	12	14	16	18	20	22	24
			−5%[a]			−10[a]						
−4,000	2.4[b]	4.7	7.1	9.4	11.8	14.1	16.5	18.8	21.2	23.2	25.9	28.2
−3,500	2.1	4.1	6.2	8.2	10.3	12.4	14.4	16.5	18.5	20.5	22.6	24.7
−3,000	1.8	3.5	5.3	7.1	8.8	10.6	12.4	14.1	15.9	17.6	19.4	21.2
−2,500	1.5	2.9	4.4	5.9	7.4	8.8	10.3	11.8	13.2	14.7	16.2	17.6
−2,000	1.2	2.4	3.5	4.7	5.9	7.1	8.2	9.4	10.6	11.8	12.9	14.1

[a] Percentage weight change for a 154-lb (70-kg) patient.
[b] Estimated weight loss in pounds.

urgency of instituting protein–calorie support. Estimation of the cumulative result of negative balance for the anticipated length of illness puts into perspective the end result of persistent negative energy balance. Representative estimates of weight losses incurred—depending on the degree of negative balance and the length of illness–are given in Table 9-4. This estimate is based on the assumption that a negative balance of 3,400 kcal represents a loss of 1 lb of body weight. In situations of metabolic stress, such a relationship is not as accurate as it is in situations of slow weight gain or loss, and this relationship does not remain constant as weight loss progresses. Also, the relationship does not take into account the adaptive processes that occur during starvation. However, it does help the clinician make a crude estimate of expected losses. A cumulative caloric deficit of greater than or equal to 10,000 calories has been associated with a survival disadvantage in intensive care patients (14).

How Should the Nutrition Support Be Provided: Enteral versus Parenteral?

The usual guideline for choosing between enteral and parenteral nutritional support is to use enteral support whenever possible. Parenteral nutrition should be reserved for patients who are or who will become malnourished and in whom enteral feeding is not an option (Figure 9-4) (15). Enteral nutrition is preferred over parenteral nutrition for several reasons: enteral nutrition provides nutrients to the gastrointestinal mucosa that are not provided by parenteral nutrition (i.e., short-chain fatty acids) (16); nutrients in the intestinal lumen have been shown to protect the integrity of the gastrointestinal tract in animals (17) and may be beneficial in humans although the data are not definitive; enteral nutrition is associated with less septic complications (15) than parenteral nutrition; and enteral nutrition is safer, more convenient, and less expensive. Even if full nutrition support by the enteral route is not feasible, it is unclear whether there is any benefit to instituting complementary parenteral nutrition (18).

What Are the Patient's Caloric and Protein Needs?

This question is covered in great detail in Chapter 5. While malnutrition and hypocaloric feeding may decrease a patients's resting energy expenditure (REE) by 15% to 20%, metabolic stress will increase the REE by as much as 40% in severe burns (19). Several equations exist to estimate the REE requirements; the most common of these are reviewed in Chapter 5. A task force convened by the American Dietetic Association (ADA) recently reviewed the use and reliability of these equations in the intensive care unit and in obese patients (20). The most commonly used was the Harris-Benedict equation; however, the Mifflin-St. Joer equation predicted REE more reliably than other equations when used in critically ill and obese patients (20).

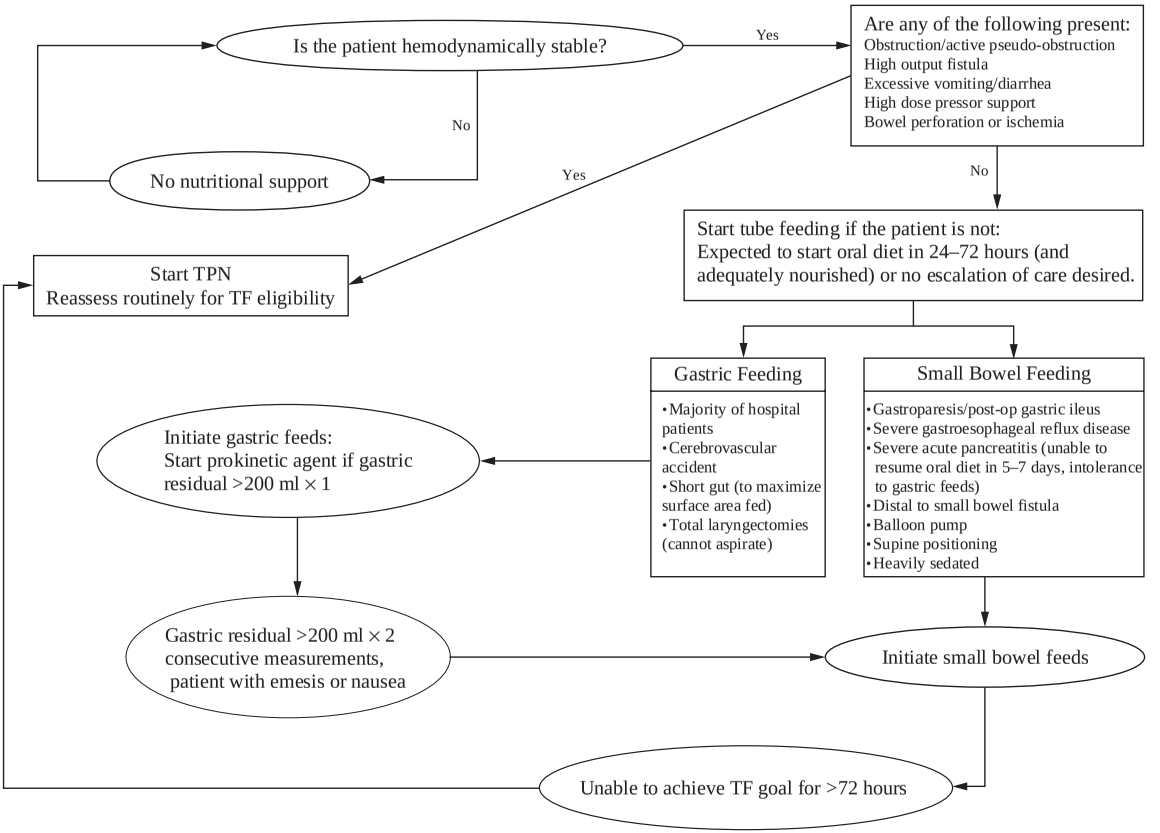


FIGURE 9-4. Determine route of intensive nutrition support. (TF, Tube feeds; TPN, Total parenteral nutrition)

Mifflin-St Joer Equation

Men:

$$\text{REE (kcal/day)} = 10(W) + 6.25(H) - 5(A) + 5$$

Women:

$$\text{REE (kcal/day)} = 10(W) + 6.25(H) - 5(A) - 161$$

W = weight in kilograms; H = height in centimeters; A = age in years.

A simple method of REE prediction based on BMI (presented in Table 5-4 in Chapter 5) is based on the premise that in general, energy given per kilogram of body weight is inversely related to BMI. The lower range within each category should be considered in insulin-resistant, critically ill patients, unless they are depleted in body fat, to decrease the risk of hyperglycemia and infection associated with overfeeding. Providing total daily energy equal to the Harris-Benedict calculation plus an additional 20% is a reasonable goal for nonobese, noncritically ill patients who have increased metabolic demands. It may be more accurate to utilize the BMI approach to estimate daily total energy for patients who are either very lean or obese.

Individual protein requirements are affected by several factors, such as the amount of nonprotein calories provided, overall energy requirements, protein quality, and the patient's nutritional status (see Chapter 5). In general, approximately 15% to 20% of total protein requirements should be in the form of essential amino acids in normal adults. Protein requirements during different clinical conditions are presented in Table 5-13 in Chapter 5. Illness, by increasing catabolism and metabolic rate, also increases requirements for protein.

NUTRITION MONITORING

Nutrition monitoring should not only address the tolerance of the nutritional support provided, but also the continued adequacy and effectiveness.

Monitoring Plan

The monitoring plan for patients at nutritional risk receiving nutrition support should include a determination of daily actual nutrition intake.

Critically Ill Patients

In critically ill patients provision of enteral nutrition within the first 48 hours with at least 60% to 70% of total estimated energy requirements received is associated with a decreased length of stay, time on mechanical ventilation, and infectious complications (21,22). Caution should be used when feeding critically ill patients as evidence exists of potential harm with overfeeding. Some researchers suggest "overfeeding" may be achieving greater than 70% of goal intake in the critically ill population (23). The detrimental effects of overfeeding are presented in Table 5-22 in Chapter 5. The concept of short-term feeding of 50% to 60% of a patient's estimated caloric needs while providing nearly 100% of their protein needs during periods of severe metabolic stress has been termed "permissive underfeeding" (24). While the preliminary research suggests there may be a benefit to underfeeding critically ill patients, no randomized control trials are presently available (23,25,26).

Noncritically Ill Patients

In noncritically ill patients, the patient should be advanced to their caloric goal within 24 to 48 hours. However, there is some evidence to suggest both critical and noncritical obese patients may benefit from the practice of permissive underfeeding (24,27–30). Other techniques to monitor intake in hospitalized patients are reviewed in Chapter 5.

Electrolytes

Electrolytes should be monitored during the administration of nutrition support. Patients at risk of refeeding (critically ill, >10% body weight loss, prolonged decreased oral intake) should be followed closely as the consequences are potentially serious (see Table 5-23 in Chapter 5). Changes in clinical status (i.e., decreasing renal function) may lead to electrolyte abnormalities

and need for alteration of the nutrition prescription. Specific recommendations for monitoring patients receiving enteral and parenteral nutrition are presented in Chapters 10 and 11.

FORMULATING A FINAL PROTEIN AND CALORIE SUPPORT PLAN

The final plan is designed according to the previously mentioned considerations. The key questions lead to decisions regarding the urgency of support and methods of protein and calorie delivery. More than one suitable method of support is usually available. An appropriate plan does not interfere with usual medical care but rather is an effective adjuvant to medical and surgical therapeutics. Of importance to the clinician is the appropriate selection of patients for intensive nutritional support (tube feeding and total parenteral nutrition). The key questions can help select these patients. Figures 9-3 and 9-4 present algorithms that are useful in the selection of patients and determination of timing and route for intensive nutrition support. The following examples illustrate possible approaches to nutrition support.

Example 1

History

A 26-year-old man with a 7-year history of Crohn disease and two prior small-bowel resections enters the hospital because of an exacerbation of symptoms. Despite outpatient therapy with immunosuppressive medications, he has continued to experience fatigue, a poor appetite, crampy postprandial abdominal pain, diarrhea, and low-grade fevers, but he does not appear dehydrated. His weight has dropped from 142 lb (usual) to 130 lb (8.5% decrease) in the past 3 months. Physical examination reveals a thin man with a tender abdominal mass in the right lower quadrant. Laboratory data include the following values: hemoglobin, 12.2 g per dL; white blood cell count, 16,000 per mm^3 (he is receiving corticosteroids); 9% lymphocytes (total lymphocyte count, 1,440 per mm^3); serum albumin, 3.2 g per dL; and total iron-binding capacity, 270 mg per dL. A small-bowel radiographic study shows multiple skip lesions typical of Crohn disease in the remaining ileum with a very narrowed distal segment proximal to the prior anastomosis.

Impression and Plan

Although the degree of recent weight loss suggests that significant protein–calorie malnutrition may be present, screening laboratory tests indicate that the degree of depletion is probably not severe. Despite the favorable assessment, total parenteral nutrition may be indicated in this situation because of the patient's poor appetite and to lessen his discomfort during the management of refractory extensive Crohn disease of the small bowel. The planned course of therapy will probably exceed 3 to 4 weeks.

Example 2

History

A 49-year-old alcoholic man is admitted with acute epigastric pain boring through to the back, nausea, and vomiting of 24 hours' duration. The diagnosis of acute pancreatitis is made; nasogastric suction and IV fluids are initiated. Although the patient denies significant weight change in the past 6 months, the admitting physician reports that the patient appears somewhat wasted. Initial laboratory values include serum albumin, 2.7 g per dL; total lymphocyte count, 1,000 per mm^3; and total iron-binding capacity, 200 mg per dL. Mumps and streptokinase-streptodornase (SKSD) skin tests are placed as controls for a tuberculin skin test, but the patient fails to react to any of these skin-test antigens.

Impressions and Plan

Laboratory data support the clinical impression of significant (moderate to severe) protein–calorie malnutrition and severe disease. Failure to react to the skin tests also may be a consequence of malnutrition. The established deficiencies are suspected to be a result of chronically poor intake accompanying alcoholism. Although the protein and calorie balances are negative while the patient is receiving IV 5% dextrose in water, the current illness is expected to be short. If the patient experiences pain with eating, a temporary nasojejunal

tube should be placed and tube feedings initiated. If the patient continues to experience pain with jejunal feedings, parenteral nutrition should be considered given the patient's premorbid nutritional status.

Example 3

History

Fever and a productive cough have developed in a 72-year-old woman in previously good health. Because her appetite is poor and her fluid intake inadequate, she is admitted for therapy. She appears acutely ill and mildly dehydrated. Radiographic examination of the chest confirms the diagnosis of lobar pneumonia. Laboratory studies reveal normal hemoglobin and albumin levels and a normal lymphocyte count. Nutritional history estimates a recent daily intake of 650 kcal and 20 g of protein.

Impression and Plan

No historical features suggest protein–calorie malnutrition in this patient, and the laboratory data support the impression. Remember, however, that albumin levels are affected by hydration. Current intake does not match calculated requirements, but the illness is expected to be short. Oral liquid supplements are offered to improve fluid, protein, and calorie balance until the pneumonia resolves and a regular diet is tolerated.

Example 4

History

Progressive respiratory failure has developed in a 58-year-old man with chronic obstructive lung disease and several recent acute respiratory infections. He is admitted and requires mechanical ventilation. His weight has fallen from 166 to 156 lb (6% decrease) in the past 6 months. Current treatment includes 150 g of IV dextrose per day as the only calorie source.

Impression and Plan

Clinical and anthropometric data suggest a moderate degree of protein–calorie malnutrition. In this case, the anticipated duration of nutritional support is unclear. Because of the existing deficiencies, it is reasonable to proceed with intensive support. Tube feeding with a small-caliber nasoduodenal tube is initiated.

Example 5

History

A 52-year-old woman is transferred from another hospital after a complicated postoperative course. Within the past 8 weeks, she has undergone a vagotomy and pyloroplasty for peptic ulcer disease and then reoperation for gastric outlet obstruction with creation of a gastrojejunostomy. The stoma is functioning poorly. She continues to require nasogastric suction because of vomiting, and a revision of the anastomosis will be necessary. She appears to be overweight (height of 65 inches), but her weight has fallen from 220 to 192 lb (13% decrease) in the past 2 months. She states that she is very weak. Laboratory values include a white blood cell count of 5,200 per mm^3, 12% lymphocytes (total lymphocyte count of 620 per mm^3), serum albumin level of 2.13 g per dL, and total iron-binding capacity of 180 mg per dL (estimated transferrin level, 100 mg per dL).

Impression and Plan

The history of recent operations and weight loss suggests that significant protein–calorie malnutrition may be present. In this case, initially excessive fat stores have prevented the appearance of wasting despite persistent negative balances and concomitant protein losses. Based on the current degree of negative balance (her only intake is IV 5% dextrose) and the fact that another laparotomy is necessary, it is felt that the anticipated duration of support may be long. The patient is appropriately selected for intensive nutritional support; because the intestinal tract is not readily available for use, total parenteral nutrition is instituted. It is decided to give the patient 3 weeks of total parenteral nutrition before her third laparotomy.

Example 6

History

A 66-year-old woman is admitted because of diarrhea, a poor appetite, and a 5% weight loss in the past 23 months. Twelve months ago, she completed a course of radiation therapy for carcinoma of the cervix. Small-bowel series reveals several long areas of fold thickening and spiculation in the distal ileum, consistent with radiation enteritis. Laboratory values include a serum albumin of 3.0 g per dL, serum transferrin level (estimated from the total iron-binding capacity) of 190 mg per dL, and total lymphocyte count of 1,200 per mm^3. A creatinine–height index of 68% is calculated from a 24-hour urinary creatinine collection, originally ordered for determining creatinine clearance. Inpatient calorie counts reveal a daily intake of 800 to 900 kcal and 20 to 30 g of protein.

Impression and Plan

At least a mild degree of protein–calorie malnutrition is suggested by the history and screening laboratory tests. Protein losses may be occurring from the intestinal tract, and these losses would accelerate the rate of protein depletion. The nearly normal serum transferrin level may be a result of concomitant iron deficiency secondary to persistent gastrointestinal blood loss. The anticipated length of negative balance is uncertain, and attempts are made to increase oral intake with low-fat, high-protein commercial supplements. Antidiarrheal medications are also used. Although the diarrhea abates, repeated calorie counts suggest that the negative balance of about 500 kcal per day is persisting because of poor appetite. Tube feeding with similar formulas via a nasoduodenal tube is offered to the patient, but she chooses to continue to try oral supplements; she wishes to be discharged and be re-evaluated in several weeks.

References

1. Lacey K, Prichett E. Nutrition care process and model: ADA adopts road map to quality care and outcomes management. *J Am Diet Assoc.* 2003;103:1061.
2. Coast KG, Morgan SL, Bartoluccii AA, Weinsier RL. Hospital-associated malnutrition: a reevaluation 12 years later. *J Am Diet Assoc.* 1993;93:27.
3. Middleton MH, Nazarenko G, Nivison-Smith I, Smerdely P. Prevalence of malnutrition and 12-month incidence of mortality in two Sydney teaching hospitals. *Intern Med J.* 2001;31:455.
4. Naber THJ, Schermer T, de Bree A, et al. Prevalence of malnutrition in nonsurgical hospitalized patients and its association with disease complications. *Am J Clin Nutr.* 1997;66:1232.
5. Waitzberg DL, Caiaffa WT, Correia MITD. Hospital malnutrition: the Brazilian National Survey: a study of 4000 patients. *Nutrition.* 2001;17:573.
6. Cederholm T, Jagren C, Hellstrom K. Outcome of protein-energy malnutrition in elderly medical patients. *Am J Med.* 1995;98:67.
7. Correia MT, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clin Nutr.* 2003;22:473.
8. de Luis DA, Arranz M, Aller R, Izaola O, Cuellar L, Terroba MC. Immuno-enhanced enteral nutrition, effect on inflammatory markers in head and neck cancer patients. *Eur J Clin Nutr.* 2005;59:145.
9. Fuhrman MP, Charney P, Mueller CM. Hepatic proteins and nutrition assessment. *J Am Diet Assoc.* 2004;104:1258.
10. Krantz MJ, Lee D, Donahoo WT, Mehler PS. The paradox of normal serum albumin in anorexia nervosa: a case report. *Int J Eat Disord.* 2005;37:278.
11. Smith G, Robinson PH, Fleck A. Serum albumin distribution in early treated anorexia nervosa. *Nutrition.* 1996;12:677.
12. Waterlow JC. On serum albumin in anorexia nervosa. *Nutrition.* 1996;12:720.
13. Howard L, Ashley C. Nutrition in the perioperative patient. *Annu Rev Nutr.* 2003;23:263.
14. Driscoll DF, Blackburn GL. Total parenteral nutrition 1990: A review of its current status in hospitalised patients, and the need for patient-specific feeding. *Drugs.* 1990;40:346.
15. Gramlich L, Kichian K, Pinilla J, et al. Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. *Nutrition.* 2004;20:843.
16. Klein S. Short-chain fatty acids and the colon. *Gastroenterology.* 1992;102:364.
17. Harvey RB, Andrews K, Droleskey RE, et al. Qualitative and quantitative comparison of gut bacterial colonization in enterally and parenterally fed neonatal pigs. *Curr Issues Intest Microbiol.* 2006;7:61.
18. Dhaliwal R, Jurewitsch B, Harrietha D, et al. Combination enteral and parenteral nutrition in critically ill patients: harmful or beneficial? A systematic review of the evidence. *Intensive Care Med.* 2004;30:1666.
19. Calculations for Nutrition Assessment. American Dietetic Association. *Nutrition Care Manual.* Available at: http://www.nutritioncaremanual.org Accessed October 20, 2007.
20. Indirect Calorimetry Evidence Analysis Project. In: *The American Dietetic Association Evidence Based Library*. Available at: http://www.adaevidencelibrary.org. Accessed October 20, 2007.

21. Hise ME, Halterman K, Gajewski BJ, et al. Feeding practices of severely ill intensive care unit patients: an evaluation of energy sources and clinical outcomes. *J Am Diet Assoc.* 2007;107:458.
22. McCowen KC, Friel C, Sternberg J, et al. Hypocaloric total parenteral nutrition: effectiveness in prevention of hyperglycemia and infectious complications—randomized clinical trial. *Crit Care Med.* 2000;28:3606.
23. Boitano M. Hypocaloric feeding of the critically ill. *Nutr Clin Pract.* 2006;21:617.
24. Eiden KA. Permissive underfeeding in the obese hospitalized patient. *Top Clin Nutr.* 2006;21:320.
25. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med.* 2001;29:2264.
26. Auboyer C, Bouletreau P. Risk of bloodstream infection can be strongly decreased by a very moderate caloric intake or strongly increased by a very low caloric intake in severely ill patients in intensive care? *Crit Care Med.* 2004;32:591.
27. Burge JC, Goon A, Choban PS, et al. Efficacy of hypocaloric total parenteral nutrition in hospitalized obese patients: a prospective, double-blind randomized trial. *JPEN J Parenter Enteral Nutr.* 1994;18:203.
28. Choban PS, Burge JC, Scales D, et al. Hypoenergetic nutrition support in hospitalized obese patients: a simplified method for clinical application. *Am J Clin Nutr.* 1997;66:546.
29. Choban PS, Flancbaum L. Nourishing the obese patient. *Clin Nutr.* 2000;19:305.
30. Choban PS, Heckler R, Burge JC, et al. Increased incidence of nosocomial infections in obese surgical patients. *Am Surg.* 1995;61:1001.

10 ENTERAL NUTRITIONAL THERAPY

GENERAL PRINCIPLES

This chapter outlines methods of providing macronutrients to individuals with inadequate intake or ineffective absorption of their usual diet. Enteral nutritional therapy may be accomplished by diet modifications of texture and content or provision of commercially available oral and forced enteral feeding products (Figure 10-1).

Modification of the Basic Diet

Modification of the basic diet may include texture or liquid consistency modifications. In addition, protein and caloric intake may also be supplemented or restricted by manipulating a patient's intake of certain whole foods.

Oral Supplements

Commercially available oral supplements are often used to improve a patient's daily intake of protein and calories. Many are now available in multiple flavors and forms to avoid taste monotony in long-term use.

Forced Enteral Feeding

Forced enteral feeding, generally referred to as tube feeding (TF), is preferred to total parenteral nutrition (TPN) if the intestinal tract can be used to aid in maintaining the structural and functional integrity of the GI tract as outlined in Chapter 9. According to the published guidelines of the American Society of Parenteral and Enteral Nutrition (1), TF is contraindicated in diffuse peritonitis, intestinal obstruction, intractable vomiting and diarrhea, paralytic ileus, and gastrointestinal ischemia. Advances in the composition of TF products allow its use in conditions previously thought to be contraindicated, such as pancreatitis, short-bowel syndrome, and enterocutaneous fistulae.

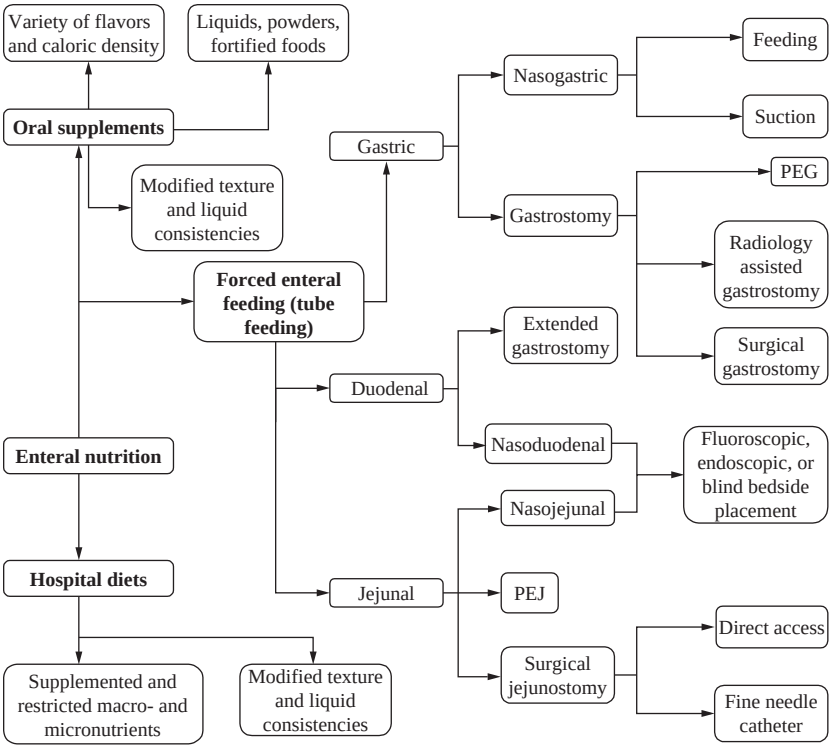


FIGURE 10-1. Overview of enteral nutrition therapy

INDICATIONS FOR ENTERAL THERAPY

Modification of Diet Texture and Content

Changes in diet texture and liquid consistency are often necessary in the nutritional management of certain diseases and neurologic conditions. In general, texture modifications are required in individuals with a neurologic deficit or head and neck abnormalities. Information on modified-texture diets can be found in Chapters 12 and 13. A change in diet content to supplement or restrict protein and calories is often required in patients with an increased metabolic rate (e.g., burns or sepsis), specific disease state (e.g., renal or liver failure), or varied oral intake. Improved nutritional intake and quality of life have been linked to patient modification of whole food intake to include higher protein and caloric choices (2). Macro- and micronutrient content may also need to be adjusted in patients with malabsorptive or inflammatory bowel disease. Techniques used in managing two special problems of protein and calorie absorption (pancreatic insufficiency and short-bowel syndrome) are discussed later in this chapter.

Oral Supplementation

Hospitalized patients are often plagued with inadequate protein or calorie intake to meet their daily requirements. Commercially available oral supplements (Table 10-1) are

TABLE 10-1. Commercially Available Oral Supplements[a]

Product type	Nestlé nutrition	Novartis medical nutrition	ROSS nutrition	Hormel health labs
Ready to feed[b]	Carnation (Instant Breakfast, Instant Breakfast for the carb conscious, Instant Breakfast lactose free, Instant Breakfast lactose free VHC), Nutren (1.0, 1.5– with/ without fiber, renal, pulmonary, heal), ProBalance, Renalcal, Peptamen	BOOST (diabetic, high protein, plus and with Benefiber), Resource (healthshake, no sugar added), Novasource (renal, pulmonary), Impact advanced recovery	Ensure (high calcium, high protein, plus), Hi-Cal, Glucerna (select, shake, weight loss shake), Nepro with carb steady, ProSure	Great shakes, Mighty shakes
Powdered	Additions, Carnation Instant Breakfast, Instant Breakfast for the carb conscious, Modulen	Resource (instant breakfast, eggnog, and milk shake)	Ensure powder	Instant mixes for shakes and breakfast drinks, ProPass
Clear liquid	Carnation juice drink	Resource (broth plus mix, Arginaid extra, diabetishield, fruit flavored beverage)	Enlive, Juven	
Fortified foods		BOOST pudding, Resource (cereal plus, cookie plus, ice cream plus, nutritious pudding)	Ensure pudding, Glucerna snackbar bar and meal bar	Nutritional cookies, Magic cup
Beverages Modified liquid consistency		Resource (dairy thick, shake, thickened coffee, thickened hydration drink, thickened juice, thickened water)		Thick and Easy (coffee, tea, dairy, juices, and Hydrolyte)
Foods/Other		Nutrisource (quick custard mix, reduced calorie custard mix, vanilla custard), Dietsource (fruit sorbet, reduced calorie low fat cake mix)		Instant mixes for custard, pudding
Modulars	Additions (protein, fat, and carbohydrate)	MCT oil (fat source) Beneprotein Benecalorie (protein/fat)	Polycose powder (carbohydrate source)	High protein powder

[a] Partial listing of products and companies; availability of products may have changed. For a complete listing of the above company products visit their websites: www.hormelhealthlabs.com/products, www.nestle-nutrition.com, www.novartisnutrition.com/Intl, www.ross.com/productHandbook/adultNut.asp.
[b] Altered macro- and micronutrient contents to meet the needs of specific patient populations.

now available in a variety of forms (e.g., cereal, pudding, soups, and liquid supplements), consistencies (e.g., nectar thick liquids, honey thick liquids), and flavors (e.g., strawberry, butter pecan, cappuccino). It is often as easy, if not easier, to instruct a patient to take one or two oral supplement servings per day with a defined nutritional content as it is to suggest a selection of foods that may be unfamiliar or unappealing to the patient. Certain groups of people are particularly good candidates for oral dietary supplements.

Patients Chronically Ill with Associated Anorexia

Patients who are chronically ill with associated anorexia, as seen in cancer and HIV+ patients, may be unable to meet their caloric needs for weight maintenance with table foods alone. Weight loss can be diminished by adding nutritional supplements (3).

Patients Requiring Liquid or Soft Diets

Patients requiring liquid or soft diets because of an inability to chew foods, painful oral lesions, strictures of the esophagus, or poor gastric antral motor activity may prefer commercially prepared supplements to the usual dietary liquids (e.g., milk, juice) or blenderized and puréed foods. Usual dietary liquids alone are deficient in daily requirements of vitamins and minerals. Commercial supplements can guarantee satisfactory vitamin and mineral allowances along with protein and calorie supplementation. The recent FOOD trial demonstrated the benefits of oral supplementation on weight maintenance or gain in this population (4).

Patients Preparing for Tests or Surgical Procedures

Radiographic studies may subject the patient to a negative caloric balance day after day in the hospital. Nutritional supplements, particularly in combination with a clear liquid diet, can minimize nutritional losses. Many low-residue commercially available supplements can be used in conjunction with the clear liquid diet. In most cases, low-residue supplements added to the diet while the colon is being prepared do not compromise the quality of a barium enema or colonoscopy. Provision of oral supplements pre-operatively has been proven to decrease postoperative weight loss and complications, especially in patients with premorbid malnutrition (5). In addition, pre- and perioperative oral supplements have also been shown to decrease overall postoperative hospital costs (6).

Specific Dietary Needs

Patients with specific dietary needs may benefit from the special characteristics of many commercially available supplements.

Commercial Supplements. Most commercial supplements are low in residue because they contain no vegetable or meat fiber. Supplements containing no fiber and no fat probably add the least to the volume entering the colon. Soy polysaccharide has been added to several supplements to increase their fiber content. High-fiber products may be beneficial to selected patients with altered bowel habits resulting from functional motor disorders.

Many Lactose-free Supplements Are Available. Corn syrup solids, sucrose, glucose, and other sugars serve as the source of carbohydrate; casein, soy protein, egg whites, or amino acids (or a combination of these) serve as a source of protein, so that the need for milk additives or lactose is avoided.

Oral Supplements. Oral supplements with modified amino acid profiles have been developed for patients with renal failure and chronic liver disease.

Patients with renal failure. For patients with renal failure, essential amino acids added to a diet low in total protein content help to promote a positive nitrogen balance without causing unacceptable increases in blood urea nitrogen (BUN). The amino acid profiles in

these supplements are designed to meet and exceed by several times the normal essential amino acid requirements. A recent meta-analysis concluded that reducing protein intake in patients with chronic renal failure effectively slows the progression of renal disease, reducing the incidence of renal death by nearly 40% as compared with greater or unrestricted protein intake (7). In contrast, a low daily protein intake in patients undergoing hemodialysis is associated with increased mortality (8). Ultimately, a diet providing less than 40 g of protein per day is not recommended for nondialysis patients and 1.2 to 1.4 g per kg per day should be provided to patients undergoing dialysis (9). Undernutrition is common in patients with chronic renal failure with uremic syndrome. Common causes of undernutrition in these patients include: reduced oral intake, restrictive dietary regimen, uremic toxicity, metabolic alterations, endocrine issues, and gastrointestinal issues (10). Studies show that more than 50% of hemodialysis patients reported an intake of less than 1 g per kg per day of protein (11), suggesting the use of high protein supplements may be beneficial in this patient population.

Patients with chronic liver disease and hepatic encephalopathy. Patients with chronic liver disease and hepatic encephalopathy also have consistently abnormal plasma amino acid profiles, with an increase in aromatic amino acids (phenylalanine, tyrosine, tryptophan) and decreased proportions of branched-chain amino acids (isoleucine, leucine, valine). Protein supplements rich in branched-chain amino acids can be added to the protein-restricted diet to assist in establishing a positive nitrogen balance without precipitating encephalopathy (12). Disease-specific protein supplements are covered later in this chapter.

Indications for Tube Feeding

1. Patients with existing severe protein or protein-calorie malnutrition or who are at risk of protein-calorie depletion because of persistent negative nitrogen balance.
2. Anorexia.
3. Fractures of the head and neck or neurologic disorders preventing satisfactory oral feeding.
4. Coma or depressed mental state.
5. Need for prolonged assisted ventilation.
6. Serious medical or surgical illnesses (e.g., burns) in which metabolic requirements are very high.
7. Specific indications for the use of enteral feeding.

Enterocutaneous Fistulae. Enterocutaneous fistulae have been reported to close with goal enteral feeds infused via a feeding tube into the intestine distal to the fistula (fistuloclysis) (13,14). However, a series of studies reporting the use of enteral feeding for the primary treatment of enterocutaneous fistulae are small and uncontrolled. Complete bowel rest with the use of TPN has been employed more commonly as a nonsurgical attempt to close fistulae before definitive surgery.

Small-bowel Adaptation. Small-bowel adaptation occurs when intraluminal nutrients are again presented to the remaining small-bowel mucosa following massive intestinal resection. TPN may not be needed in these patients when vitamin and mineral supplements and large amounts of calories and protein are provided enterally (15,16).

Crohn Disease of the Small Bowel. Crohn disease of the small bowel can be managed with enteral nutrition. In children, exclusive enteral feeds induced remission in 80% of those with newly diagnosed disease (17). Enteral nutrition is also recommended as the sole therapy in adults when treatment with corticosteroids is not feasible (18), otherwise steroid therapy is a more effective treatment when compared to enteral nutrition (19). Controlled trials have found elemental and intact protein tube feeding diets in these patients to be equally effective (19).

Severe Acute Pancreatitis. Severe acute pancreatitis was for years considered an indication for TPN. Enteral nutrition was considered contraindicated because it was thought that it would worsen pancreatic damage. Recent studies have demonstrated that enteral nutrition is well tolerated in acute pancreatitis (20–23). Nasojejunal enteral feeds are well

tolerated and are recommended as the first line of nutrition support in severe acute pancreatitis on the basis of theoretical considerations, but data showing a clear benefit over nasogastric feeding are not available (24–27).

METHODS OF PROVIDING ORAL ENTERAL NUTRITION THERAPY

Supplementation with Whole Foods

Supplementation with whole foods should be utilized for patients with normal appetites who are not meeting their daily protein and caloric requirements.

Protein Supplementation with Whole Foods

The quality of a protein supplement as a source of amino acids for growth is referred to as the biologic value of the protein. The protein content of various foods is listed in Table 10-2. Certain characteristics of these foods may limit their use depending on coexisting intestinal disorders.

Milk Products. The lactose content is high; hard cheeses contain the least lactose per serving. The fat content is at least 4 g per serving (serving sizes are listed in Table 10-2) except for skim and nonfat dry milk, both of which have less than 1 g per cup. Most cheeses are high in fat, but a selection made with skim milk is available.

Eggs. Egg whites contain protein without lipid. The cholesterol is in the yolk.

Peanut Butter. Peanut butter contains 8 g of fat per tablespoon (50% of its weight is fat).

Beef, Poultry, and Fish. Flat fish are lowest in triglyceride, whereas steaklike fish have a fat content quantitatively similar to that of beef.

Calorie Supplementation with Whole Foods

Calorie supplementation with whole foods is conceptually attractive but often practically unfeasible. A normal diet with adequate calorie content restores glycogen and fat stores in the patient who has voluntarily or involuntarily starved. However, a lack of available calorie sources is not usually the reason for negative calorie balance and fat store depletion in the

TABLE 10-2. Common Foods that Should Be Included in a High Protein Diet

Protein source	Biologic value	Food	Serving size	Protein content (g per serving)
Milk	85	Whole milk	1 cup	8.5
		Skim milk	1 cup	9
		Nonfat dry milk	1 tbs	2.7
		Ice cream	1 cup	6
		Ice milk	1 cup	6
		Cottage cheese	1 cup	30
		Yogurt (low-fat)	1 cup	8
		Cheese slice	1 oz	6–8
Egg	85	Egg	1 large	7
		Eggnog	1 cup	12
Vegetable	70–75	Peanut butter	1 tbs	4
Meat	75–90	Lean beef	1 oz	7
		Fresh fish	1 oz	7
		Tuna	1 oz	7
		Chicken/turkey (without skin)	1 oz	8

United States. If increasing the usual diet with good calorie sources satisfies the daily requirements, then this is the ideal way of managing calorie deficiency. In 2002, the United States Department of Agriculture published an updated version of *Nutritive Value of Foods* which is available online at www.nal.usda.gov/fnic/foodcomp/Data/HG72/hg72_2002.pdf. They also provide an online search engine of an extensive listing of foods available in the United States at www.ars.usda.gov/Services/docs.htm?docid=7783. Nongovernment references are also available including the newest edition of *Bowes and Church's Food Values of Portions Commonly Used* (28).

Supplementation with Commercially Available Modular Products

Almost all the familiar commercial products for oral supplementation or tube feeding are "complete" formulas that provide a mixture of macronutrients and micronutrients. These products supply a person's nutritional needs completely if taken in sufficient quantity. In addition to the "complete" formulations, commercial sources produce feeding modules that provide a single macronutrient. These macronutrient modulars can be used to alter commercial formulas or as an oral supplement, to tailor both TFs and oral diets to a patient's unique nutritional requirements. The modulars are generally more expensive than "complete" formulations.

Protein Modulars

Protein modulars are generally a concentrated source of whey protein isolate that are designed to mix instantly into a wide variety of foods without affecting their taste or texture.

Carbohydrate Modulars

Carbohydrate modulars are usually composed of glucose polymers formed by the partial hydrolysis of starch. Modules with smaller polymers are sweeter and have a higher osmolality than those with large polymers.

Fat Modular

The only fat modular on the market at present consists of medium-chain triglycerides (MCT) in an oil form. MCT are fatty acids with chains that have 6 to 12 carbon atoms, whereas long-chain triglycerides (LCT), the predominant lipid in both vegetable and animal fats, contain fatty acids with chains that have 14 or more carbon atoms. The advantages and disadvantages of MCT versus LCT are presented in Table 10-3. The theoretical caloric value is 8.3 kcal per g. The caloric value per serving is estimated at about 115 kcal per tbs (15 mL). MCT oil can be used as a caloric supplement in patients with fat malabsorption of any cause.

TABLE 10-3. Medium Chain Triglycerides—Advantages and Disadvantages

Advantages	Disadvantages
■ Hydrolyzed more rapidly ■ Bile acids not required for absorption ■ Absorbed as an intact triglyceride molecule ■ Highly water soluble ■ Transported to the liver directly via the portal vein ■ Does not require re-esterification within chylomicrons ■ Crosses the mitochondrial membrane rapidly in the liver without carnitine ■ Readily oxidized	■ Lack linoleic and linolenic acids so small amounts of LCTs[a] are needed to prevent EFAD[b] ■ More ketogenic and should be avoided in patients with diabetes, ketosis, or acidosis ■ Contra-indicated in patients with cirrhosis (particularly those with portal systemic shunts) ■ May cause gastrointestinal symptoms of nausea, vomiting, and diarrhea if daily amount exceeds 500 calories per day

[a] Long chain triglycerides.
[b] Essential fatty acid deficiency.

FORMULAS FOR FORCED ENTERAL FEEDING OR TUBE FEEDING

Formulas for forced enteral feeding or tube feeding are available with many variations in specific characteristics and nutritional content. These formulas can be divided into four general categories: standard, elemental/semi-elemental, disease specific, and immune modulating products (Table 10-4). A very large number of commercial enteral formulations are available, and new formulations are introduced frequently. The most suitable diet for an individual patient is one that provides the planned, desired allowances of macronutrients and micronutrients and also is appropriately restricted and varied according to any intestinal or metabolic disorders that are present. Table 10-5 groups commercial diets by the major categories and provides detailed nutritional information and the special characteristics of these formulas. For clarity table definitions are provided.

Definitions

The following are definitions of some terms used in the tables:

Low-residue

This term is applied to diets that contain no meat or vegetable fiber.

Caloric Density

The caloric densities of commercial enteral products range from 1.0 to 2.0 kcal per mL.

Osmolality

Whole proteins and complex polysaccharides contribute a large number of calories to a formulation but relatively few milliosmoles. In contrast, free amino acids and monosaccharides contribute many more milliosmoles for the same number of calories. As a result,

TABLE 10-4. Classification of Commercially Available Complete Enteral Nutrition Products

Standard	Disease specific	Elemental/semi-elemental
1.0–1.2 calorie/ml ■ IsoCal/IsoCal HN ■ Nutren 1.0 ■ Osmolite/Osmolite 1 cal ■ Osmolite 1.2 cal **1.5–2.0 calories/ml** ■ IsoSource ■ NovaSource 2.0 ■ Nutren 1.5/Nutren 2.0 ■ Osmolite 1.5 ■ TwoCal HN **High protein >18% of calories** ■ IMPACT ■ Promote ■ Replete **Fiber containing** ■ Fibersource/HN ■ IsoSource 1.5 ■ Jevity 1.2 cal/1.5 cal ■ Nutren Fiber	**Pulmonary** ■ NovaSource Pulmonary ■ Nutren Pulmonary ■ Pulmocare **Diabetic** ■ Diabetisource AC ■ Glucerna ■ Glucerna Select ■ Glytrol **Renal** ■ Nepro Carb Select ■ Novasource Renal ■ NutriRenal ■ RenalCal ■ Suplena Carb Select **Liver** ■ NutriHep	**Peptide based** ■ Optimental ■ Peptamen ■ Peptamen AF ■ Peptamen VHP ■ Peptamen 1.5 ■ Pivot 1.5 **Free amino acid based** ■ F.A.A. ■ Vivonex TEN/RTF **Immune modulating** ■ Crucial ■ IMPACT 1.5/glutamine ■ Nutren Replete ■ Oxepa ■ Peptamen AF ■ Perative ■ Pivot 1.5

TABLE 10-5. Nutrient Analysis of Various Commercially Available Protein and/or Calorie Supplements and Diets

Product	Manufacturer	Oral (O) Tube (T)	Macronutrient major sources			Caloric distribution (%)			Caloric density (kcal/mL)	Osmolality[a] (mOsmol/kg)	Fiber (g/1,000 kcal)
			Protein	CHO	Fat	Protein	CHO	Fat			
Alitra Q	Rose	O, T	S, M, AA	CS, S, F	MCT, SA	21	66	13	1.0	575	0
Amin-Aid	Rand D	O	AA	MD, S	S	4	74.8	21.2	2.0	700	0
Boost	Novartis	O	M	CS, S	CA, C, SU	17	67	16	1	610–670	0
Boost HP	Novartis	O	C	CS, S	S	24	55	21	1	650–690	0
Boost Plus	Novartis	O	C	CS, S	C	16	50	34	1.52	630–670	0
Boost with Benefiber	Novartis	O	C, S	MD, S	C, CA, MCT	17	53	30	1.06	480	10
Boost Diabetic	Novartis	O	C	CS, F, FOS	CA	22	36	42	1.06	400	14.8
CIB	Nestlé	O	M	MD, S, L	MF	25	73	2	0.8	NA	0
CIB carb conscious	Nestlé	O	M	MD, L	MF	33	63	4	0.56	NA	0
CIB juice	Nestlé	O	M	CS, MD		16	84	0	1	990	0
CIB lactose free VHC	Nestlé	O	CH	CS	CA	16	34	50	2.25	950	0
Crucial	Nestlé	T	CH, AR	MD, CS	MCT, FI, S	25	36	39	1.5	490	0
Diabeti-Source	Novartis	O	C, P	MD, S	CA, SU	17	53	30	1.06	480	10
Ensure	Ross	O, T	C, S	CS, S	C	14.4	64	21.6	1.06	590–600	0
Ensure Plus	Ross	O, T	C, S	C	CS, S	14.8	57	28.2	1.5	680	0
Ensure high calcium	Ross	O, T	C, S	S, MD	C	18.3	56.9	24.8	0.95	540	
Ensure Plus HN	Ross	O, T	C, S	C	CS, S	17	30	53	1.5	650	0
Ensure with fiber	Ross	O	C, S	FOS, CS, S	C	14.5	55	30.5	1.1	480	14
Glucerna	Ross	O, T	C	CS, F	SA, S, F	16.7	34.3	49	1	355	14.4
Glucerna Select	Ross	O, T	C	MD, F, FOS	C, SA, F	20	31	39	1	470	21.1
Impact	Novartis	T	C, AR	CS	FI	22	53	25	1	375	0
Impact with fiber	Novartis	T	C, AR	CS, GV	FI	22	53	25	1	375	10
Impact 1.5	Novartis	T	C, AR	MD	F, FI	22	38	40	1.5	550	
Isocal	Novartis	T	C, S	MD	S, MCT	13	50	37	1.06	300	10
Isocal HN	Novartis	T	C, S	MD	S, MCT	17	47	36	1.06	300	0
Isosource	Novartis	O, T	CS, C, S	CS	CA, MCT	14	56	30	1.2	490	0
Isosource 1.5	Novartis	T	C	CS, S	CA, MCT, S	18	44	38	2	650	8
Isosource HN	Novartis	O, T	CS, C, S	CS	CA, MCT	18	52	30	1.2	330	0
Jevity 1 cal	Ross	T	C	CS, FOS	MCT, C, S	16.7	54.3	29	1.06	300	14.4
Jevity 1.2	Ross	T	CS, C, S	CS, FOS, MD	MCT, C, CA	18.5	52.5	29	1.2	450	18
Jevity 1.5	Ross	T	CS, C, S	CS, FOS, MD	MCT, C, CA	17	53.6	29.4	1.5	525	22
Nepro w/ carb steady	Ross	O, T	C	FOS, CS, S	SA, C	18	34	48	1.8	600	8.6
Nova-Source 2.0	Novartis	O, T	C	CS, S	CA, MCT	18	43	39	2	790	0
Nutren 1.0	Nestlé	T	C	MD, CS	MCT, CA	16	51	33	1	412	0
Nutren 1.0 with Fiber	Nestlé	T	C	MD, CS	MCT, CA, C	16	51	33	1	310–370	14
Nutren 1.5	Nestlé	T	C	MD, CS	MCT, CA, C	16	45	39	1.5	430–530	0
Nutren Glytrol	Nestlé	T	C	MD, FOS	MCT, F, CA, S	18	40	42	1	280	15.2
NutriHep	Nestlé	T	AA, HP	MD, CS	MCT, CA, C	11	77	12	1.5	620–650	0
Nutren Pulmonary	Nestlé	O	C	MD, S	CA, MCT	18	27	55	1.5	450	0
Nutren Replete	Nestlé	T	C	MD, CS	CA, MCT	25	45	30	1	290	0
Nuten Renal	Nestlé	T	C	CS, MD, C	MCT, F, CA	14	40	46	2	650	0
Optimental	Ross	T	S, C	FOS, MD, S	F, MCT, CA	20.5	55	24.5	1	540	0
Osmolite 1 cal	Ross	T	C, S	G	C, S, MCT	16.7	53.3	34.8	1.06	300	0
Osmolite	Ross	T	C, S	G	MCT, C, S	14	54.6	31.4	1.06	300	0
Osmolite 1.5	Ross	T	C, S	MD	MCT, Ca, S	16.7	54.2	29	1.5	525	0
Oxepa	Ross	O, T	C	MD, S	CA, MCT, FI	16.7	28.1	55.2	1.5	535	0
Peptamen	Nestlé	O, T	M	MD, ST	MCT, SU	16	51	33	1	270	0
Peptamen w/Prebio	Nestlé	O, T	HP	MD, CS, FOS	MCT, S	16	51	33	1	300	4

TABLE 10-5. Nutrient Analysis of Various Commercially Available Protein and/or Calorie Supplements and Diets (*Continued*)

Non-protein calorie/ nitrogen ratio	Protein (g/1,000 kcal)	CHO (g/1,000 kcal)	Fat (g/1,000 kcal)	Per 1,000 kcal											Nutri-tionally complete[a]
				Na (mg)	K (mg)	Cl (mg)	Ca (mg)	P (mg)	Mg (mg)	Fe (mg)	I (μg)	Cu (mg)	Zn (mg)	Mn (mg)	
120:1	52.5	165	15.5	1,000	1,200	1,300	733	733	267	15	100	1.3	20	3.4	Yes
NA	10	187	24	<173	<117	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
125:1	43	170	18	550	1,690	1,440	1,270	1,060	420	15.2	161	1.7	19	3	Yes
78:1	60.4	140	22.8	921	2,079	1,465	1,000	921	326	16.7	138	2	13.8	2.8	Yes
134:1	40.1	125	137.5	559	974	836	559	559	224	10	84	1.1	11.1	1.6	Yes
120:1	43.4	131.1	33	679	1,311	1,311	792	660	264	12	99	1.3	13.1	1.7	Yes
89:1	58.2	84	49.4	14.9	1,040	928	1160	928	338	15	127	2	13	2	Yes
NA	62.5	182	2.2	1018	2,400	NA	1,600	1,200	400	18	180	2	15	NA	NA
NA	82.5	157.5	4.4	1,105	3,158	NA	2,105	1,579	632	23.7	237	2.63	19.7	NA	NA
131:1	40	210	0	153	276	349	509	1018	202	9.2	73.6	1.04	9.8	1.53	NA
131:1	40	87.8	54.6	518	785	533	550	550	193	10	81	1.16	27	2	
67:1	62.5	90	45	779	1,248	1,160	667	667	267	12	100	2	24	2.7	Yes
120:1	50	90	49	1,000	1,400	1,100	670	870	270	12	100	1.3	15	3.3	Yes
153:1	36	160	24	800	1,480	1,240	500	500	200	9	75	1	11.25	2.5	Yes
144:1	37	142.5	31.3	704	1,296	1,296	470	470	189	8.5	70	0.96	10.6	2.34	Yes
138:1	45.7	142	27.5	1318	2,272	1,454	2272	1136	454	2.2	172	2	26	5	
125:1	41.7	133.2	33.2	786	1,265	1,066	705	705	282	12.7	106	1.42	15.9	3.52	Yes
148:1	36	147	34	786	1,265	1,066	705	705	282	12.7	106	1.42	15.9	3.52	Yes
150:1	41.8	93.7	55.7	928	1,561	1,435	704	704	282	12.7	106	1.5	1.5	15.9	Yes
100:1	50	77.5	43	940	1,810	1,360	705	705	285	13	110	1.4	16	3.6	Yes
71:1	56	132	28	110	1,300	1,300	800	800	270	12	100	1.7	1.7	15	Yes
71:1	56	140	28	1,100	1,300	1,300	800	800	270	12	100	1.7	1.7	15	Yes
71:1	55	95	44	986	1,360	1,066	640	640	213	9	80	1.3	1.2	1.6	No
71:1	32	125	42	500	1,245	1,000	595	500	200	9	75	1	10	2.5	Yes
125:1	42	117	42	877	1,500	1,360	800	800	320	14	120	1.6	12	4.3	Yes
148:1	36	140	34	1,000	1,400	940	560	560	220	10	83	1.1	14	2.8	Yes
116:1	45.3	113.3	43.3	867	1,400	1,067	733	733	287	12.7	107	1.4	21.3	1.4	Yes
116:1	44	130	34	1,000	1,400	940	560	560	220	10	83	1.1	14	2.8	Yes
125:1	42	144	35	880	1,480	1,240	860	716	286	12.9	107	1.44	16.1	3.56	Yes
110:1	55.5	169	39	1125	1,541	1,250	1000	1000	333	15	125	1.6	19	4.1	Yes
122:1	42.5	144	33	933	1,433	906	800	800	266	12	100	1.3	15.3	3	Yes
114:1	45	85	53	588	588	470	589	389	117	10.5	89	1.1	14.4	1.1	Yes
116:1	45	110	44	380	800	550	500	550	210	9.5	80	1.1	8	1.1	Yes
131:1	40	127	38	876	1,248	1,200	668	668	268	12	100	1.4	14	2.7	Yes
131:1	40	127	38	876	1,248	1,200	668	668	268	12	100	1.4	14	2.7	Yes
131:1	40	113	45	500	1,253	1,000	693	693	333	12	100	1.3	13.3	2.7	Yes
114:1	45	100	15.2	740	1,400	1,200	720	720	286	12.8	120	1.5	15.2	3	Yes
209:1	26	193	14	213	880	1,000	667	667	267	12	101	1.3	10.1	2.7	Yes
116:1	45	67	63	415	528	505	686	343	105	9.5	78.9	NA	1.1	11.8	Yes
146:1	37	130	35	850	1,400	1,100	470	470	210	9.6	70	1.1	16	1.4	Yes
151:1	35	102	52	370	628	570	700	350	100	12	100	1.2	10	2.6	Yes
97:1	51.3	138.5	28.4	1,060	1,760	1,340	1,060	1,060	425	13	160	1.9	16	3.6	Yes
125:1	42	133.6	34.8	880	1,480	1,360	715	715	286	13	107.2	1.43	16.08	3.57	Yes
153:1	35.2	137.2	36.4	600	960	800	500	500	200	9	75	1	11.5	2.5	Yes
125:1	42	135	32	933	1200	1133	555	555	267	12	100	1.3	15	3	Yes
125:1	45	100	47.5	872	1,308	1,125	703	703	287	12.7	107	1.4	16	3.7	Yes
131:1	40	127	39	500	1,252	1,000	800	700	400	12	100	1.4	14	2.7	Yes
131:1	40	127	39	560	1,500	1,000	800	700	300	18	148	2	24	2.8	Yes

(*continued*)

TABLE 10-5. Nutrient Analysis of Various Commercially Available Protein and/or Calorie Supplements and Diets

Product	Manufacturer	Oral (O) Tube (T)	Macronutrient major sources			Caloric distribution (%)			Caloric density (kcal/mL)	Osmolality[a] (mOsmol/kg)	Fiber (g/1,000 kcal)
			Protein	CHO	Fat	Protein	CHO	Fat			
Peptamen AF	Nestlé	T	HP	MD, CS	MCT, FI, S	25	36	39	1.2	390	0
Perative	Ross	T	C, L, AR	CS	CA, MCT	20.5	55	25	1.3	425	0
Pivot 1.5	Ross	T	C	CS, FOS	MCT, S, FI	25	45	30	1.5	595	5
Promote	Ross	O, T	C, S	CS, S	CA, MCT	25	52	23	1	340	0
Promote with fiber	Ross	O, T	C, S	CS, S	CA, MCT	25	50	25	1	380	14.4
Pulmocare	Ross	O, T	C	S, CS	C, MCT, SA	16.7	28.1	55.2	1.5	465	0
Renalcal	Nestlé	T	AA, HP	MD, CS	MCT, C, FI	7	58	35	2	600	0
Resource Shake	Novartis	O	M, C	CS, MD	C	13	67	20	1.5	1100	0
Subdue	Novartis	O, T	HP	MD, S	CA, MCT	20	50	30	1	525	0
Suplena	Ross	O, T	C	CS, S, FOS	SA, S	10	42	48	1.8	600	0
TraumaCal	Novartis	O, T	C	CS, S	S, MCT	22	38	40	1.5	490	0
TwoCal HN	Ross	O, T	C	CS, S	C, MCT	16.7	43.2	40.1	2	690	0
Ultracal	Novartis	T	C	MD	C, S, MCT	17	50	33	1.06	300	14
Vital HN	Ross	O, T	P, AA	CS, S	MCT, SA	16.7	73.9	9.4	1	500	0
Vivonex T.E.N.	Novartis	T	AA	MD, S, T	SA	15	82	3	1	630	0

Formulations may have changed since the preparation of this table; consult the manufacturers' literature.
Protein sources: AA, amino acids; AR, arginine; C, casein salts; CH, casein hydrolysate; DL, delactosed lactalbumin; E, egg white solids; HP, hydrolyzed proteins other than casein; L, lactalbumin; M, milk proteins; P, mixed protein sources; S, soy protein. **Carbohydrate sources:** CS, cornstarch or corn syrup solids; F, fructose; FOS, fructose oligosaccharides; G, glucose; GO, glucon oligosaccharides; L, lactose; M, mixed carbohydrate sources; MD, malt dextrin; MS, monosaccharides; S, sucrose; SP, soy polysaccharides; T, tapioca starch.
Fat sources: C, corn; CA, canola oil; F, mixed fat sources; FFA, free fatty acids; FI, fish oil; MCT, medium-chain triglycerides; MF, milk fat; S, soy oil; SA, safflower oil; SU, sunflower.
Other abbreviations: CHO, carbohydrates; NA, not available.

the osmolalities of elemental/semi-elemental and chemically defined diets tend to be higher than those of standard formulations with intact proteins and complex carbohydrates. The electrolyte content of the formulation also contributes to the osmolality without affecting caloric density. Isotonic formulations have an osmolality of about 300 mOsmol, which is similar to that of blood. Hypertonic solutions (>400 mOsmol) can cause delayed gastric emptying with nausea, vomiting, and distention. Hypertonic solutions entering the small bowel cause intestinal fluid secretion; if this fluid is not reabsorbed in the intestine, diarrhea and dehydration develop.

Ratio of Nonprotein Calories to Nitrogen

For most patients receiving forced enteral feeding, the quantity of amino acids provided in standard enteral formulas is large enough to provide for protein synthesis so long as enough formula is given to provide for caloric needs. In a few patients (e.g., those who have sustained severe trauma), the requirements for protein synthesis are so great that a lower ratio of calories to protein may be optimal. This ratio is expressed as nonprotein calories to nitrogen (kilocalories per gram of nitrogen). The conversion of nitrogen to protein and vice versa is as follows:

$$\text{Grams of Nitrogen} = (\text{Grams of Protein})/6.25$$

Standard Formulas

Standard formulas contain intact proteins, lipid in the form of long-chain triglycerides (LCT), and possibly fiber. Most standard formulas are gluten and lactose free. The

TABLE 10-5. Nutrient Analysis of Various Commercially Available Protein and/or Calorie Supplements and Diets (*Continued*)

Non-protein calorie/ nitrogen ratio	Protein (g/1,000 kcal)	CHO (g/1,000 kcal)	Fat (g/1,000 kcal)	Per 1,000 kcal											Nutritionally complete[a]
				Na (mg)	K (mg)	Cl (mg)	Ca (mg)	P (mg)	Mg (mg)	Fe (mg)	I (μg)	Cu (mg)	Zn (mg)	Mn (mg)	
76:1	62.5	90	43	666	1,333	1,133	667	667	267	12	110	2	24	2.6	Yes
97:1	51	136	29	800	1,330	1,269	667	667	267	12	100	1.3	14	1.5	Yes
75:1	62.5	112	33	933	1,333	1,067	667	667	267	12	100	1.3	16	3.3	Yes
75:1	62.5	130	26	928	1,980	1,263	960	960	320	14.4	120	1.6	18	4	Yes
75:1	62.5	139	28	928	1,980	1,263	960	960	320	14.4	120	1.6	18	4	Yes
125:1	41.7	70.4	61.4	873	1,155	1,126	704	704	282	12.7	106	1.4	1.4	15.9	Yes
300:1	17	145	41	0	0	0	0	0	0	0	0	0	7	0	No
162:1	32	168	22	667	1,111	NA	740	740	222	13	111	1.5	11	NA	No
100:1	50	127	34	1,110	1,610	1,390	850	850	340	15.2	127	1.7	16.1	2.5	Yes
226:1	25	105	53	439	622	519	589	389	117	10	89	1.1	14	1.1	Yes
91:1	55	95	45	787	927	1,067	500	500	133	5.9	50	NA	1	9.9	Yes
125:1	41.7	108.2	45.3	653	1,221	821	526	526	211	9.5	78.9	1.05	11.85	2.63	Yes
124:1	42	125	37	1280	1,760	1,400	960	960	380	17	140	1.9	20	3.8	Yes
125:1	41.7	185	10.8	566	1,400	1,032	667	667	267	12	100	1.4	15	3.4	Yes
149:1	38	210	2.8	460	780	820	500	500	200	9	75	1	10	0.9	No

[a] When served full strength prepared in the usual way or diluted to suggested caloric density. The supplement or diet is said to be nutritionally complete if 2,000 mL or less meets the recommended dietary allowance (RDA) of all vitamins and minerals for the average adult.

composition of these formulas will supply the reference values for macro- and micronutrients for a healthy population within a caloric value (approximately 1500 calories) that will meet the majority of patients' needs. In Table 10-5, the column labeled "Nutritionally Complete" indicates whether 1,500 calories of the enteral formula meets the RDA for the average adult. For many patients the normal RDA will not be sufficient because of impaired absorptive function and intestinal losses.

Fiber-containing Enteral Formulas

Fiber-containing enteral formulas may be beneficial for patients with diarrhea or constipation. In most cases, soy polysaccharide is the fiber added to enteral formulas to increase stool bulk and regulate transit time. Fiber is fermented by colonic bacteria to short-chain (butyric, acetic, and propionic) fatty acids that serve as energy sources for colonocytes. Fiber also decreases the rate of gastric emptying and delays the absorption of dietary glucose. Theoretically, a reduction of the levels of short-chain fatty acids in the colonic lumen may be associated with adverse effects on the function of the colonic epithelium. Recently, some manufacturers have added fructo-oligosaccharides to enteral nutrition formulations. Fructo-oligosaccharides are mixtures of oligomers composed primarily of β-D-fructose monomers linked by β2-1 glycosidic bonds. Fructo-oligosaccharides are fermented by bacteria in the colon to form short-chain fatty acids (see Chapter 12). Long-term ingestion of an elemental diet in rats results in diminished production of short-chain fatty acids in the colonic lumen and atrophy of the colonic mucosa. A significant reduction in inflammation was noted in the defunctionalized colon when short-chain fatty acids were instilled in the affected portion of the colon of patients with diversion colitis (29). In view of the important role of short-chain fatty acids in the

maintenance of colonic structural and functional integrity, the use of fiber-containing formulations should be seriously considered in any patient for whom tube feedings are expected to be the sole source of nutrition for an extended period of time, especially patients with intestinal disease or injury.

Calorically Dense Formulas

Calorie dense formulas may be beneficial in patients with fluid overload (e.g., renal failure, congestive heart failure, and ascites). Adults require 1 mL of water per kilocalorie or 30 to 35 mL per kg of their usual body weight. Tube-fed patients may not get enough free water, especially when nutrient-dense formulas are used. Denser formulas are frequently hypertonic; the added osmolar load may cause diarrhea (although hypertonicity is not a common cause of the diarrhea seen with enteral feeding).

Elemental/Semi-elemental Formulas

Elemental formulas contain free amino acids and glucose polymers. They are low in fat with only about 2% to 3% of calories derived from long-chain triglycerides (LCT). In general, elemental products are used in patients with severe fat malabsorption or a chyle leak. However, these costly products are often not palatable, requiring administration via a feeding tube. Semi-elemental formulas contain proteins that have been hydrolyzed (oligopeptides) containing some free amino acids, dipeptides, and tripeptides, but larger peptides predominate. These formulas also include carbohydrate in the form of simple sugars, glucose polymers, or starch along with fat generally with a higher MCT:LCT ratio than a standard product. Often semi-elemental formulas are labeled "elemental" since these products contain some free amino acids, but the terms are not regulated by any governing body. Theoretically dipeptides and tripeptides are more easily absorbed than free amino acids or intact proteins because of the specific transport mechanisms for their intact uptake (30–32). These formulas may be beneficial in patients with some degree of malabsorption; generally they can be used as a bridge to standard formulas as tolerance improves. At present only small studies support the suggestion that oligopeptides are advantageous in patients with small-bowel disease (33,34). However these results have not been reproduced in large prospective randomized control trials (32,35–37).

Disease Specific Formulas

Disease specific formulas include formulas that have been altered in their macro- or micronutrient content to address the needs of a specific disease and/or digestive or metabolic disorder, including pulmonary failure, hepatic insufficiency, renal failure, diabetes, and critical illness. In general, the clinical advantage of the majority of these disease specific formulas over less-expensive, standard intact-protein formulas remains controversial (38,39).

Pulmonary Disease

When a calorie of carbohydrate is metabolized, more carbon dioxide is produced than when a calorie of fat is metabolized. The rapid administration of a large carbohydrate load to a patient with severe pulmonary disease may increase the carbon dioxide tension. Several companies make calorically dense enteral formulas that have a higher fat to carbohydrate ratio for patients with severe pulmonary disease. However, the usefulness of these formulas when compared to standard products has not been proven in randomized trials (40). It is important to remember that the amount of carbon dioxide produced is more a function of the number of calories consumed than of the macronutrient source of the calories. Overfeeding should be avoided in patients with pulmonary disease. However, there is increasing evidence that products with a higher ratio of omega-3 fatty acids to omega-6 fatty acids are beneficial in patients with an acute lung inflammatory process such as acute respiratory distress syndrome (41–44).

Hepatic Disease

Chronic liver disease is associated with an abnormal pattern of circulating amino acids; the concentrations of aromatic amino acids (phenylalanine, tyrosine, and tryptophan) are

increased, and the concentrations of branched-chain amino acids (leucine, isoleucine, and valine) are decreased. It has been postulated that this imbalance contributes to encephalopathy because it leads to the production of false neurotransmitters. A double-blind randomized trial compared 1 year of nutritional supplementation with branched-chain amino acids (BCAA), leucine, isoleucine, and valine, containing formula with two standard formulas in 174 patients with advanced cirrhosis (12). The BCAA arm experienced a significantly lower average hospital admission rate, stable or improved nutritional parameters and liver function tests, as well as improved health-related quality of life (12). Other studies have only reported small differences. The special hepatic formulations are very expensive, and their use can be justified only in patients who are encephalopathic (see Chapter 12). Alcoholism, the most frequent cause of chronic liver disease, is associated with other nutritional problems, including deficiencies of thiamine, folate, vitamin C, zinc, and magnesium. According to a recent meta-analysis abstinence and nutrition support remain the cornerstones of management of alcoholic liver disease (45). Chronic liver disease is frequently associated with ascites and edema. Control of salt and water balance is an important component of the management of chronic liver disease. The sodium content of enteral formulas rarely exceeds 2 grams per day when meeting a patient's caloric requirements. A calorically dense (1.5 to 2.0 kcal per ml) formula aids in the restriction of fluids in these patients.

Renal Disease

In chronic renal failure, the ability of the kidney to excrete urea and electrolytes is limited. An important part of the management of chronic renal disease is the adjustment of dietary and fluid intake to accommodate for the diminished functional capacity of the kidneys. One estimate of the demands placed by a nutritional product on the kidneys is the renal solute load, which is determined primarily by the protein and electrolyte content of the formula. The major contributors to the renal solute load are urea, the end-product of protein digestion, and the electrolytes (sodium, potassium, and chloride). The greater the renal solute load, the greater the obligatory water loss through the kidneys. As renal function decreases, the ability of the kidney to concentrate solutes is diminished. Thus, the greater the impairment of renal function, the greater the obligatory water loss for a given solute load. Commercial enteral formulas developed specifically for patients with chronic renal disease not receiving dialysis are calorically dense and electrolyte and protein restricted with a high percentage of essential amino acids. The diminished protein content combined with a high percentage of essential amino acids allows for adequate protein synthesis with minimal urea production. These formulas also have an altered vitamin and mineral content. Supplementation with vitamin and mineral formulation developed for patients in renal failure may be necessary. Patients with renal disease on enteral nutrition should be monitored frequently. Particular attention should be given to serum electrolytes, daily weights, and inputs and outputs. Patients who have milder degrees of renal impairment or on dialysis can be managed with standard calorically dense formulas (see discussion of the dietary management of renal disease in Chapter 13).

Diabetes

In diabetes use of complex carbohydrates, such as fructose, cornstarch, and fiber improves glycemic control by delaying gastric emptying and reducing intestinal transit time. With regard to macronutrients, the American Diabetes Association and the European Association for the Study of Diabetes recommend a combination of 60% to 70% of calories be divided between carbohydrates and monounsaturated fat, 10% from polyunsaturated fat, 10% from saturated fat, and 15% to 20% of the calories from protein (46–48). Simple carbohydrates should be limited to less than 10% of calories. The diabetic formulas are based on this premise. Few long-term studies of diabetic formulas in a hospital population exist, making it impossible to draw firm conclusions about the benefit of these formulas. One study reported better glycemic control with the use of a diabetic formula compared to a standard formula and several others have reported

lower mean, fasting, and/or postprandial glucose levels (49–54). However, some of these were conducted in "healthy volunteers" and cannot be extrapolated to a hospital population, and in all of the studies, only trends toward decreased HbA1c and insulin requirements were recorded. In addition, although a trend toward reduced infections and hospital length of stay have been mentioned, no significant differences in clinical outcome (length of stay, ventilator support, infection rate, or mortality) have been reported. Hence, while the use of a diabetic formula can affect blood glucose levels, the effect has yet to be shown to be clinically important. Now that there is greater attention to glycemic control in the hospitalized setting, the utility of these products is further diminished.

Immune Modulating Formulas

Over the last 10 years more than 500 articles have been published addressing the benefits and risks of immunonutrition. Immunonutrition formulas are supplemented with any single or combination of immune stimulants, such as arginine, glutamine, omega-3 fatty acids, and nucleotides. A meta-analysis of randomized clinical trials comparing immunonutrition to standard products concluded there were no significant effects on mortality, infectious complications, length of stay, or time on the ventilator in critically ill patients (55). A higher mortality rate has been observed in septic patients receiving immunonutrition when compared to similar patients receiving parenteral nutrition (56). However, in the same study a significant reduction in infectious complications and length of stay was observed in elective surgery patients. Interpreting the data on immunonutrition is hampered by differing study populations, inconsistent use of blinding, the use of different control feeds, and small sample sizes. Similarly, studies reviewing the effect of a single nutrient or class of nutrients demonstrate minimal benefit. Keep in mind that any recommendations regarding components of immunonutrition products are based on current data, most of which involves safety. The evidence that these products or individual components are efficacious is rather sparse and/or conflicting (see Chapter 15).

Glutamine

Glutamine is a nonessential amino acid that accounts for about 8% of the amino acids in dietary protein and can be synthesized by virtually all tissues in the body. Glutamine is involved in acid-base balance, protein synthesis, nitrogen transport, energy generation, and provision of nitrogen for nucleic acid synthesis. In catabolic states, glutamine is released from skeletal muscle and is taken up by the intestine, where it is burned for fuel. Depletion of plasma glutamine is associated with loss of intestinal integrity, villous atrophy, ulcerations, and necrosis. In rats, mucosal atrophy predisposes to bacterial translocation and the development of sepsis. This would be especially undesirable in severely ill patients; however, evidence is scarce that this occurs in humans (57). All standard enteral formulas contain glutamine (approximately 2.9 g per 1,000 calories); however, several commercial companies offer immunonutrition products that contain especially high levels (>10 g per 1,000 calories). Supplementation with high levels of glutamine is used because some investigators believe that glutamine is a "conditionally essential" amino acid in catabolic states (58). In a double-blind, randomized trial of 48 severe burn patients, enteral glutamine treatment of 0.5 g per kg per day compared with a control group receiving 0.5 g per kg of glycine led to a shorter hospital stay ($P < 0.05$) (59). This study did not report on infectious morbidity or mortality. In another large trial in critically ill patients, no benefit was associated with the supplementation of enteral glutamine (see Chapter 12) (60).

Circulating Levels of Anti-oxidants

Circulating levels of anti-oxidants (beta-carotene, vitamin A, vitamin C, vitamin E, zinc, and selenium) are known to decrease rapidly in sepsis, trauma, or surgery and possibly remain low for a prolonged period of time (61–63). A randomized prospective study conducted in 595 critically ill surgical patients (91% trauma patients) compared those supplemented with α-tocopherol and ascorbate versus those receiving standard care with a

primary endpoint of pulmonary morbidity (64). Although a 19% reduction in incidence of pulmonary morbidity was noted in the supplemented group, the study was inadequately powered to detect a significant difference at an α of 0.05 (64). The longest and largest trial of vitamin E supplementation was completed in 39,876 healthy women as part of the Women's Health Study (65). The data from this trial indicated that 600 IU of vitamin E taken every other day provided no significant benefit in reducing the risk of cancer, cardiovascular disease, or overall mortality. Caution should be taken when extrapolating studies in healthy volunteers to a hospital population (65). A meta-analysis looking specifically at the effect of supplemental enteral anti-oxidants found no significant benefit in terms of infectious complications, length of stay, or mortality when they were provided via the enteral route (see Chapter 6) (66).

Arginine

Arginine is also considered "conditionally essential" in injury or stress situations (67). Plasma arginine levels are affected by surgery (decrease of 30% to 50% seen in abdominal surgery patients), burn (decrease of 57% in severely burned children), and sepsis (70% drop in septic patients when compared to healthy controls) (68). The interaction of arginine with growth hormone is thought to be involved in tissue repair and immune cell function (69). Arginine has been associated with maintaining T-cell immune function (70) after trauma (71), reducing the cellular immune suppression associated with injury, and enhancing collagen synthesis at the wound site (such as during tissue repair and wound healing) (71–75). Arginine is also associated with nitrogen retention (see Chapter 12) (76).

Omega-3 Fatty Acids

Marine oil (Menhaden oil) is a rich source of omega-3 fatty acids and contains EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). Increasing the omega-3 fatty acid content of the diet may displace the omega-6 fatty acids within the cell membrane, thereby favoring production of the less inflammatory eicosanoids. The literature suggests omega-3 fatty acids are less inflammatory and more immunostimulatory than omega-6 fatty acids (77). A ratio of 4:1 (omega-6:omega-3) has been suggested for healthy adults; a lower ratio may be appropriate for short periods of time when excessive inflammation is a factor and modified immune support is desired. Three prospective randomized controlled trials have been completed to determine the influence of a high omega-3 fatty acid containing formula on patients with acute respiratory distress syndrome (ARDS) (78–80). Patients receiving these products have shown significant improvement in gas exchange, required significantly fewer days on the vent, and had decreased LOS in the ICU when compared to a control high fat (primarily omega-6 fatty acids) type formula. No difference in mortality has been noted. However, the question has been raised about the possibility that the high omega-6 fat content of the control formula may have exacerbated the ARDS symptoms. The high omega-3 fat containing formulas have not been compared to a standard product.

CHOOSING AN ENTERAL PRODUCT FOR TUBE FEEDING

There is generally more than one product that would be acceptable for any given patient (Figure 10-2). Therefore, the algorithm suggests product types based on patient assessment as according to a combination of the 2002 ASPEN guidelines for use of parenteral and enteral nutrition in adult patients (81), the Canadian Critical Care Nutrition Guidelines (82), and the 2006 ESPEN Guidelines on Enteral Nutrition (complete guidelines available at www.espen.org/Education/guidelines.htm).

Enteral Feeding Access Devices

Physical characteristics are presented in Table 10-6. These devices vary in the type of construction material, length and diameter, presence of a stylet or guidewire, weighting of the tube, number of lumens, number of exit ports, and the presence of a Y-port.

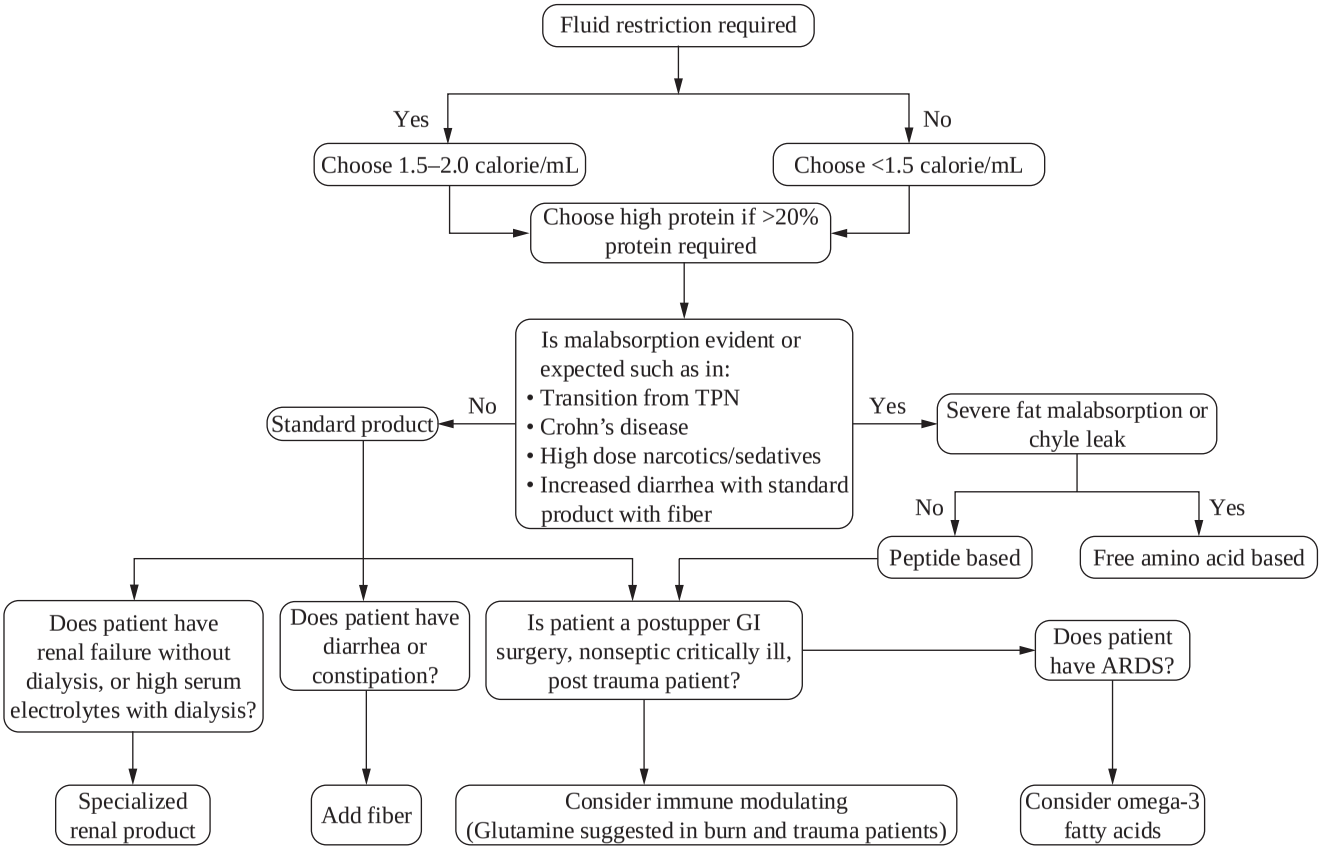


FIGURE 10-2. Choosing a tube feeding product

TABLE 10-6. Characteristics of Adult Enteral Access Devices

Tube type	Material	Length	French (Fr) size	Stylet or guidewire	Manufacturers
Nasogastric Salem sump	Polyvinyl chloride or silicone	36 to 48 inches	12 to 20 Fr	No	Argyle, Tyco/ Kendall
Nasoenteric feeding tube	Polyurethane, silicone, or mixture	36 to 60 inches	8 to 14 Fr	Yes/No	Viasys, Tyco/ Kendall, Ross, Norvartis
Percutaneous endoscopic gastrostomy (PEG)	Silicone or polyurethane	Cut to fit	14 to 24 Fr	Yes/No	Wilson-Cook, BARD, Viasys, Kimberly Clark
Gastrostomy	Silicone or polyurethane	4 to 6 inches	12 to 28 Fr	No	Norvartis, Wilson-Cook, BARD, Viasys, Kimberly Clark
Jejunostomy	Silicone or polyurethane	6 to 10 inches	8 to 14 Fr	No	Norvartis, Wilson-Cook, BARD, Viasys, Kimberly Clark
Jejunostomy via PEG	Silicone or polyurethane	35 to 45 inches	8 to 10 Fr	Yes	Wilson-Cook
Gastrojejunostomy	Silicone or polyurethane	Jejunal length: 35 to 45 inches	G port: 22 to 24 Fr J port: 8 to 12 Fr	Yes	Norvartis

Material

Most enteral feeding tubes are constructed with polyurethane, silicone, or a combination of these materials. Silicone tubes are the softest; however, they may collapse when checking for gastric residuals. Occasionally, Foley catheters will be used for long-term feeding access; however, the practitioner should remember these are made of latex, which can be irritating to the skin of some patients and dangerous to those who have latex allergies. In addition, Foley catheters have been shown to migrate, with the balloon often obstructing the pylorus or duodenum (83,84). In general all tubes designed for enteral feeding delivery are completely radiopaque or have a radiopaque strip to facilitate radiographic confirmation of placement.

Tube Length and Diameter

The length of the enteral feeding tube is determined both by the site of insertion and desired site of feeding. The shortest surgically implanted tubes are called "button" or "skin-level" tubes. Surgically placed gastrojejunostomy tubes are available with a shorter gastric lumen for decompression and a longer jejunal limb for feeding. Some percutaneous endoscopically gastrostomy tubes can accommodate placement of a jejunal tube through the gastric part allowing for simultaneous feeding and decompression. In addition to differing to lengths, the diameters of tubes can also vary. The tube diameter is measured in French units (one French unit = 0.33 mm). Smaller diameter tubes are more comfortable for the patient and less likely to produce sinusitis, but they are also more likely to clog following infusion of medications or viscous tube feeding product, especially if flushing is inadequate.

Stylets

Stylets are frequently used to stiffen polyurethane or silicone feeding tubes to facilitate placement. Stylets generally have a flow-through design that allows flushing of air or water through the tube ports while the stylet is in place. The stylets do not extend the entire length of the tube, and they end in a blunt loop or a spring tip to decrease the risk of tube puncture during placement.

Y-ports

Y-ports on the end of nasoenteric feeding tubes allow for tube flushing and medication administration without disconnection of the feeding administration set. This can minimize contamination of the nutrition formulation. If only a single port is present on the end of the feeding tube, generally a Y extension set can be added. The ports should be labeled clearly to avoid confusion with respect to the purpose (e.g., "gastrostomy port," "feed," "for flushing only").

Tungsten Tips

Tungsten weighted or non-weighted tips are available on nasoenteric feeding tubes. Initially it was believed the weighted tip would facilitate tube placement into the small bowel; however, some studies suggest increased ease of placement with nonweighted tubes (85,86). Presently the preference of the person placing the tube determines the use of weighted versus nonweighted tips.

Feeding Methods

Enteral feedings can be infused either continuously or intermittently. Continuous feedings require a feeding pump in order to regulate the infusion rate. Intermittent feedings may be administered either by gravity (over 20 to 40 minutes), using a gravity drip bag or pump assisted, or via a syringe to provide a bolus feeding (over 5 to 15 minutes).

Feeding Equipment

Administration Sets

Administration sets are designed for either gravity or pump feedings; or to provide simultaneous continuous or intermittent bolus water flushing. Administration sets are preattached to hydration, gravity, or pump feeding bags, which prevents separation. The gravity feeding delivery sets have a roller clamp to help control the flow rate. Generally, the sets designed for continuous feeding are pump-specific. For safety purposes, many pump sets have an antifree flow device to avoid inadvertent delivery of a large feeding bolus. In addition, the connectors on a feeding set cannot attach to an intravenous (IV) needle or a leur connector, making it virtually impossible to inadvertently administer enteral feeding into an IV line.

Enteral Feeding Containers

Enteral feeding containers vary in size and hold different volumes. Bag sets are used with cans of formula and typically hold a maximum of 1 L. The bag and administration set should be discarded after 24 hours. However, if formula remains in the bag for longer than 8 hours, both the formula and bag should be discarded. Closed system containers are available in bag or hard plastic form and are pre-filled with a specific volume, generally 1 to 1.5 L. A spike set is necessary to access the enteral product in a closed system container. In general, for safety purposes the closed containers and spike sets are clearly marked "not for IV use." Per most manufacturers, a closed system may hang for 48 hours after initial spiking when clean techniques and only one new feeding set is used; otherwise the hang time reverts to 24 hours. Theoretically, the closed system should decrease the risk of contamination. However, to avoid wasting enteral product, it may be prudent to use cans during initial patient testing or in the intensive care setting where the patient's clinical status may change quickly.

Enteral Feeding Pumps

Enteral feeding pumps should be accompanied by clear instructions and should be simple to use. Feeding pumps should be quiet, provide accurate volumetric delivery, and have both

audio and visual alarms to protect against overinfusion. Pumps provided with an 8- to 24-hour battery back up and built-in IV pole clamp are highly desirable.

Feeding Tube Tip Location

The optimal feeding tube tip location for the patient continues to be debated (87–89). Some common indications, advantages, and disadvantages of various tubes are listed in Table 10-7. The evidence for the advantage of postpyloric feeding tubes is not documented, and the recommendation for use of these tubes is based more on theoretical advantage and the fact that such feeding can be delivered with no less safety than gastric feeding.

Gastric (Prepyloric)

Gastric (prepyloric) feeding advantages include preservation of the reservoir function of the stomach, which allows for a large volume of hyperosmolar feeding without cramping, distention, or vomiting; easy tube placement for short-term access; and decreased cost because a pump is not required. The disadvantages are related to prolonged retention of formula in the stomach (high residuals) with delayed gastric emptying. This could lead to delay in the achievement of caloric goals, reflux, and possible tracheobronchial aspiration. However, one study suggested residual volume of enteral feeding in the stomach should not be used as a marker for the risk of aspiration (90).

Small Bowel (Postpyloric)

Small bowel (postpyloric) feeding advantages include bypassing the pylorus if gastric emptying is a problem and a theoretical decreased risk of aspiration (91). The decreased risk of aspiration pneumonia associated with small bowel feeding as opposed to gastric feeding continues to be debated. A study of almost 6,000 tracheal secretions was assayed for pepsin; 31.3% were found to be positive. In the study, patients with pneumonia on day 4 had a significantly higher percentage of pepsin-positive tracheal secretions than did those without pneumonia ($P < 0.001$) (92). The disadvantages of small bowel feeding relate to the increased costs associated with the additional use of equipment (feeding pump) and availability of trained personnel for placement (bedside, endoscopy, or fluoroscopy) (93,94). There also may be a safety risk associated with intrahospital transport (95).

Insertion of Feeding Tubes

The selection of a specific device and placement technique to install enteral feeding is based, in part, on whether the patient will be fed into the stomach (prepyloric feeding) or the small bowel (postpyloric feeding) and whether the patient is likely to need short-term (<4 weeks) or long-term (≥4 weeks) enteral access. An overview of various tube types and their associated access duration, placement techniques, advantages and disadvantages, and potential patients in whom placement would be appropriate are presented in Table 10-8.

TABLE 10-7. Gastric versus Small Bowel Feeding

Gastric feeding	Small bowel feeding
■ Majority of ICU patients ■ Cerebrovascular accident ■ Short gut (to maximize surface area fed)	■ Gastroparesis/post-op gastric ileus ■ Severe gastroesophageal reflux disease ■ Severe acute pancreatitis (unable to resume diet in 5–7 days) ■ Intolerance to gastric feeds (despite prokinetic use)—high residuals, emesis ■ Patient status does not allow for elevated head of bed ■ Heavy sedation

ICU, intensive care unit.

TABLE 10-8. Tube Types and Associated Characteristics

Tube type	Access duration	Placement technique and expertise level	Advantages	Disadvantages and risks	Patient types
Nasogastric Salem sump	Short-term	Bedside/RN	Large bore; less clogging; nasal or oral route; staff RN can replace if needed; used for decompression	Aspiration risk; patient discomfort; sinusitis; nasal necrosis	Normal gastric emptying; low risk of aspiration
Nasoenteric feeding tube—gastric or small bowel placement	Short-term	Bedside gastric placement/RN Bedside small bowel placement/ trained RN, RD, MD Endoscopy, Fluoroscopy/MD	Softer more flexible material for improved patient comfort; nasal or oral placement; patient can swallow "around" tube; if larger than 8 French unlikely to clog with good flushing techniques; available for immediate use after placement verification	Cannot be used for decompression; sinusitis. If placed in stomach, may migrate easily into the small bowel; aspiration risk. If placed in small bowel, tube may "flip" back to stomach; may not be able to be placed in patients with altered anatomy	Gastric—low risk of aspiration Small bowel—delayed gastric emptying, increased risk of aspiration secondary to condition or positioning
Percutaneous endoscopic gastrostomy (PEG) or fluoroscopically placed gastrostomy	Long-term	Endoscopy, fluoroscopy/MD	Large bore; low risk of clogging; may feed via intermittent or syringe method; may accommodate a small bowel feeding tube, if necessary	Hemorrhage; infection at insertion site; risk of peritonitis; may have to wait 24 hours to use; persistent gastrocutaneous fistula if tract does not close when removed. Cannot be placed if endoscopy unable to be done	Normal gastric emptying, low risk of aspiration; need for long-term enteral feeding
Surgical gastrostomy	Long-term	Surgical/MD	Large bore; low risk of clogging; may feed via intermittent or syringe method.	Requires surgical placement; hemorrhage, infection at incision or insertion site; anesthetic complications; may have to wait 24 hours to use; persistent gastrocutaneous fistula if tract does not close when removed	Normal gastric emptying, low risk of aspiration; need for long-term enteral feeding; unable to place gastrostomy via endoscopic or fluoroscopic techniques

Percutaneous endoscopic jejunostomy (PEJ)	Long-term	Endoscopy/MD	Decreased risk of aspiration; can provide supplemental feeds at night; may use immediately postplacement; bypasses the stomach if decreased gastric motility a problem	Hemorrhage; infection at insertion site; risk of peritonitis; may "flip" back into stomach; difficult to replace; cannot check residuals; requires continuous infusion; smaller bore; may occlude easily; persistent gastrocutaneous fistula if tract does not close when removed. Cannot be placed if endoscopy unable to be done	Increased risk of aspiration, gastric motility disorders
Jejunostomy via PEG	Long-term	Endoscopy, fluoroscopy/MD	Decreased risk of aspiration; can provide supplemental feeds at night; may use immediately postplacement; simultaneous gastric decompression and small bowel feeding possible	May be difficult to get tube in position, jejunal extension may "flip" back into stomach; requires continuous infusion; smaller bore; may occlude easily	Increased risk of aspiration, gastric motility disorders
Double lumen gastro-jejunostomy	Long-term	Surgical/MD	Decreased risk of aspiration; can provide supplemental feeds at night; may use immediately postplacement; simultaneous gastric decompression and small bowel feeding possible	Requires surgical placement; hemorrhage, infection at incision or insertion site; anesthetic complications; jejunal extension may "flip" back into stomach; small bore tube; may clog easily; unable to be replaced if inadvertently pulled; persistent gastrocutaneous fistula if tract does not close when removed	Increased risk of aspiration, motility disorders; endoscopic placement not feasible
Surgical jejunostomy	Long-term	Surgical/MD	Decreased risk of aspiration, can provide supplemental feeds at night; may use immediately postplacement; bypasses the stomach if decreased gastric motility a problem	Requires surgical placement, hemorrhage, infection at incision or insertion site; anesthetic complications; small bore tube may clog easily; unable to easily replace if inadvertently pulled	Increased risk of aspiration, motility disorders, gastric outlet obstruction or other anatomy precluding gastric placement

PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; RD, registered dietitian; RN, registered nurse.

Short-term Access

Short-term access feeding devices are utilized when enteral feeding is required for <4 weeks. These tubes are nasally or orally placed (in the event a patient has facial or sinus fractures) and may terminate in the stomach or small bowel. Many hospitalized patients will have a large-bore tube inserted for gastric decompression. Frequently these tubes will be used for medication and feedings when decompression is no longer needed. Unfortunately, these tubes are uncomfortable, may harden over time, and are more likely to cause sinusitis or nasal necrosis than a smaller-bore, more flexible nasoenteric feeding tube (96,97). The bedside nurse can place a nasogastric flexible enteric feeding tube. If the patient's condition precludes gastric feeding, a nasoduodenal or nasojejunal enteric feeding tube can be placed. Trained personnel are required for the placement by any method of a nasoduodenal or nasojejunal tube. Success rates of blind bedside placement of small bowel feeding tubes by a placement team are approaching those of endoscopic or fluoroscopic assisted placement (93,94,98). Several techniques for blind placement of small bowel feeding tubes have been described in the literature (85,99–101). An example of one technique is presented in Table 10-9 (102). Given the increasing popularity of bedside placement secondary

TABLE 10-9. Sample Bedside Small Bowel Feeding Tube Placement Policy and Procedure

Bedside small bowel feeding tube placement

A variation of the "10-10-10" protocol

Policy Statement: A Nutrition Support Service member or APN who has shown clinical competency with insertion will place a small bowel feeding tube (SBFT) at the bedside with verification of placement by KUB prior to initiation of feeding.

Description: A protocol involving the insertion of all but **10** cm of a nonweighted 43" or 55" Viasys® feeding tube with a stylet. If first attempt unsuccessful give 10 mg IV metoclopramide wait **10** minutes then reattempt advancement of SBFT.

Procedure:

1. Administer 10 mg IV metoclopramide (5 mg if patient in renal failure) over 1–2 minutes approximately 10 minutes prior to tube insertion.
2. Put on gloves.
3. If NGT or OGT in place obtain aspirate, noting color and pH, clamp NGT/OGT for SBFT insertion.
4. Set the hub of the stylet firmly into main port of feeding tube, close the medication port with cap.
5. Flush tube with approximately 10 cc tap water to check for patency or leaks; activate lubricant.
6. Elevate patient's HOB as tolerated.
7. Insert SBFT into nostril and advance to nasopharynx and into esophagus. Flexion of patient's neck or having patient swallow will facilitate passage of tube into esophagus.
8. Advance tube to 55–60 cm and auscultate over the epigastric area and attempt to aspirate gastric contents comparing aspirate with previous NGT aspirate if available. Gastric aspirate is bilious in appearance. The pH may range from 1–7 depending on the use of gastric prophylaxis medication.
9. Continue to advance SBFT slowly with a gentle touch. Infuse approximately 60 cc air slowly starting at 70–75 cm to help open the pylorus. Never force the tube, if resistance is met, pull back and attempt to readvance. Continue to advance to the 100 cm mark. There should be a vacuum present on the syringe when the tube is in the small bowel.
10. Aspirate and check pH and color of output when tube at 100 cm mark. Color of small bowel aspirate is generally yellow in appearance with a pH of 7+.
11. Remove stylet and check for kinks or loops, then attempt to re-insert. The stylet should be easy to insert. Upon re-insertion of stylet, if any resistance is met, pull tube back until stylet is easily inserted. After stylet is in place, re-advance tube.
12. When tube is in position, remove stylet and secure tube with tape to nose. Place stylet in plastic bag to use in future if SBFT needs to be repositioned.
13. Return NGT to suction, if on prior to procedure.
14. Order KUB to verify placement.
15. If SBFT pulled back from original insertion cm marking, re-insert stylet and advance SBFT per above procedure. Obtain KUB to verify position.

APN, advanced practice nurse; HOB, head of bed; IV, intravenous; NGT, nasogastric tube; OGT, orogastric tube ; SBFT, small bowel feeding tube.

to reduced costs and decreased risk to the patient by avoiding intrahospital transport, several devices to assist with placement have been developed. Devices include an external handheld magnet combined with a feeding tube fitted with a small magnet at the tube's distal end (103); an electrocardiographically (ECG) guided verification technique (100); and most recently a technique involving a styleted feeding tube with an electromagnetic transmitter on the tip of the stylet in combination with a receiver unit placed at the patient's xiphoid process with the signal of the tube's path displayed on a computer monitor. The last technique allows for an immediate response by the placer if the tube does not follow the expected path. The success rate with this technique according to abstracts on the company's website is 96% (www.viasyshealthcare.com). Regardless of the technique used, abdominal radiographs were still used to confirm placement prior to use.

Long-term Feeding Access

Long-term feeding access, or surgical placement of a feeding tube, should be considered if feeding is expected for longer than 4 weeks. These tubes are generally less disturbing to the patient and will eliminate the risk of sinusitis and nasal necrosis. Because implanted feeding tubes transverse two epithelial barriers—the skin and mucosa of the gastrointestinal tract—risk for infection at the insertion site is increased (104,105). In addition, if the tube is inadvertently removed before the tube tract has matured (generally 2 to 3 weeks postplacement when significant adhesions form between the stomach and the abdominal wall), an operative procedure may be needed to prevent spillage of gastrointestinal contents into the peritoneum (106). Several options are available for the placement of gastrostomy tubes; currently the most common technique is the percutaneous endoscopic gastrostomy or PEG (107,108). Percutaneous techniques have advantages over surgical techniques in that they are less expensive and do not require general anesthesia. Placement of a PEG requires passage of an endoscope into the stomach to see and manipulate the insertion site. The PEG procedure can be accomplished with either a push or pull technique, in that the gastrostomy tube may either be pulled through the stomach and out the anterior abdominal wall or pushed over a guidewire into the stomach and out the hole in the abdominal wall (109). After placement, an external bolster holds the tube in position and keeps the stomach up against the abdominal wall to prevent leakage of feedings or gastric contents. At present good documentation regarding the benefit of a PEG versus feeding via a nasogastric tube (NGT) does not exist. In FOOD trial, 3 of 321 dysphagic stroke patients allocated to either a PEG or NGT, PEG was associated with an increase in absolute risk of death of 1.0% (95% CI 10.0 to 11.9; p=0.9) and an increased risk of death or poor outcome of 7.8% (95% CI 0.0 to 15.5; p=0.05) (110).

Basic Requirements for Use of the Percutaneous Endoscopic Gastrostomy Technique

The basic requirements for use of the percutaneous endoscopic gastrostomy technique include ability to pass the endoscope (not possible in some patients with severe neurologic disease); ability of the patient to tolerate sedation; an unobstructed esophagus if the pull-through technique is used; absence of excessive obesity; and no history of a complicated surgical procedure in the upper abdomen that may have caused bowel loops to adhere between the stomach and abdominal wall.

The general practice is to wait 24 hours postinsertion to initiate feedings, although there is evidence that feeding can begin as early as 4 to 6 hours post placement (111). Major complications (peritonitis, necrotizing fasciitis, severe hemorrhage) and lesser complications (tube extrusion or migration, gastrocolic fistula) occur less often in patients receiving a PEG as compared to a surgical gastrostomy (112,113). However, for patients who have conditions that preclude endoscopic placement as stated above, or who are undergoing laparotomy for other reasons, a surgical gastrostomy is a viable alternative. Although a higher complication rate is associated with a surgical approach, because the stomach is secured to the abdominal wall directly, the risk of leakage of gastric contents usually is lower than with other techniques (114).

Short Silicone Post Low-Profile Tube

A short silicone post low-profile tube (e.g., "the button tube") may be used to replace a standard gastrostomy tube. The intragastric component of the post is a mushroom tip, and the external part is a small, tablike cross-piece. An attached flap closure provides a flush surface. During feeding, a tube is inserted into the open post. This device, which can be placed 4 to 6 weeks or more after the gastrostomy procedure, allows a better cosmetic effect and the regression of granulation tissue from the original tube in some patients, and it reduces skin irritation. The button is designed as a one-way antireflux valve. A special adapter is needed to cannulate the valve and check the residual volume or detect decompression.

Long-term Small Bowel Access

If long-term small bowel access is desired, some PEGs will accommodate the passage of a jejunal extension through the gastrostomy and into the duodenum or jejunum. Alternatively, a percutaneous endoscopic jejunostomy (PEJ) can be placed using a technique similar to that for a PEG, with the tube positioned endoscopically beyond the pylorus into the jejunum (111,115,116). Some authors believe a direct PEJ placement is preferable to a PEG tube with jejunal extension because of the ability to place a larger bore tube that can be anchored in the jejunum, preventing proximal migration into the stomach (117). The same benefit is obtained by placing a feeding jejunostomy at time of laparotomy via a surgically constructed serosal tunnel. Smaller bore needle catheter jejunostomy tubes are a viable alternative when enteral feeding is only required for a short period of time because patency may be difficult to maintain, and the tube cannot be replaced if inadvertently removed (118).

Care of the Insertion Site

Care of the insertion site for both short- and long-term tubes should begin as soon as the tube is placed and continue until the tube is removed and the exit site is healed (Table 10-10). As previously mentioned, a tube inadvertently removed before the tract has matured leaves the patient at risk of leakage of gastric contents into the peritoneal cavity and should be considered a medical emergency. A mature tract should be recannulated within a few hours to avoid permanent closure.

Maintenance of Tube Patency

Small-bore, more flexible enteric feeding tubes are more prone to clogging than the larger-bore stiffer decompression tubes. The best method to prevent clogging continues to be regular flushing with water or normal saline. The tube should be flushed with a minimum of 30 ml of water or saline before and after each intermittent feeding and medication administration. If the patient is fed continuously, a 30-ml flush is recommended every 4 hours. Medications should never be mixed with the enteral formula because either coagulation of the formula and clogging of the tube or precipitation of the medication and loss of its effectiveness could occur. If enteral feedings are held for any reason, the tube should continue to be flushed every 4 hours to maintain patency. If the enteral feeding tube does become clogged, several maneuvers can be attempted to clear the tube (Table 10-11) (119).

Initiation of Enteral Feedings

Regardless of the route and feeding tube type, enteral feeds are generally started at a low rate and gradually increased over a 24-hour period to a final infusion rate calculated from the desired daily provision of calories and protein (Figure 10-3).

Maintaining a 45-degree Elevation

Maintaining a 45-degree elevation of the head of the bed during tube feeding infusion is still one of the best defenses against tracheobronchial aspiration (92). It is good practice to

TABLE 10-10. Care of the Tube Insertion Site

Type of placement	Evaluate	Assess	Care	Precautions
Nasal or oral	Daily	Redness, dryness, or fissures noted around nose or mouth	Lubricate nares with water-soluble lubricant. Change anchoring method	If condition worsens, may need to change site of insertion
Nasal or oral	Twice daily	Decreased oral hygiene	Mouth care	
Nasal	Daily	Sores or increased nasal drainage	Replace via the oral route, may require antibiotics	May indicate sinusitis, report to physician
Gastrostomy or jejunostomy	Daily—start 24 hours postplacement	Check exit site	Clean tube site twice daily with soap and water and the area immediately around the skin opening. If covered by a bolster use cotton swab for cleaning	
	Immediately postplacement then daily	Increased bleeding or drainage at exit site	Place additional gauze dressing around the site and the tube	Do not place dressings directly under the external bolster—may dislodge tube Report to physician
	Daily	Increased tenderness, swelling, or redness	More frequent cleaning, cap feeding ports when not in use, possibly antibiotics or tube removal	Report immediately to physician; may be signs of an infection
	Daily	Inadvertent tube removal	Contact physician—may be able to re-insert through established tract if done quickly	If tract not mature, this should be considered a medical emergency

keep the head elevated even when feeding ports are near or distal to the ligament of Treitz. Patients receiving gastric tube feedings should not recline for at least 2 hours after instillation of a feeding, even one as small as 100 mL. Regurgitation is possible with a nasogastric tube because it interferes with the function of the upper and lower esophageal sphincters, which normally prevent tracheobronchial aspiration during recumbency.

TABLE 10-11. Steps to Unclog Enteral Access

1. Irrigate the tube with warm water and alternate with aspiration of the tube.[a]
2. If unsuccessful with step 1, infuse crushed pancrelipase dissolved in a bicarbonate solution and allow to sit for 30 minutes.
3. Repeat step 1.
4. If tube remains clogged, it must be replaced.

[a] To prevent rupture of the tube, avoid applying excessive pressure by using a 60-mL syringe.

Feeding Formulas in Cans or Closed Systems

These systems do not need to be refrigerated. If they are refrigerated, they should be brought to room temperature before infusion. Formula in cans should be allowed to hang no more than 8 hours in a feeding solution administration set. The longer the formula hangs in the bag at room temperature, the higher the level of bacterial contamination (120).

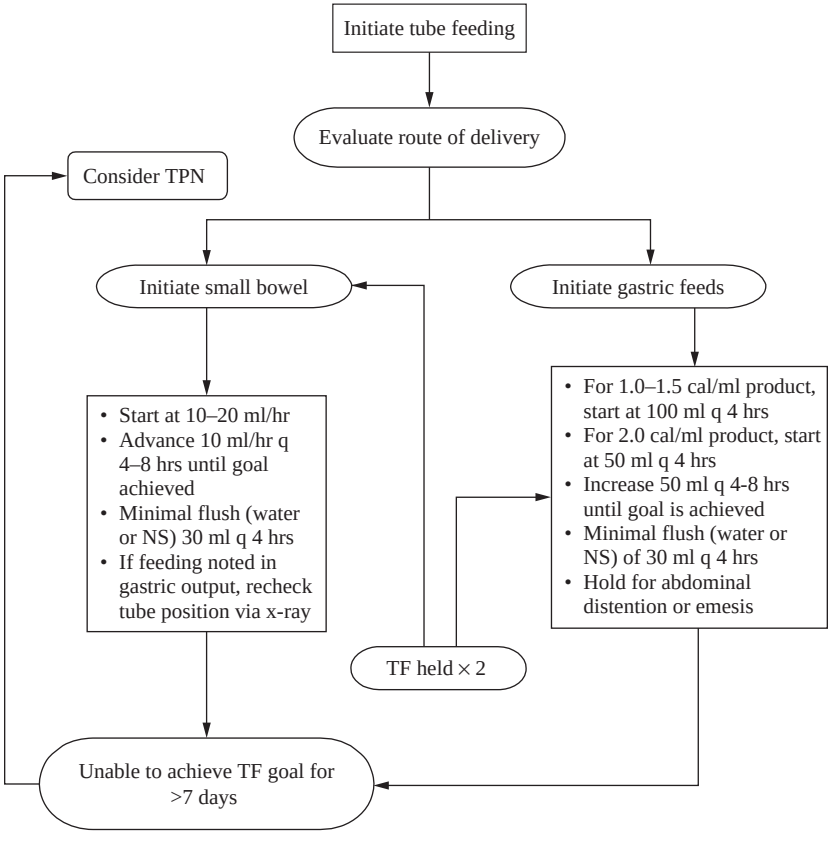


FIGURE 10-3. Initiation of tube feeding

Ready-to-hang or closed systems hang times range from 24 to 48 hours. Absence of microbial growth in enteral feeding samples from a closed system was demonstrated at the completion of a 48-hour hang time with strict adherence to label instructions for clean technique (121,122). Optimally, the feeding bag and administration set should be discarded after 24 hours. However, in home settings this may not be feasible secondary to cost; therefore, the feeding bag should be washed thoroughly every 24 hours to prevent bacterial contamination. Theoretical complications related to bacterial growth in the feeding formula rarely develop into true clinical problems.

Intermittent or Bolus Feeding

Intermittent or bolus feeding directly into the small bowel through nasoduodenal or jejunostomy tubes is not recommended because the secretory osmotic response of the small bowel to hypertonic bolus feedings will generally lead to dumping syndrome.

Constant-infusion Techniques

Constant-infusion techniques used with nasoduodenal tubes also can be used for gastrostomy and nasogastric tube feeding. Constant infusion into the stomach may be advantageous in a few conditions, including short-bowel syndrome (15). However, in most cases, because of the possibility of gastric retention of the infusate, intermittent feeding through tubes with feeding ports in the stomach is the recommended technique.

Aspirate

Aspirate through the nasogastric or gastrostomy tube before initiating the feeding to determine whether retained gastric secretions are present. Although almost all centers use the residual volume as a guide to managing tube feedings, the recommended cutoff volume varies considerably, and few data are available on which to base a recommendation. One study demonstrated low residual volumes (RV) did not assure the absence of aspiration events (90). The frequency of aspiration was 23% when RV was <150 ml. When the RV trigger to hold gastric feedings was increased to 200 ml and then to 400 ml the frequency of aspiration did not significantly change, 21.6% and 22.6%, respectively (90). In another study focusing on aspiration, a subset of 182 patients fed consistently into the stomach was analyzed to determine the risk of aspiration associated with RV. While the overall mean RV was greater in the patients experiencing aspiration than those not aspirating, the finding had no clinical or statistical significance ($P = .058$) (92). However, if there is concern for aspiration, the use of prokinetic agents and caloric dense formula can be used in an attempt to reduce residual volumes. Persistent gastric retention of feeding formula may indicate gastric outlet obstruction, proximal small-bowel obstruction, or ileus involving the stomach and proximal small bowel.

Monitoring Patients

Monitoring patients receiving enteral nutrition should be completed in a regular fashion to detect complications and evaluate the efficacy of the nutritional support (Table 10-12). All members of the health care team should be involved in monitoring the enterally fed patient (123). Positive signs of the efficacy of nutritional support come slowly. Weight gain, wound healing, and other signs of anabolism may not be seen until weeks of nutritional support. Many tube-fed patients receive less than the amount prescribed. This may be due to several reasons including tube dislodgement, gastrointestinal intolerance, medical procedures that interrupt feeding, and problems with the position of the feeding tube.

COMPLICATIONS OF TUBE FEEDINGS

Metabolic Complications

Fluid and electrolyte problems are common in patients receiving tube feedings, and in many cases, the formula must be modified to solve these problems. Hypokalemia, hyponatremia,

TABLE 10-12. Monitoring the Patient Receiving Tube Feedings

Assessment	Frequency/Rationale
Gastric residuals (gastric feedings only)	Before each feeding. Amounts >250 mL twice in succession should be evaluated for appearance. If TF product is noted in residual, this may indicate delayed gastric emptying. Consider prokinetic agent. If residuals continue, consider small bowel access
Emesis	May indicate delay of gastric emptying, follow recommendations for high residuals
Auscultate bowel sounds and abdominal exam, patient complaints	Every 8 hours. Absent bowel sounds and abdominal distention and patient complaints of fullness may indicate ileus
Bowel movements	Every 8 hours. Change in consistency may indicate malabsorption (diarrhea) or decreased bowel motility (constipation), requiring addition of fiber or change in product
Head of bed	Should be kept at 45° during gastric feeding and for 2 hours postfeeding
Vital signs—temp, respiratory rate, effort, and breath sounds	Daily. Increased temperature, respiratory rate and effort may be associated with pneumonia. Breath sounds should be clear
Weight	Daily. Weight gain of 1 to 1½ pounds per week may indicate actual weight gain; daily increases are more indicative of fluid status
I/O	Daily at first, then as needed. To aid in monitoring fluid status and potential need to adjust caloric density of enteral product
Lab data	
Serum sodium, potassium, chloride, bicarbonate, BUN, creatinine	Daily until stable, then bi-weekly. To evaluate for changing metabolic status and renal function
Potassium, magnesium, and phosphorus	Daily until stable. To evaluate for refeeding syndrome
Liver function tests, albumin, calcium, hematocrit, prothrombin time	Baseline, then once a week
Triglycerides, cholesterol	Follow in patients at risk of pancreatitis, history of hyperlipidemia
Glucose	Nondiabetics: check every 6 hours; diabetics every 4 hours until within normal limits, then every 8–12 hours to determine glycemic control. Cover with sliding scale insulin as needed. For diabetics begin basal and scheduled insulin as indicated

BUN, blood urea nitrogen; I/O, inputs/outputs; TF, tube feeding.

hypophosphatemia, and hyperglycemia are among the most frequent metabolic complications. Some of the complications result from the use of commercial products, all of which have fixed electrolyte content. This disadvantage is easily outweighed by their convenience of use and modest expense.

Electrolyte Disturbances

The mineral contents of the formulas are given in Table 10-4 and are based on the usual requirements (see Chapter 7). Some patients may require additional supplements or may not tolerate the pre-established amounts of individual minerals. Problems are especially likely to develop in patients with renal, hepatic, or cardiac disease. Periodic monitoring of serum levels of sodium, potassium, chloride, calcium, phosphorus, and magnesium detects the most frequent electrolyte abnormalities.

Deficiencies of Trace Minerals

Deficiencies of trace minerals may appear in patients on long-term tube feeding. Clinically relevant zinc deficiency has been noted. Zinc deficiency is especially likely in patients with zinc loss from the gastrointestinal tract, as in active Crohn disease. Patients receiving defined formulas as their only source of nutrition for prolonged periods must be observed for micronutrient deficiencies.

Hyperosmolarity Syndrome

Hyperosmolarity syndrome is an uncommon complication resulting from inadequate intake of free water despite continuous ingestion of a high osmotic load. The clinical syndrome includes lethargy, obtundation, appearance of dehydration, and at times fever. Serum electrolytes reveal hypernatremia and hyperosmolarity. The treatment includes increasing daily free water by supplementing the usual routine with water. IV 5% dextrose in water or 0.45% sodium chloride solution may be necessary, as in the management of hypernatremia, if changes in mental status are significant.

Refeeding Syndrome

Refeeding syndrome may develop when patients who are severely malnourished are begun on enteral (or parenteral) nutrition. With refeeding, potassium, phosphate, and magnesium move from the extracellular to the intracellular space, causing hypokalemia, hypophosphatemia, and hypomagnesemia. Patients with decreased levels should be repleted before the start of feeding. Serum magnesium, potassium, and phosphate levels should be monitored carefully in all patients who are being refed.

Warfarin Resistance

Warfarin resistance may result from the unsuspected delivery of vitamin K in enteral supplements or feeding formulas. The estimated safe and adequate daily intake of vitamin K is 70 to 140 μg, yet the average diet in the United States contains 300 to 500 μg of this vitamin. Warfarin resistance is an uncommon development with the vitamin K content of currently available products.

Nonmetabolic Complications

Diarrhea and Constipation

Diarrhea and constipation are common complications of enteral feeding, occurring in as many as 20% of patients. Steps to take with trouble-shooting diarrhea and constipation are outlined in Table 10-13. The incidence of diarrhea in tube feeding depends on the definition of diarrhea. If diarrhea is defined broadly (one or more liquid stools per day), the incidence in tube-fed patients is more than 70%; if a more stringent definition is used (four or more liquid stools per day or five or more stools per day), the incidence falls to 21% (124).

Esophagitis or Esophageal Ulcer

Nasally placed tubes can cause esophagitis by directly irritating the esophageal mucosa and by interfering with normal protective mechanisms against esophageal damage by gastric acid. Competence of the lower esophageal sphincter, normal esophageal stripping by primary and secondary peristalsis, and swallowing of saliva all appear to help prevent reflux esophagitis in normal persons; and all these mechanisms may be impaired in patients with feeding tubes.

Complications

Very rare complications include small bowel perforation, pneumatosis intestinalis, rupture and division of the feeding tube, and inadvertent IV administration of the formula. Bronchopulmonary complications, including perforation of the lung, can occur if a stylet is used and the tube inadvertently enters the trachea during placement. This complication can occur even in the presence of an inflated tracheostomy tube cuff.

TABLE 10-13. Troubleshooting Tube Feeding Complications of Diarrhea or Constipation

Diarrhea

First quantify the diarrhea; a tube-fed patient may experience 4–5, moderate amount, loose to soft-formed stools per day normally. If the patient is experiencing diarrhea or an increase in their normal stooling, try the following:

1. Review all medications: Often when enteral access is obtained, meds are changed to the enteral route. If the diarrhea is severe, change meds to IV form at least as a trial. Medications that may contribute to diarrhea include: antibiotics, antineoplastics, magnesium containing antacids, potassium and phosphate supplements, laxatives, medications with sorbitol base (i.e., theophylline), and colchicine.
2. Check for *Clostridium difficile.*
3. Try adding fiber (i.e., Benefiber^{R} 1 tbsp TID).
4. If infusing a hypertonic formula, change to an isotonic product.
5. Once infectious causes are ruled out (and bowel surgery patients are at least 10–14 days post-op) and if diarrhea persists, try an antidiarrheal agent on a routine dose: loperamide 2 mg q 6 hours, increase to 4 mg q 6 hours if diarrhea persists
6. KEEP FEEDING!!!

Constipation

Constipation is defined as no bowel movement for >3 days after tube feedings are at goal or difficulty passing stools.

1. Check for signs of dehydration—increased Na, Cl, BUN; dark and/or decreased amount of urine—if present, increase amount of water flush.
2. Try adding fiber.
3. Start patient on docusate 100 mg/day.
4. Rectal exam.
5. Bisacodyl suppository prn.

BUN, blood urea nitrogen; IV, intravenous; prn, as needed; TID, three times per day; TBSP, table spoon.

ADMINISTERING MEDICATIONS THROUGH FEEDING TUBES

For many patients with feeding tubes, especially those at home or in extended-care facilities, the tube is the only practical avenue for administering medications. However, not all medications can be administered successfully by feeding tube. Some general guidelines have been developed, but the guidelines may not be applicable to certain combinations of drugs, enteral formula, and feeding tube.

The Tube

The location of the tube must be considered. Drugs administered beyond the pylorus are absorbed more rapidly. Antacids and carafate should not be delivered beyond the pylorus. The diameter of the tube must be considered. The smaller the diameter, the more likely it is to become clogged. Thick liquids such as antacids should not be administered through a tube with a diameter smaller than 10 F.

The Drug

1. Slow-release drugs (e.g., Calan SR, Cardizem, Isordil Tembid) and enteric-coated drugs (e.g., MI-Cebrin, Azulfidine EN-tabs) should not be crushed because crushing may increase the rate of absorption (for slow-release formulations), expose the drug to degradation in the stomach, or cause gastric upset.
2. Pancreatic enzymes (e.g., pancrease) are usually enteric-coated. If they are crushed and administered by nasogastric tube, they can be inactivated by gastric acid.

However powdered Viokase may be mixed in 30 mL of water and administered via the feeding tube.

3. The use of liquid preparations is generally preferable to crushing and dissolving tablets. A liquid formulation of a drug should be used if it is available.

Administration

1. Crushed tablets should be reconstituted in at least 10 to 15 mL of water.
2. Hard gelatin capsules should be opened and the powder dissolved in at least 10 to 15 mL of water.
3. Drugs that are hypertonic or that irritate the gastrointestinal mucosa should be dissolved in larger volumes of water before administration.
4. Drugs should not be added to the enteral formula.
5. The enteral formula should be stopped before medication is administered.
6. The feeding tube should be flushed with water to remove residual formula before medication is administered.
7. The feeding tube should be flushed with water (10 to 30 mL) after the drug is administered.
8. For patients on intermittent gastric feeding schedules, the timing of administration of medications that should be taken on a full or empty stomach should be adjusted according to the patient's feeding schedule.

Drugs with Specific Requirements

The absorption of several medications may be impaired when given via the enteral feeding access (Table 10-14) (125–127). To decrease this effect, the TF should be held for 1 hour before and after the time of medication dosing if possible (128,129). In addition, when applicable, blood levels of medication should be monitored. Many medications may form a precipitate when combined with enteral formula and clog the feeding tube (Table 10-14) (130). If at all possible, these medications should be given via a separate enteral access or with adequate tube flushing before and after administration. Patients receiving medications with a high sorbitol content (Table 10-14) should be monitored closely for diarrhea, abdominal cramping, and bloating. Any medications given directly into the small bowel should be diluted with water prior to administration given the lack of a reservoir and the potential for ulceration (130). A quality improvement effort aimed at the correct administration of medications via enteral feeding tubes in two Dutch hospitals led to a significant decrease in administration errors and clogged feeding tubes (131). Given the increased usage of enteral feeding in the hospital setting and the potential for errors, a quality improvement effort may lead to decreased morbidity as well and should be considered for implementation.

PANCREATIC DISEASE

Chronic Pancreatitis

Chronic pancreatitis is a chronic irreversible inflammatory process of the pancreas that may lead to fibrosis with calcification (132). Eventually the patient will experience impairment of endocrine and exocrine function of the pancreas. The patient with chronic pancreatitis generally presents with chronic abdominal pain and normal or mildly elevated pancreatic enzyme levels. Diabetes mellitus and steatorrhea will present as the pancreas loses its endocrine and exocrine function (132). Fat malabsorption does not become significant until lipase output is less than 10% of normal, and consequently, a considerable portion of the gland must be destroyed before fat malabsorption is clinically recognized (133). Steatorrhea usually occurs prior to protein deficiencies since lipolytic activity decreases faster than proteolytic activity. In the United States the most common etiology of exocrine pancreatic insufficiency in adults is alcoholism, accounting for approximately 60% of the cases (134). Other causes of pancreatic insufficiency include cystic fibrosis, hereditary pancreatitis, surgical resection,

TABLE 10-14. Potential Medication and Enteral Feeding Interactions

Medications that cause precipitates and may clog feeding tubes (≤10 French)
Brompheniramine/phenylephrine (Dimetane)
Brompheniramine/phenylpropanolamine (Dimetapp)
Calcium glubionate (Neo-calglucon)
Chlorpromazine (Thorazine Concentrate)
Clarithromycin (Biaxin)
Ferrous sulfate (Feosol)
Guaifenisin (Robitussion products)
Lithium citrate (Cibalith-S)
MCT oil—separates and clogs tube
Metoclopramide (Reglan)
Opium tincture (Paragoric)
Potassium chloride
Pseudoephedrine (Sudafed)
Sodium biphosphate (Fleets Phospho-Soda)
Thioridazine (Mellaril Concentrate)
Zinc sulfate capsules
Medications that have decreased bioavailability when given with enteral feeding
Carbamazepine (Tegretol)—May bind with tube and have 10% to 20% loss of medication. Flushing with NS decreases this interaction
Ciprofloxin (Cipro) (Possibly other quinolones such as levofloxacin, etc.)—inactivates medication
Itraconazole (Sporonax)—inactivates medication
Phenytoin (Dilantin)—inactivates medication
Theophylline (Theolair)—inactivates medication
Medications containing high levels of Sorbitol
Acetaminophen elixir
Aluminum hydroxide gel
Aluminum hydroxide/magnesuim carbonate (Gaviscon)
Aluminum hydroxide/magnesium hydroxide (Maalox)
Amantadine H Cl (Amantadine)
Aminocaproic acid (Amicar)
Carbamazepine (Tegretrol)
Charcoal, activated (Actidose with sorbitol)

NS, normal saline.

and obstruction of the pancreatic duct by calculi, inflammation, stricture, or cancer (135). Abstinence from alcohol, dietary modifications, and pancreatic enzyme supplementation are sufficient in over 80% of patients with chronic pancreatitis (136).

Diet

A diet low in fat (50 to 70 g per day) and high in protein (1.0 to 1.5 g per kg) and complex carbohydrates provided over 6 small meals should be tried initially in patients with steatorrhea (136). Adequate nutritional therapy combined with pain management may have a positive effect on nutritional status by allowing for increased caloric intake after an attenuation of postprandial pain. If steatorrhea persists, fat intake should be reduced to 0.5 g per kg per day and pancreatic enzymes initiated (Table 10-15). The intake of fat can be liberalized (to 30% of calories) as control of diarrhea with supplemental enzymes is achieved. If steatorrhea is persistent, then medium-chain triglycerides can be administered to provide approximately 400 calories per day (~4 tbsp per day). However MCT are not very palatable and may induce abdominal pain and diarrhea at higher doses, making it difficult to determine when the chronic pancreatitis symptoms are subsiding. Protein supplementation via oral supplements is generally recommended because the intake of dietary protein is restricted along with the intake of fat. Tube feeding is only indicated if the patient cannot ingest enough calories for weight maintenance.

TABLE 10-15. Pancreatic Enzyme Preparations[a]

	Lipase (units)	Amylase (units)	Protease (units)	Distributor
Pancreatin products				
Donnazyme tablet	1,000	12,500	12,500	Wyeth
KU-Zyme capsules	1,200	15,000	15,000	Schwartz
Kutrase capsules	2,400	30,000	30,000	Schwartz
Pancreatin 4X USP tablet	12,000	60,000	60,000	Vitaline
Pancreatin 8X USP tablet	22,500	180,000	180,000	Vitaline
Pancrelipase products				
Creon 5 capsule	5,000	16,600	18,750	Solvay
Creon 10 capsule	10,000	33,200	37,500	
Creon 20 capsule	20,000	66,400	75,000	
Donnazyme tablet	1,000	12,500	12,500	Robbins
KU-Zyme capsules	1,200	15,000	15,000	Schwartz
Kutrase capsules	2,400	30,000	30,000	
Lipram 4500 capsule	4,500	20,000	25,000	Global
Lipram CR5 capsule	5,000	16,600	18,750	Global
Lipram PN10 capsule	10,000	30,000	30,000	Global
Pancrecarb MS 4 capsule	4,000	25,000	25,000	Digestive Care
Pancrecarb MS 8 capsule	8,000	40,000	45,000	Digestive Care
Pancrease capsule	4,500	20,000	25,000	Ortho-McNeil
Pancrease MT 4	4,000	12,000	12,000	
Pancrease MT 10	10,000	30,000	30,000	
Pancrease MT 16	16,000	48,000	48,000	
Pancrease MT 20	20,000	56,000	44,000	
Ultrase capsule	4,500	20,000	25,000	Axcan Scandipharm
Ultrase MT 12	12,000	39,000	39,000	
Ultrase MT 18	18,000	58,500	58,500	
Ultrase MT 20	20,000	65,000	65,000	
Viokase powder 1/4 tsp	16,800	70,000	70,000	Robbins
Viokase 8 tablet	8,000	30,000	30,000	
Viokase 16 tablet	16,000	60,000	60,000	
Zymase capsule	12,000	24,000	24,000	Organon

[a] This is not meant to be a complete listing. Products may have changed since this list was compiled.

Enzyme Replacement

Enzyme replacement is used to aid digestion in patients with pancreatic enzyme deficiency. Several commercial preparations exist (Table 10-15), although they are of two types: pancreatin and pancrelipase. Pancreatin is an extract of hog pancreas standardized for amylase and trypsin activity, and pancrelipase is a lipase-enriched extract. Tablets, capsules, and enteric-coated preparations all may be effective in reducing or abolishing steatorrhea if adequate amounts of enzymes are supplied. Approximately 30,000 IU of lipase must be taken with each meal to eliminate steatorrhea completely, and even then enzyme is inactivated by gastric acid. Taking all the tablets at once with a meal is as effective as taking them intermittently with and after a meal. The usual doses of products with *in vitro* enzyme activity that can be given to reduce steatorrhea are given in Table 10-15.

Vitamin Supplementation

Fat-soluble vitamin supplementation is rarely needed once the previously mentioned measures are taken to reduce steatorrhea because the concentrations of bile acids required to solubilize the fat-soluble vitamins are usually normal. Moreover, the fat-soluble vitamins

do not depend on pancreatic hydrolysis for absorption. Vitamin B_{12} deficiency can result from pancreatic insufficiency. Pancreatic proteolytic enzymes are needed to digest haptocorrin and so liberate ingested cobalamin and bind to intrinsic factor. Enzyme supplementation partially corrects this error, but vitamin B_{12} supplements should still be given to ensure that chronic neural damage does not develop.

Acute Pancreatitis

Acute pancreatitis is an earlier pathological stage than chronic pancreatitis. In acute pancreatitis inflammation exists even between clinical episodes, but acinar and endocrine cell function is preserved. In acute pancreatitis the patient presents with acute and severe abdominal pain, nausea, and vomiting. The pancreas is acutely inflamed (neutrophils and edema), and the serum levels of pancreatic enzymes (amylase and lipase) are elevated. The severity of acute pancreatitis is classified by the Atlanta criteria (137). Approximately 80% of the patients have mild disease associated with minimal or no organ dysfunction or necrosis (138). These patients are usually managed with analgesics, IV fluids, and NPO status for 5 to 7 days, after which they are generally able to resume an oral low-fat (<30% of calories) diet. Typically nutritional management is not required in this patient subset. In the most severe cases, mortality can rise to 25% to 50% with infected necrosis (139, 140). Until recently it was believed enteral nutrition was harmful secondary to stimulation of the exocrine pancreatic secretion. This was considered a risk for exacerbating the autodigestive process. At present, it is believed enteral nutrition may help to preserve gut integrity. Theoretically this might maintain the gut barrier and immune function, therefore decreasing the risk of infectious complications, but the data available do not prove that improved clinical outcomes are due to the preservation of gut integrity.

Diet

In severe necrotizing pancreatitis, 80% of the patients are catabolic with high energy expenditure (141). In all likelihood these patients will be unable to consume an oral low-fat diet without pain within 5 to 7 days. In one study, previously healthy men who developed severe pancreatitis who were not fed for at least 5 days developed decreased muscle function proportional to decreased protein stores (142). This, combined with the ASPEN recommendations to provide nutrition support to patients expected to have a prolonged NPO status of >7 days, suggests nutrition support should be instituted when the patient is hemodynamically stable. Two landmark trials comparing enteral to parenteral nutrition in the patient population found enteral nutrition significantly attenuated the acute phase response in these patients when compared to parenteral nutrition (143,144). More recently, several authors continue to demonstrate the benefit of enteral nutrition (delivered in the jejunum) over parenteral nutrition or NPO status in these patients (145–148). Caloric provision, combined with a higher infection rate in TPN-treated patients, may be the reasons for the improved results. The preferred site to deliver enteral feeds, the jejunum, is based on the theoretical benefit that decreasing pancreatic enzyme and bicarbonate secretion stimulation will be associated with jejunal feeding and that such a decrease will have clinical benefit. However, in one recent study, tolerance was demonstrated in patients fed into the stomach (149). Most of the trials mentioned previously provided peptide based enteral formulations, although one of the more recent trials demonstrated tolerance with a polymeric formula (147). At present the following recommendations can be made based on the evidence:

1. Small bowel feeding is as safe as gastric feeding, and is well tolerated, but clinical outcomes may not be improved.
2. Obtain small bowel feeding access, if easily done. Do not persist in attempting small bowel access, as gastric feeding is an equally valid alternative.
3. Begin enteral feeds utilizing a peptide based product at a slow rate of 10 to 20 mL per hour as soon as the patient is hemodynamically stable.
4. Advance the enteral feeds slowly over 48 hours to the patient's goal rate.

5. Most patients' needs can be met by providing 25 to 30 calories per kg and 1.0 to 1.5 g per kg protein.

SHORT-BOWEL SYNDROME

Short-bowel syndrome (SBS), which usually results from extensive small-bowel resection, is not strictly defined. Several potential nutritional consequences exist in SBS including malabsorption of fluid, electrolytes, minerals, and other essential nutrients, which may lead to malnutrition and dehydration. The degree to which nutrition support will be required depends on the extent and site of the surgical resection, the underlying disease, and level of intestinal adaptation in the remaining bowel (150). Massive surgical resection of diseased, ischemic small bowel (arterial or venous occlusion, strangulation in hernia, volvulus) is the leading cause of the most severe form of the syndrome. Gradual "whittling away" of small intestine with multiple resections for Crohn disease (151), on the other hand, is a common cause of the less severe clinical picture. Parenteral nutrition is the mainstay of treatment in SBS with severe malabsorption. In less severe cases, maintenance of adequate protein and calorie balance is the only major problem, which can generally be overcome by oral supplementation.

Intestinal Adaptation after Massive Resection

Intestinal adaptation after massive resection is highly individualized and maximal adaptation may take up to 2 years (152). Enteral nutrition is essential to aid in maximal adaptation. However, most patients with SBS will require at least short-term TPN during the initial postoperative period, the initial adaptation phase. The ability of the bowel to adapt will depend on a number of things.

1. The length of remaining bowel: >50% usually requires no significant intervention; 25% to 50% often requires dietary modifications, antimotility agents, and vitamin and mineral supplementation; <25% will most likely require long term parenteral nutrition or intestinal transplantation (150,153,154);
2. The presence of the colon: while malabsorption of energy can be an issue in patients with or without a colon, those without do not derive energy from anaerobic bacterial fermentation of carbohydrate to the short-chain fatty acids, which has been shown to provide 5% to 10% of energy in healthy subjects (155). In addition, the colon aids with fluid and electrolyte re-absorption.
3. The presence of the ileal cecal valve, which acts as the "ileal brake" slowing transit time (153). Patients lacking this valve may have a higher requirement for antimotility medications.

Initiate TPN

To prevent nutritional deterioration during the restoration of electrolyte and water balance TPN should be initiated. Gradual attempts at enteral feeding can be made while the functional capacity of the remaining bowel is assessed. The major objective of nutrition support in SBS is to reduce or eliminate the need for parenteral nutrition.

Monitor

Monitor serum electrolytes, calcium, phosphorus and magnesium regularly. Calcium supplementation in Crohn disease patients with SBS who have been on steroids for long periods of time is essential given their increased risk for bone fractures, osteopenia, and osteoporosis at baseline (156). Patients with SBS may have significant losses of zinc and selenium, requiring additional supplementation (152). In addition, these patients may develop magnesium deficiencies while maintaining a normal serum concentration; therefore measurement of 24-hour urine magnesium levels may be beneficial (157).

Following Adaptation after Massive Resection, or for Long-term Management of Less Severe Short-bowel Syndrome

Diet Therapy

In general, food should be provided over 5 to 6 small meals per day. Dependening on the amount of malabsorption, 130% to 150% of estimated caloric and protein needs may be necessary. Fluid intake should exceed stool losses to maintain hydration. Complex carbohydrates are preferred to simple carbohydrates, since simple carbohydrates will increase the hyperosmolar load in the intestine and therefore decrease the fluid absorption.

High-Carbohydrate, Low-fat Diet. A high-carbohydrate (60%), low-fat (20%) diet in patients with SBS and a normally functioning colon lead to a significant ($P < 0.001$) increase in energy absorption compared with patients fed an isocalorie low-carbohydrate (20%), high-fat (60%) diet (158). No difference in caloric absorption was noted between the two diets when given to SBS patients without a colon. Patients with a colon have a higher risk of developing calcium oxalate renal stones and may benefit from a low oxalate diet.

Patients with an Ileostomy or a Jejunostomy. Patients with an ileostomy or jejunostomy are more likely to experience deficiencies in fluid, electrolyte, vitamin, and mineral status. These should be monitored frequently and supplementation adjusted as needed. Vitamin and mineral supplementation is important, especially in patients not receiving parenteral nutrition. Specific supplementation will depend on the remaining bowel; potential requirements are presented in Table 10-16. If ≥60 cm of terminal ileum is resected, a vitamin B_{12} deficiency is likely. Historically B_{12} supplementation has been

TABLE 10-16. Vitamin and Mineral Supplementation in Short Bowel Syndrome (152,168)

Supplement (representative product)	Dose	Route
Prenatal multivitamin with minerals[a]	1 tab q day	PO
Vitamin D[a]	1,600 U DHT daily	PO
Calcium[a]	300–800 mg elemental daily	PO
Vitamin B_{12}[b]	1 mg q day 100–500 μg q 1–2 mo	PO/nasally SC
Vitamin A[b]	5,000–20,000 U q day	PO
Vitamin K[b]	5 mg/day	PO
(Mephyton; AquaMEPHYTON)	5–10 mg/wk	SC
Vitamin E[b] (Aquasol E(®)	30–400 IU/day	PO
Magnesium gluconate[b] (Magonate(®) or magnesium oxide capsules (URO-MAG)	50–500 mg elemental daily	PO
Magnesium sulfate[b]	290 mg elemental 1–3 times/ week	IM/IV
Zinc sulfate[b]	220–440 mg/day	PO
Selenium[b]	60–100 μg/day	PO
Ferrous sulfate[b]	60 mg elemental iron TID	PO
Iron dextran[b]	≤100 mg elemental iron per day based on formula or table	IV

DHT, dihydrotachysterol; IM, intramuscular; IV, intravenous; PO, oral; SC, subcutaneous.
[a] Recommended routinely for all patients.
[b] Recommended for patients with documented nutrient deficiency or malabsorption.

provided via monthly intramuscular injections. An intranasal spray formulation of cyanocobalamin was approved by the FDA, and may be useful for some patients (see Chapter 7) (159).

Lactose. Lactose is restricted initially until the symptoms are under best control. Liberalization with monitoring of the clinical response is then appropriate.

Enteral Feeding. Enteral feeding during both the adaptation and postadaptation periods is feasible. It has been suggested that a peptide-based product may be more readily absorbed than one with intact protein in patients with SBS. While a few small studies support this conclusion, none found a significant increased absorption of energy, fat, electrolytes, fluid, or minerals (160–162). Enteral tube feedings should be provided continuously in the stomach to increase the contact time between the luminal nutrients and the intestinal mucosa allowing for maximal absorption.

Oral Rehydration Solutions. Oral rehydration solutions (ORS) may aid with sodium and fluid absorption by taking advantage of both the passive and active transport of sodium in the jejunum (Table 10-17) (163). Maximal absorption is achieved with a solution containing 120 mmol per L of sodium; however, if the patient finds this unpalatable, a 90 mmol per L solution can be tried. ORS are encouraged over restricted sugar-containing beverages (hyperosmotic) and hypo-osmotic solutions, such as water. Hypo- and hyperosmotic solutions in large amounts will lead to increased diarrhea and thus increased fluid and electrolyte losses. For best results fluids should be taken in small amounts between meals throughout the day to avoid dumping syndrome (increased bowel movements shortly after eating) (164).

Adjunctive Medications

These can prove useful in the management of patients with SBS.

Antimotility Agents. Antimotility agents will be useful in helping to reduce food induced diarrhea. An example approach is as follows:

Begin with 2 mg loperamide every 6 hours, gradually increasing the dosage up to 10 mg every 6 hours if needed. If this approach is unsuccessful, discontinue the loperamide and start 3 drops (0.15 ml) of deodorized tincture of opium 4 times per day, increasing to 15 drops (0.75 ml) per dose as needed. If the deodorized tincture of opium alone is unsuccessful,

TABLE 10-17. Oral Rehydration Solutions

Product	Na mEq/L	K mEq/L	Cl mEq/L	Citrate mEq/L	kcal/L	CHO g/L	mOsm
CeraLyte 70(®)[a]	70	20	98	30	165	40	235
CeraLyte 90(®)[a]	90	20	98	30	165	40	260
Gatorade(®)[b]	20	3	N/A	N/A	210	45	330
WHO	90	20	80	30	80	20	200
Washington University	105	0	100	10	85	20	250

[a] Cumberland Pharmaceuticals, Nashville, TN.
[b] Not to be used as an oral rehydration solution—included for comparison purposes only.

Home Recipes

WHO (World Health Organization) formula: Mix 3/4 tsp sodium chloride, 1/2 tsp sodium citrate, 1/4 tsp potassium chloride, and 4 tsp glucose (dextrose) in 1 L (4 1/4 cups) of distilled water.
Washington University formula: Mix 3/4 tsp sodium chloride, 1/2 tsp sodium citrate, and 3 tbsp + 1 tsp Polycose powder in 1 L (4 1/4 cups) of distilled water.
Mix formulas with sugar-free flavorings as needed for palatability.

Clonidine may be tried, starting at 0.05 mg BID, increasing to a maximum of 0.15 mg BID. Case reports have demonstrated the successful use of Clonidine in patients with SBS (165).

Control Gastric Hypersecretion. About 50% of patients who have undergone massive resection have transient gastric hypersecretion that can result in severe peptic ulcer disease. The mechanism is unclear but is felt to be hormonal (loss of an inhibitory control mechanism). Proton pump inhibitors or histamine$_2$-receptor antagonists may be required for 6 months after surgery (154).

If the fluid losses exceed 3 L per day, the use of long-acting somatostatin analog octreotide may be useful to decrease secretory diarrhea. However, studies in animals suggest that octreotide may impair intestinal adaptation (166,167).

References

1. American Society of Parenteral and Enteral Nutrition. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr.* 2002;26(1 supplement):1S.
2. Ravasco P, Monteiro-Grillo I, Marques P, et al. Impact of nutrition on outcome: A prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head & Neck.* 2005;27:659.
3. Bauer J, Capra S, Battistutta D, Davidson W, Ash S. Compliance with nutrition prescription improves outcomes in patients with unresectable pancreatic cancer. *Clin Nutr.* 2005;24:998.
4. Dennis MS, Lewis SC, Warlow C, The Food Trial C. Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial. *Lancet.* 2005; 365(9461):755.
5. Smedley F, Bowling M, James E, et al. Randomized clinical trial of the effects of preoperative and postoperative oral nutritional supplements on clinical course and cost of care. *Br J Surg.* 2004;91:983.
6. Braga M, Gianotti L, Vignali A, et al. Hospital resources consumed for surgical morbidity: effects of preoperative arginine and [omega]-3 fatty acid supplementation on costs. *Nutrition.* 2005;21:1078.
7. Pedrini MT, Levey AS, Lau J, et al. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann Intern Med.* 1996;124:627.
8. Shinaberger CS, Kilpatrick RD, Regidor DL, et al. Longitudinal associations between dietary protein intake and survival in hemodialysis patients. *Am J Kidney Dis.* 2006;48:37.
9. National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. *Am J Kid Dis.* 2000;35(Supple 2):51–140.
10. Cano N, Fiaccadori E, Tesinsky P, et al. ESPEN Guidelines on enteral nutrition: adult renal failure. *Clin Nutr.* 2006;25:295.
11. Dowell SA, Welch JL. Use of electronic self-monitoring for food and fluid intake: A pilot study. *Nephrol Nurs J.* 2006;33:271.
12. Marchesini G, Bianchi G, Merli M, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. *Gastroenterology.* 2003;124:1792.
13. Sathyanarayana N, Shenoy KR, Alvares JF, Pai SB. Enteral feeding by fistuloclysis in a midjejunal fistula. *Indian J Gastroenterol.* 2005;24:124.
14. Teubner A, Morrison HR, Ravishankar ID, et al. Fistuloclysis can successfully replace parenteral feeding in the nutritional support of patients with enterocutaneous fistula. *Br J Surg.* 2004;91:625.
15. Jeejeebhoy KN. Management of short bowel syndrome: avoidance of total parenteral nutrition. *Gastroenterology.* 2006;130(2 Suppl 1):S60.
16. O'Keefe SJ, Buchman AL, Fishbein TM, et al. Short bowel syndrome and intestinal failure: consensus definitions and overview. *Clin Gastroenterol Hepatol.* 2006;4:6.
17. Day AS, Whitten KE, Lemberg DA, et al. Exclusive enteral feeding as primary therapy for Crohn's disease in Australian children and adolescents: A feasible and effective approach. *J Gastroenterol Hepatol.* 2006;21:1609.
18. Lochs H, Dejong C, Hammarqvist F, et al. ESPEN Guidelines on Enteral Nutrition: Gastroenterology. *Clin Nutr.* 2006;25:260.
19. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for inducing remission of Crohn's disease. *Cochrane Database Syst Rev.* 2001(3):CD000542.
20. Abou-Assi S, Craig K, O'Keefe SJ. Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: results of a randomized comparative study. *Am J Gastroenterol.* 2002;97:2255.
21. Olah A, Pardavi G, Belagyi T, et al. Early nasojejunal feeding in acute pancreatitis is associated with a lower complication rate. *Nutrition.* 2002;18:259.
22. Louie BE, Noseworthy T, Hailey D, et al. 2004 MacLean-Mueller prize enteral or parenteral nutrition for severe pancreatitis: a randomized controlled trial and health technology assessment. *Can J Surg.* 2005;48:298.
23. Kumar A, Singh N, Prakash S, et al. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. *J Clin Gastroenterol.* 2006;40:431.
24. McClave SA, Chang WK, Dhaliwal R, Heyland DK. Nutrition support in acute pancreatitis: a systematic review of the literature. *JPEN J Parenter Enteral Nutr.* 2006;30:143.

25. Greenwood JK, Lovelace HY, McClave SA. Enteral nutrition in acute pancreatitis: a survey of practices in Canadian intensive care units. *Nutr Clin Pract.* 2004;19:31.
26. Nathens ABMDP, Curtis JRMDMPH, Beale RJM, et al. Management of the critically ill patient with severe acute pancreatitis. *Crit Care Med.* 2004;32:2524.
27. Meier R, Ockenga J, Pertkiewicz M, et al. ESPEN Guidelines on Enteral Nutrition: Pancreas. *Clin Nutr.* 2006;25:275.
28. Jean A Pennington PhD JSDMR. *Bowes & Church's Food Values of Portions Commonly Used*. 18th ed: Lippincott Williams and Wilkins, New York 2004.
29. Harig JM, Soergel KH, Komorowski RA, et al. Treatment of diversion colitis with short-chain fatty acid irrigation. *N Engl J Med.* 1989;320:23.
30. Silk DB, Fairclough PD, Clark ML, et al. Use of a peptide rather than free amino acid nitrogen source in chemically defined "elemental" diets. *JPEN J Parenter Enteral Nutr.* Nov-1980;4:548.
31. Silk DB. Digestion and absorption of dietary protein in man. *Proc Nutr Soc.* 1980;39:61.
32. Ksiazyk J, Piena M, Kierkus J, Lyszkowska M. Hydrolyzed versus nonhydrolyzed protein diet in short bowel syndrome in children. *J Pediatr Gastroenterol Nutr.* 2002;35:615.
33. Rees RG, Hare WR, Grimble GK, et al. Do patients with moderately impaired gastrointestinal function requiring enteral nutrition need a predigested nitrogen source? A prospective crossover controlled clinical trial. *Gut.* 1992;33:877.
34. Brinson RR, Hanumanthu SK, Pitts WM. A reappraisal of the peptide-based enteral formulas: clinical applications. *Nutr Clin Pract.* 1989;4:211.
35. Cosnes J, Evard D, Beaugerie L, et al. Improvement in protein absorption with a small-peptide-based diet in patients with high jejunostomy. *Nutrition.* 1992;8:406.
36. Tiengou LE, Gloro R, Pouzoulet J, et al. Semi-elemental formula or polymeric formula: is there a better choice for enteral nutrition in acute pancreatitis? Randomized comparative study. *JPEN J Parenter Enteral Nutr.* 2006;30:1.
37. Lochs H, Dejong C, Hammarqvist F, et al. ESPEN Guidelines on Enteral Nutrition: Gastroenterology. *Clin Nutr.* 2006;25:260.
38. Russell MK, Andrews MR, Brewer CK, et al. Standards for specialized nutrition support: adult hospitalized patients. *Nutr Clin Pract.* 2002;17:384.
39. Russell MK, Charney P. Is there a role for specialized enteral nutrition in the intensive care unit? *Nutr Clin Pract.* 2002;17:156.
40. Malone AM. The clinical benefits and efficacy of using specialized enteral feeding formulas. *Support Line.* 2002;24:3.
41. Pontes-Arruda A, Aragao AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. *Crit Care Med.* 2006;34:2325.
42. Gadek JE, DeMichele SJ, Karlstad MD, et al. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Enteral Nutrition in ARDS Study Group. *Crit Care Med.* 1999;27:1409.
43. Pacht ER, DeMichele SJ, Nelson JL, et al. Enteral nutrition with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants reduces alveolar inflammatory mediators and protein influx in patients with acute respiratory distress syndrome. *Crit Care Med.* 2003;31:491.
44. Singer P, Theilla M, Fisher H, et al. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. *Crit Care Med.* 2006;34:1033.
45. Zhang FK, Zhang JY, Jia JD. Treatment of patients with alcoholic liver disease. *Hepatobiliary Pancreat Dis Int.* 2005;4:12.
46. American Diabetes Association. Standards of Medical Care in Diabetes 2006. *Diabetes Care.* 2006;29(Supplement 1):S4.
47. Recommendations for the nutritional management of patients with diabetes mellitus. *Eur J Clin Nutr.* 2000;54:353.
48. Escott Stump S. *Nutrition and Diagnosis-Related Care*. 5th ed. Philadelphia: Lippincott Williams and Wilkins; 2002.
49. Craig LD, Nicholson S, SilVerstone FA, Kennedy RD. Use of a reduced-carbohydrate, modified-fat enteral formula for improving metabolic control and clinical outcomes in long-term care residents with type 2 diabetes: results of a pilot trial. *Nutrition.* 1998;14:529.
50. Garg A, Grundy SM, Koffler M. Effect of high carbohydrate intake on hyperglycemia, islet function, and plasma lipoproteins in NIDDM. *Diabetes Care.* 1992;15:1572.
51. Gumbiner B, Low CC, Reaven PD. Effects of a monounsaturated fatty acid-enriched hypocaloric diet on cardiovascular risk factors in obese patients with type 2 diabetes. *Diabetes Care.* 1998;21:9.
52. Leon-Sanz M, Garcia-Luna PP, Sanz-Paris A, et al. Glycemic and lipid control in hospitalized type 2 diabetic patients: evaluation of 2 enteral nutrition formulas (low carbohydrate-high monounsaturated fat vs high carbohydrate). *JPEN J Parenter Enteral Nutr.* 2005;29:21.
53. Low CC, Grossman EB, Gumbiner B. Potentiation of effects of weight loss by monounsaturated fatty acids in obese NIDDM patients. *Diabetes.* 1996;45:569.

54. McCargar LJ, Innis SM, Bowron E, et al. Effect of enteral nutritional products differing in carbohydrate and fat on indices of carbohydrate and lipid metabolism in patients with NIDDM. *Mol Cell Biochem.* 1998;188:81.
55. Heyland DK, Novak F, Drover JW, et al. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA.* 2001;286:944.
56. Bertolini G, Iapichino G, Radrizzani D, et al. Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. *Intensive Care Med.* 2003;29:834.
57. Alpers D. Is glutamine a unique fuel for small intestinal cells? *Curr Opin Gastroenterol.* 2000;16:155.
58. Lacey JM, Wilmore DW. Is glutamine a conditionally essential amino acid? *Nutr Rev.* 1990;24:297.
59. Peng X, Yan H, You Z et al. Clinical and protein metabolic efficacy of glutamine granules-supplemented enteral nutrition in severely burned patients. *Burns.* 2005;21:342.
60. Hall JC, Dobb G, Hall J, et al. A prospective randomized trial of enteral glutamine in critical illness. *Intensive Care Med.* 2003;29:1710.
61. Metnitz PG, Bartens C, Fischer M, et al. Antioxidant status in patients with acute respiratory distress syndrome. *Intensive Care Med.* 1999;25: 180.
62. Alonso de Vega JM, Diaz J, et al. Oxidative stress in critically ill patients with systemic inflammatory response syndrome. *Crit Care Med.* 2002;30:1782.
63. Motoyama T, Okamoto K, Kukita I, et al. Possible role of increased oxidant stress in multiple organ failure after systemic inflammatory response syndrome. *Crit Care Med.* 2003;31:1048.
64. Nathens AB, Neff MJ, Jurkovich GJ, et al. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Ann Surg.* 2002;236:814.
65. Lee IM, Cook NR, Gasiana JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer. *JAMA.* 2005;294:56.
66. Heyland DK, Dhaliwal R, Suchner U, Berger MM. Antioxidant nutrients: a systematic review of trace elements and vitamins in the critically ill patient. *Intensive Care Med.* 2005;31:327.
67. Bansal V, Syres KM, Makarenkova V, et al. Interactions between fatty acids and arginine metabolism: implications for the design of immune-enhancing diets. *JPEN J Parenter Enteral Nutr.* 2005;29(1 Suppl):S75.
68. Bansal V, Ochoa JB. Arginine availability, arginase, and the immune response. *Curr Opin Clin Nutr Metab Care.* 2003;6:223.
69. Collier SR, Casey DP, Kanaley JA. Growth hormone responses to varying doses of oral arginine. *Growth Horm IGF Res.* 2005;15:136.
70. Rodriguez PC, Quiceno DG, Ochoa AC. L-Arginine availability regulates T lymphocyte cell cycle progression. *Blood.* 2007;109:1568.
71. Wittmann F, Prix N, Mayr S, et al. L-arginine improves wound healing after trauma-hemorrhage by increasing collagen synthesis. *J Trauma.* 2005;59:162.
72. Barbul A, Lazarou SA, Efron DT, et al. Arginine enhances wound healing and lymphocyte immune responses in humans. *Surgery.* 1990;108:331; discussion 336.
73. Stechmiller JK, Childress B, Cowan L. Arginine supplementation and wound healing. *Nutr Clin Pract.* 2005;20:52.
74. Collins N. Arginine and wound healing. *Adv Skin Wound Care.* 2001;14:16.
75. Canturk NZ, Vural B, Canturk Z, et al. The role of L-arginine and neutrophils on incisional wound healing. *Eur J Emerg Med.* 2001;8:311.
76. Witte MB, Thornton FJ, Tantry U, Barbul A. L-Arginine supplementation enhances diabetic wound healing: involvement of the nitric oxide synthase and arginase pathways. *Metabolism.* 2002;51:1269.
77. Mizock BA, DeMichele SJ. The acute respiratory distress syndrome: role of nutritional modulation of inflammation through dietary lipids. *Nutr Clin Pract.* 2004;19:536.
78. Gadek JE, DeMichele SJ, Karlstad MD, et al. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Enteral Nutrition in ARDS Study Group. *Crit Care Med.* 1999;27:1409.
79. Singer P, Theilla M, Fischer H, et al. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. *Crit Care Med.* 2006;34:1033.
80. Pontes-Arruda A, Aragao AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid and antioxidants in mechanically ventilated patients with sever sepsis and septic shock. *Crit Care Med.* 2006;34:2325.
81. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr.* 2002;26(1 supplement):1SA.
82. Heyland DK, Dhaliwal R, Drover JW, et al., Canadian Critical Care Clinical Practice Guidelines Committee. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr.* 2003;27:355.
83. Date RS, Das N, Bateson PG. Unusual complications of ballooned feeding tubes. *Indian Med J.* 2002;95:181.
84. O'Keefe KP, Dula DJ, Varano V. Duodenal obstruction by a nondeflating Foley catheter gastrostomy tube. *Ann Emerg Med.* 1990;19:1454.

85. Lord LM, Weiser-Maimone A, Pulhamus M, Sax HC. Comparison of weighted vs unweighted enteral feeding tubes for efficacy of transpyloric intubation. *JPEN J Parenter Enteral Nutr.* 1993;17:271.
86. Levenson RTW, Dyson A, Zike L, Reisch J. Do weighted nasoenteric feeding tubes facilitate duodenal intubations? *JPEN J Parenter Enteral Nutr.* 1988;12:135.
87. Haslam D, Fang J. Enteral access for nutrition in the intensive care unit. *Curr Opin Clin Nutr Metab Care.* 2006;9:155.
88. Jabbar A, McClave SA. Pre-pyloric versus post-pyloric feeding. *Clin Nutr.* 2005;24:719.
89. Marik PE, Zaloga GP. Gastric versus post-pyloric feeding: a systematic review. *Crit Care.* 2003;7:R46.
90. McClave SA, Lukan JK, Stefater JA, et al. Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. *Crit Care Med.* 2005;33:324.
91. Heyland DK, Drover JW, MacDonald S, et al. Effect of postpyloric feeding on gastroesophageal regurgitation and pulmonary microaspiration: results of a randomized controlled trial. *Crit Care Med.* 2001;29:1495.
92. Metheny NA, Clouse RE, Chang YH, et al. Tracheobronchial aspiration of gastric contents in critically ill tube-fed patients: frequency, outcomes, and risk factors. *Crit Care Med.* 2006;34:1007.
93. Ott DJ, Mattox HE, Gelfand DW, et al. Enteral feeding tubes: placement by using fluoroscopy and endoscopy. *AJR Am J Roentgenol.* 1991;157:769.
94. Stone SJ, Pickett JD, Jesurum JT. Bedside placement of postpyloric feeding tubes. *AACN Clin Issues.* 2000;11:517.
95. Shirley PJ, Bion JF. Intra-hospital transport of critically ill patients: minimizing risk. *Intensive Care Med.* 2004;30:1508.
96. Caplan ES, Hoyt NJ. Nosocomial sinusitis. *JAMA.* 1982;247:639.
97. Montgomery RC, Bar-Natan MF, Thomas SE, Cheadle WG. Postoperative nasagastric decompression: a prospective randomized trial. *South Med J.* 1996;89:1063.
98. Taylor B, Schallom L. Bedside small bowel feeding tube placement in critically ill patients using a dietitian/nurse team approach. *Nutr Clin Pract.* 2001;16:258.
99. Zaloga GP. Bedside method for placing small bowel feeding tubes in critically ill patients. A prospective study. *Chest.* 1991;100:1643.
100. Slagt C, Innes R, Bihari D, et al. A novel method for insertion of post-pyloric feeding tubes at the bedside without endoscopic or fluoroscopic assistance: a prospective study. *Intensive Care Med.* 2004;30:103.
101. Thurlow PM. Bedside enteral feeding tube placement into duodenum and jejunum. *JPEN J Parenter Enteral Nutr.* 1986;10:104.
102. Taylor B, Schallom M, Muckova N. Bedside small bowel placement in over 1200 critically ill patients—a success story. *Crit Care Med.* 2003;31(supple):A85.
103. Gabriel SA, Ackermann RJ. Placement of nasoenteral feeding tubes using external magnetic guidance. *JPEN J Parenter Enteral Nutr.* 2004;28:119.
104. Shellito PC, Malt RA. Tube gastrostomy. Techiniques and complications. *Ann Surg.* 1985;201:180.
105. Ephgrave KS, Buchmiller C, Jones MP, Cullen JJ. The cup is half full. *Am J Surg.* 1999;178:406.
106. DeLegge MH. Enteral access in home care. *JPEN J Parenter Enteral Nutr.* 2006;30(suppl 1):S13.
107. Gauderer MW, Ponsky JL, Izant RJ. Gastrostomy without laparotomy: a percutaneous endoscopic technique. *J Pediatr Surg.* 1980;15:872.
108. Gauderer MW. Pecutaneous endoscopic gastrostomy—20 years later: a historical perspective. *J Pediatr Surg.* 2001;36:217.
109. Hogan RB, DeMarco DC, Hamilton JK, et al. Percutaneous endoscopic gastrostomy—to push or pull: A prospecitve randomized trial. *Gastrointest Endosc.* 1986;32:253.
110. Dennis M, Lewis S, Cranswick G, Forbes J, FOOD Trial Collaboration. FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke. *Health Technol Assess.* 2006;10:1.
111. Byrne KR, Fang JC. Endoscopic placement of enteral feeding catheters. *Curr Opin Gastroenterol.* 2006;22:546.
112. Rustom IK, Jebreel A, Tayyab M, et al. Percutaneous endoscopic, radiological and surgical gastrostomy tubes: a comparison study in head and neck cancer patients. *J Laryngol Otol.* 2006;120:463.
113. Ljungdahl M, Sundbom M. Complication rate lower after percutaneous endoscopic gastrostomy than after surgical gastrostomy: a prospective randomized trial. *Surg Endosc.* 2006;20:1248.
114. DeLegge RL, DeLegge MH. Percutaneous endoscopic gastrostomy evaluation of device materials: Are we "failsafe"? *Nutr Clin Pract.* 2005;20:613.
115. McGonigal MD, Lucas CE, Ledgerwood AM. Feeding jejunostomy in patients who are critically ill. *Surg Gynecol Obstet.* 1989;168:275.
116. Duh QY, Senokozlieff-Englehart AL, Siperstein AE et al. Prospective evaluation of the safety and efficacy of laparoscopic jejunostomy. *West J Med.* 1995;162:117.
117. Baron TH. Direct percutaneous endoscopic jejunostomy. *Am J Gastroenterol.* 2006;101:1407.
118. Chin KF, Townsend S, Wong W, Miller GV. A prospective cohort study of feeding needle catheter jejunostomy in an upper gastrointestinal surgical unit. *Clin Nutr.* 2004;23:691.
119. Taylor B, Mazuski J. Enteral access devices and placement techniques. *Support Line.* 2005;27:3.
120. Kohn CL. The relationship between enteral formula contamination and length of enteral delivery set usage. *JPEN J Parenter Enteral Nutr.* 1991;15:567.

121. Curtas S. Bacteriological safety of closed enteral nutrition delivery system. *Nutrition*. 1991;7:340.
122. Chan L. Evaluation of the bacteriological contamination of a closed feeding system for enteral nutrition. *Med J Malaysia*. 1994;49:62.
123. Howard P, Jonkers-Schuitema C, Furniss L, et al. Managing the patient journey through enteral nutritional care. *Clin Nutr.* 2006;25:187.
124. Bliss DZ, Guenter PA, Settle RG. Defining and reporting diarrhea in tube-fed patients—what a mess. *Am J Clin Nutr.* 1992;55:753.
125. Kotake T, Takada M, Goto T, et al. Serum amiodarone and desethylamiodarone concentrations following nasogastric versus oral administration. *J Clin Pharm Ther.* 2006;31:237.
126. Beringer P, Nguyen M, Hoem N, et al. Absolute bioavailability and pharmacokinetics of linezolid in hospitalized patients given enteral feedings. *Antimicrob Agents Chemother.* 2005;49:3676.
127. Fay MA, Sheth RD, Gidal BE. Oral absorption kinetics of levetiracetam: the effect of mixing with food or enteral nutrition formulas. *Clin Ther.* 2005;27:594.
128. Marvel ME, Bertino JS. Comparative effects of an elemental and a complex enteral feeding formulation on the absorption of phenytoin suspension. *JPEN J Parenter Enteral Nutr.* 1991;15:316.
129. Mimoz O, Binter V, Jacolot A, et al. Pharmacokinetics and absolute bioavailability of ciprofloxacin administered through a nasogastric tube with continuous enteral feeding to critically ill patients. *Intensive Care Med*. 1998;24:1047.
130. Magnuson B, Clifford T, Hoskins L, Bernard A. Enteral nutrition and drug administration, interactions, and complications. *Nutr Clin Pract*. 2005;20:618.
131. van den Bernt P, Cusell M, Overbeeke P, et al. Quality improvement of oral medication administration in patients with enteral feeding tubes. *Qual Saf Health Care*. 2006;15:44.
132. Ammann RW, Akovbiantz A, Hacki W. Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. *Gastroenterology.* 1984;86:281.
133. Samer M, Cotton PB. Classification of pancreatitis. *Gut.* 1984;25:756.
134. Steer ML, Waxman I, Freedman S. Chronic pancreatitis. *N Engl J Med.* 1995;332:1482.
135. Singer MV, Gyr KE, Sarles H. Revised classification of pancreatitis: report of the Second International Symposium on the Classification of Pancreatitis in Marseille, France, March 28–30, 1984. *Gastroenterology.* 1985;89:683.
136. Meier R, Ockenga J, Pertkiewicz M, et al. ESPEN Guidelines on enteral nutrition: pancreas. *Clin Nutr.* 2006;25:275.
137. Bradley EL. Members of the Atlanta International Symposium. A clinically based classification system for acute pancreatitis: summary of the International Symposium on Acute Pancreatitis. Atlanta, GA, September 11–13, 1992. *Arch Surg*. 1993;128:586.
138. Winslet MC, Hall C, London NJM, Neoptolemos JP. Relationship of diagnostic serum amylase to aetiology and prognosis in acute pancreatitis. *Gut*. 1992;33:982.
139. Flint R, Windsor J, Bonham M. Trends in the management of severe acute pancreatitis: interventions and outcome. *ANZ J Surg*. 2004;74:335.
140. Karsenti D, Bourlier P, Dorval E. Morbidity and mortality of acute pancreatitis. Prospective study in a French university hospital. *Presse Med*. 2002;31:727.
141. Dickerson RN, Vehe KL, Mullen JL, Feurer ID. Resting energy expenditure in patients with pancreatitis. *Crit Care Med*. 1991;19:484.
142. Hill GL. Body composition research: Implication for the practice of clinical nutrition. *JPEN J Parenter Enteral Nutr.* 1992;16:197.
143. Windsor ACJ, Kanwar S, Li AGK, et al. Compared with parenteral nutrition, enteral feeing attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut*. 1998;42:431.
144. Kalfarentzos F, Kehagias J, Mead N, et al. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *Br J Surg*. 1997;84:1665.
145. Abou-Assi S, Craig K, O'Keefe SJD. Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: results of a randomized comparative study. *Am J Gastroenterol.* 2002;97:2255.
146. O'Keefe SJ, Lee RB, Anderson FP. Physiological effects of enteral and parenteral feeding on pancreaticobiliary secretion in humans. *Am J Physiol Gastrointest Liver Physiol*. 2003;284:G27.
147. Gupta R, Patel K, Calder PC. A randomised clinical trial to assess the effect of total enteral and total parenteral nutritional support on metabolic, inflammatory and oxidative markers in patients with predicted severe acute pancreatitis. *Pancreatology.* 2003;3:406.
148. Austrums E, Pupels G, Snippe K. Postoperative enteral stimulation by gut feeding improves outcomes in severe acute pancreatitis. *Nutrition.* 2003;19:487.
149. Eatock FC, Brombacher GD, Steven A, et al. Nasogasatric feeding in severe acute pancreatitis may be practical and safe. *Int J Pancreatol*. 2000;28:23.
150. Matarese LE, Steiger E. Dietary and medical management of short bowel syndrome in adult patients. *J Clin Gastroenterol.* 2006;40(suppl):S85.
151. Thompson JS, Iyer KR, DiBaise JK, et al. Short bowel syndrome and Crohn's disease. *J Gastrointest Surg*. 2003;7:1069.
152. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. *Gastroenterology.* 2003;124:1111.

153. Jeejeebhoy KN. Short bowel syndrome: a nutritional and medical approach. *CMAJ*. 2002;166:1297.
154. American Gastroenterological Association. Position statement: short bowel syndrome and intestinal transplantation. *Gastroenterology*. 2003;124:1105.
155. McNeil NI. The contribution of the large intestine to energy supplies in man. *Am J Clin Nutr*. 1984;39:338.
156. Scott EM, Gaywood I, Scott BB. Guidelines for osteoporosis in coeliac disease and inflammatory bowel disease. British Society of Gastroenterology. *Gut*. 2000;46 (suppl):i1.
157. Fleming CR, George L, Stoner GL, et al. The importance of urinary magnesium values in patients with gut failure. *Mayo Clin Proc*. 1996;71:21.
158. Nordgaard I, Hansen BS, Mortensen PB. Colon as a digestive organ in patients with short bowel. *Lancet*. 1994;343:373.
159. US Food and Drug Administration Center for Drug Evaluation and Research. Available at: http//www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails Accessed January 5, 2007. Sept 2005.
160. Cosnes J, Evard D, Beaugerie L, et al. Improvement in protein absorption with a small-peptide based diet in patients with high jejunostomy. *Nutrition*. 1992;8:406.
161. Levy E, Frileux P, Sandrucci S, et al. Continuous enteral nutrition during the early adaptive stage of the short bowel syndrome. *Br J Surg*. 1988;75:549.
162. McIntyre PB, Fitchew M, Lennard-Jones JE. Patients with a high jejunostomy do not need a special diet. *Gastroenterology*. 1986;91:25.
163. Fordtran JS. Stimulation of active and passive sodium absorption by sugars in the human jejunum. *J Clin Invest*. 1975;55:728.
164. DiBaise JK, Young RJ, Vanderhoof JA. Intestinal rehabilitation and the short bowel syndrome: part 2. *Am J Gastroenterol*. 2004;99:1823.
165. McDoniel K, Taylor B, Huey W, et al. Use of Clonidine to decrease intestinal fluid losses in patients with high-output short-bowel syndrome. *JPEN J Parenter Enteral Nutr*. 2004;28:265.
166. Bass BL, Fischer BA, Richardson C, et al. Somatostatin analogue treatment inhibits post-resectional adaptation of the small bowel in rats. *Am J Surg*. 1991;172:107.
167. Seydel AS, MIller JH, Sarac TP, et al. Octreotide diminishes luminal nutrient transport activity, which is reversed by epidermal growth factor. *Am J Surg*. 1996;172:267.
168. Klein S, Taylor B, Rubin D. Nutrition support in the patient with gastrointestinal disease. In: Wolfe MM, ed. *Therapy of Digestive Disorders*. 2nd ed. Philadelphia: Saunders Elsevier; 2006:41–66.

PARENTERAL NUTRITIONAL THERAPY 11

GENERAL PRINCIPLES

Parenteral nutrition (PN) can be used to supply all the essential nutrients without the use of the intestinal tract. In most cases, parenteral nutrition is reserved for patients who are unable to meet their nutritional requirements through enteral routes as infusing nutrients directly into the bloodstream is the least preferred method of providing nutritional therapy (1). However, for patients with no other option for nutrition support, parenteral nutritional is a lifesaving therapy.

Background

The successful establishment of a positive nitrogen balance and growth by means of PN was demonstrated successfully more than 30 years ago (2). Since then patients have been maintained on PN at home and have survived for many years. According to the American Society of Enteral and Parenteral Nutrition (ASPEN), in the hospital setting PN should be reserved for those patients without a functioning gastrointestinal (GI) tract who cannot, should not, or will not eat adequately for a "prolonged" period of time and in whom the benefits outweigh the risks (3). In general, "prolonged" is defined as 14 days for well-nourished

patients and 7 to 10 days in those with pre-existing medical illnesses or high levels of metabolic stress. In those patients undergoing surgery, only in severely malnourished patients has preoperative PN been shown to be beneficial (4,5). A review of four meta-analyses involving more than 5,000 patients showed that total parenteral nutrition (TPN) given 7 to 10 days before surgery in "severely malnourished patients" (defined as >20% body weight loss or serum albumin <2.5 gm/dL) had fewer noninfectious complications than their better nourished counterparts (5% vs. 43%, respectively) (5).

Indications for Parenteral Nutrition

Indications for PN can be divided into three subcategories: those patients in whom PN is *indicated*, *possibly indicated,* and *contraindicated* (Table 11-1) (3,6).

Complete Bowel Rest

Complete bowel rest combined with PN has often been used to treat patients with certain GI disorders. The premise is that excluding all oral intake minimizes trauma to and contractile activity in the diseased bowel. The gastrointestinal tract maintains a cyclic motility pattern even during fasting. Periodic surges of pancreatic and gastric secretion also occur in relation to the migrating motor complex, which in humans cycles at approximately 2-hour intervals. PN does not alter this periodic activity in laboratory animals. Despite continued motor and secretory activity between periods of digestion, most experience supports the idea that limiting oral intake reduces symptoms of abdominal pain and diarrhea in patients with gastrointestinal disorders, at least for the duration of the therapy. However, satisfactory data to support the careful use of bowel rest and PN as primary therapy does not presently exist either for acute pancreatitis (3) or for inflammatory bowel disease (7).

TABLE 11-1. Indications, Possible Indications, and Contraindications for PN

PN indicated in:

- Documented severe malabsorption of nutrients from the GI tract as in:

  Massive small bowel resection (at least initially)
  Intractable diarrhea
  Radiation enteritis
  Scleroderma of the bowel

- Complete bowel obstruction
- Inability to obtain enteral access for feeding for at least 7 to 10 days
- Persistent GI bleeding
- High output fistula (>500 mL) and inability to gain enteral access distal to fistula
- Diffuse peritonitis
- GI ischemia
- Catabolic state with or without malnutrition when GI tract not usable for 7 to 10 days
- Preoperatively in severely malnourished patients without functioning GI tract
- Severe acute pancreatitis with documented abdominal pain with jejunal enteral feeds

PN possibly indicated in:

- Enterocutaneous fistula if poor tolerance of distally infused enteral nutrition
- Inflammatory bowel disease not responding to medical therapy
- Chylous ascites or chylothorax if increased output continues with low fat enteral nutrition
- Intractable vomiting (such as in hyperemesis gravidarum) and jejunal feeding is not an option
- Prolonged small bowel ileus expected for at least 7 to 10 days
- Severe acute pancreatitis in ventilated patient with signs of malabsorption of jejunal feeding

PN contraindicated in:

- Functional GI tract
- Inability to access GI tract anticipated to be <7 days
- Venous access not available
- When the associated risks of PN determined to outweigh the potential benefit

Nutritional deficiencies are frequently seen in the two most common forms of inflammatory bowel disease, Crohn disease and ulcerative colitis. Often decreased oral intake, malabsorption, accelerated nutrient losses, increased requirements, and drug–nutrient interactions are the culprits of these deficiencies. In many cases enteral nutrition is effective in inducing clinical remission in adults. Use of enteral nutrition in these patients is reviewed in Chapter 10.

Crohn's disease of the small bowel remits with complete bowel rest, so that most patients experience symptomatic improvement, but the effect is not specific. Four early studies compared short-term remission rates in patients treated with either PN combined with bowel rest or enteral nutrition. All of these studies found similar remission rates in the two groups (Table 11-2).

Ulcerative colitis involving the entire colon, often referred to as pancolitis, usually prohibits enteral feeding making PN the nutritional therapy of choice. However, in less severe cases, enteral feeding is often an option.

Enterocutaneous fistulas are often a consequence of active inflammatory bowel disease. In cases of high fistula output, PN combined with bowel rest is generally used to correct and prevent nutritional disturbances. A review of the literature regarding nutrition and management of enterocutaneous fistulas found malnutrition to be a common problem; the administration of nutrition support, primarily PN, appeared to reduce the mortality rate and allow for spontaneous fistula closure in some of the patients (8,9).

The adaptation period after intestinal resection in **short-bowel syndrome** may need to be managed with PN if attempts of enteral nutrition are plagued with continued nutrient and electrolyte deficiencies secondary to malabsorption. Enteral nutrition management of short-bowel syndrome is reviewed in Chapter 10. Patients who have undergone resection of more than 75% of the small bowel usually require long-term PN, whereas those with <75% resection may not require permanent PN support (10)

Severe acute pancreatitis may be an indication for PN in patients experiencing pain with enteral feeding or those with complications such as necrosis, abscess, pseudocyst, fistula, and ascites. However, even in the presence of these complications, enteral feeding should be considered. While most investigators recommend feeding beyond the ligament of Treitz, this has not been proven to be significantly superior to gastric feeding in this patient population. Pancreatitis is sometimes accompanied by hypertriglyceridemia. Lipid emulsions should not be given to any patient with a serum triglyceride level above 400 mg/dL (3).

Types of Parenteral Nutrition

Types of PN are not defined by the initial point of entry into the vascular system, but by the position of the distal catheter tip. Access information will be covered in more depth in the next section (Venous Access).

Central parenteral nutrition (CPN) is delivered via a central venous access with the catheter tip located in the superior vena cava. In cases where intravascular access is limited the inferior vena cava may be used. CPN is the most commonly utilized form of PN. This route is

TABLE 11-2. Incidence of Short-term Remission in Patients Receiving Parenteral Nutrition Plus Bowel Rest Versus Enteral Nutrition in Crohn Disease

Study	PN + bowel rest	EN
Lochs et al. (80)	7/10 (70%)	8/10 (80%)
Jones (81)	14/19 (88%)	11/17 (85%)
Greenberg et al. (82)	12/17 (71%)	11/19 (58%)
Wright and Adler (83)	4/5 (80%)	3/6 (50%)
Total	38/51 (75%)	32/52 (62%)

PN, parenteral nutrition; EN, enteral nutrition.

chosen when a central catheter is already in position for other reasons, or the expected length of therapy is long term (>7 days).

Peripheral parenteral nutrition (PPN) is delivered via a peripheral venous access with the catheter tip located outside of the inferior or superior vena cava. This route is chosen when the expected length of therapy is short term (≤7 days).

VENOUS ACCESS

The various types of venous access for PN and the general disadvantages and advantages are presented in Table 11-3.

Central Venous Catheter

The central venous catheter (CVC) is most commonly used in patients receiving PN, as this allows for the infusion of solutions with an osmolarity >900 mOsm/L. Central PN solutions range from approximately 1400 to 2600 mOsm/L. A central venous access may be tunneled (i.e., Hickman®, Broviac®, Groshong®), nontunneled (Hohn®, general multilumen catheters), peripherally inserted (PICC), or an implanted intravenous (IV) port device. The three most common sites for CVC insertions are the subclavian vein, internal jugular, and femoral veins. If a CVC has multiple lumens, the most distal lumen should be designated for PN to decrease risk of contaminated blood draws and mixing of PN with other medications (11). A chest X-ray should always be obtained post-placement to confirm position prior to catheter use. Complications of CVC can be divided into early and late complications.

Potential early complications of CVC placement include the following:

1. Pneumothorax
2. Brachial plexus injury
3. Subclavian and carotid artery puncture
4. Hemothorax
5. Thoracic duct injury
6. Chylothorax

Mechanical complications are less likely to occur if the CVC is inserted by a more experienced physician, not placed in the femoral vein, and placed with the use of ultrasound guidance during internal jugular placements (12,13).

To avoid the possibility of an **air embolus**, never disconnect the tubing from an unclamped catheter with the patient in an upright position. Air embolism can also occur during insertion or afterwards if the connection between the catheter and intravenous tubing is not well secured.

Late complications associated with CVC include the following:

1. Catheter dislodgement
2. **Catheter occlusions** are commonly related to the formation of a thrombus within the lumen, the formation of a fibrin sheath around the catheter end, the malpositioning of a catheter tip against the vessel wall or within a small branch vessel, or the presence of thrombosis or stenosis in the native vein.
3. **Catheter thrombosis** may be treated with thrombolytic agents, such as tissue-type plasminogen activator (tPA), e.g., alteplase (Activase; Genentech, Inc., South San Francisco, CA) or reteplase (Retavase; Centocor Inc., Malvern, PA). This technique should be completed by a physician or nurse with special training (13). The entire lumen of the catheter is filled with approximately 2 mg of tPA diluted in the appropriate volume to fill the catheter. This is left in place for 15 to 30 minutes. Care must be taken to infuse just enough solution so that it fills only the lumen of the catheter and to prevent systemic administration of the thrombolytic agent. After the appropriate time, the thrombolytic agent is aspirated.
4. **Catheter-related infections (Table 11-4).** Blood stream infections are most commonly caused by *Staphylococcus epidermidis* and *S. aureus*. In long-term PN patients, *Enterococcus*,

TABLE 11-3. Venous Access Devices: Advantages and Disadvantages (6,13)

Line type	Advantages	Disadvantages	Dwell time
Peripheral lines			
Short peripheral catheter	■ Easily inserted by nurse or other trained personnel ■ Least expensive ■ Minimal care and maintenance ■ Low risk of catheter-related sepsis ■ Easy to remove	■ Only lasts for 48 to 72 hours; need to change frequently ■ Risk of phlebitis high ■ Patient my not have adequate peripheral veins ■ Limited to osmolality 600 to 900 mOsm/L, so can only use peripheral PN ■ Cannot instill acidic solutions (<pH 5) or medications which cause severe phlebitis	48 to 72 hours
Midline peripheral catheter	■ Same as short ■ May last 3 to 5 days longer (not proven if used for PPN) ■ Allows access to larger vessel (still not a central line)	■ Same as short ■ Higher cost than short ■ Higher level of training required for placement	48 to 72 hours
Central lines	Able to give solutions >900 mOsm/L		
Peripheral inserted central catheter (PICC)	■ No risk of pneumothorax or puncture of internal carotid or subclavian arteries ■ Bedside insertion ■ Inserted by specially trained nurses ■ Available in single, double, and triple lumens ■ External portion can be repaired if damaged ■ Lower risk of catheter-related sepsis than CVC ■ Less costly than CVC ■ Can be used for short or long term PN	■ Smaller diameter and greater length than CVC increasing risk of occlusion ■ Insertion site on arm may increase risk of dislodgement and hinder self care of catheter ■ Placement unsuccessful in 25% of attempts ■ More likely to coil than CVC ■ More difficult to draw blood than CVC	Up to 1 year
Nontunneled CVC	■ Low cost ■ Can be removed by trained RN ■ May be placed at bedside or radiology by MD ■ Multiple lumens	■ Increased infection rate compared to single lumen and tunneled catheters ■ Only for use in acute care	2 weeks
Tunneled CVC (Hickman®, Broviac®)	■ Long term catheter ■ May have multiple lumens	■ Requires surgical procedure for placement and removal ■ Higher cost ■ Removal by MD	Several years
Port	■ Lowest infection risk of all options ■ Site care needed only when accessed ■ Useful for intermittent access ■ Access underneath the skin	■ Requires surgical procedure for placement and removal ■ Requires “stick” to access with Huber needle	Several years

TABLE 11-4. Common Types of Catheter-related Infections

Type	Description
Catheter colonization	Present if the catheter is removed or exchanged over a guidewire and >15 CFU of microorganisms grows from a culture from a catheter segment and the patient has no signs of systemic sepsis
Catheter-related blood stream infection	The most severe catheter infection, diagnosed when the line tip culture and a peripheral blood culture grow the same microorganism and the patient has systemic sepsis with no other identifiable source: fever, leukocytosis, or tachycardia
Exit-site infection	Erythema, tenderness, induration, or purulence within 2 cm of the CVC skin exit site

Candida species, *Escherichia coli*, *Pseudomonas*, *Klebsiella*, *Enterobacter*, *Acinetobacter*, *Proteus*, and *Xanthomonas* should also be considered. Table 11-5 reviews one suggested management approach for suspected catheter-related infection (14).

Techniques to decrease infectious risk associated with CVC (12,15) are as follows:

1. **Femoral access should be avoided if at all possible.** The lowest infectious risk exists with subclavian catheterization, the highest with femoral sites (16,17).
2. **Use of maximal sterile-barrier precautions during catheter insertion:** mask, cap, sterile gown, sterile gloves, and large sterile drape have been shown to reduce the rate of infection (18).

TABLE 11-5. Management of Suspected Catheter-related Infection

1. Initial evaluation:
   - **a.** Evaluate catheter insertion site and culture any drainage
   - **b.** Obtain blood cultures from both peripheral and central veins
   - **c.** Look for other causes of infection (e.g., urinalysis, chest X-ray, sputum, wounds)

2. Stop TPN for 48 to 72 hours

3. Indications for central venous catheter removal:
   - **a.** Immediate removal
     - **(1)** Purulent discharge or abscess at insertion site
     - **(2)** Septic shock without another etiology for the source of infection
   - **b.** Positive culture from both sites or persistent signs of infection without other cause for infection identified

4. Antibiotic therapy
   - **a.** Empiric antibiotic therapy administered through central venous catheter until culture results are back:
     - **(1)** Vancomycin 1 g q 12 hr (adjust dose for creatinine/GFR)
     - **(2)** Cefepine 1 g q 12 hr (if gram negative infection suspected)
   - **b.** Specific antibiotic therapy administered through central venous catheter once culture results are available
   - **c.** If a catheter is "irreplaceable," consider trial of antibiotic therapy with line in place
   - **d.** Duration of antibiotic therapy usually ranges from 2 to 6 weeks depending on patient, organism, and whether central line has been left in place

5. Repeat blood cultures in 48 and 72 hours to ensure clearance of bacteremia

6. Fever should resolve within 72 to 96 hours if given appropriate antibiotics; remove catheter if fever persists

3. **Avoid the use of antibiotic ointments** which may increase the rate of fungi colonization and promote the development of antibiotic resistant bacteria (19).
4. **Do not change catheter routinely** (i.e., every 7 days) as this does not reduce the risk of infection. In fact, routine exchange over a guidewire is associated with a trend toward a higher infection rate (20)
5. **Antimicrobial CVCs** were tested in a prospective randomized controlled trial in 539 patients; no significant differences in colonization or bacteremia rates between the test and control catheters were found (17). Another group compared the infection rate of silver-platinum-carbon–**impregnated catheters** with rifampicin-minocycline–coated catheters in a prospective randomized study of 574 patients. Infection rates were low with both catheters with no significant difference between the two (21). A "control" arm was not available. At present the data do not support a change to "treated" catheters for all patients. Large-scale studies in "high risk" patients need to be completed to determine if a difference can be made in this population.

Peripheral Venous Catheters

Peripheral venous catheters are the quickest, simplest, least expensive, and most common method of venous access (13). However, peripheral veins are prone to phlebitis and subcutaneous infiltration, and the catheter should not remain in one site for longer than 48 to 72 hours (22). Peripheral catheters should only be used to infuse PPN in the patient with adequate peripheral veins. They are contraindicated in patients with poor peripheral veins, requiring PN for longer than 7 days, or with intolerance to fluid load. Given the need to restrict the osmolality of solutions infused to <900 mOsm/L, PPN requires a relatively large fluid volume to administer significant amounts of protein and calories.

Catheter Maintenance

Tubing and Filters

Tubing should be changed every 24 hours. Use of unnecessary tubing and extension sets is discouraged. A stopcock should not be part of the tubing assembly because it is easily contaminated. In addition the tubing–catheter junction should be wiped with alcohol before being disconnected to avoid inadvertent contamination of the catheter hub.

In-line filters are recommended by the FDA for use when PN is being infused. This recommendation was prompted by two deaths caused by calcium phosphate precipitates in three-in-one PN admixtures, referred to as total nutrient admixtures (TNA) (see discussion of total nutrient admixtures under Designing the Solution for Parenteral Nutrition). A 0.22-μm filter is used for base solutions (dextrose and amino acids only); however, this is too small to allow for lipid emulsions to be administered. Filters with larger pores (≥1.2 μm) are used with TNA. Insertion of the filter creates an additional opportunity for contamination in the tubing assembly. Despite their filtering capabilities, in-line filters do not appear to significantly reduce catheter infection rates. However, filters do reduce the infusion of particulate matter in the solution.

Occlusive Dressing

An occlusive dressing is an important part of central venous catheter maintenance. The dressing must be occlusive on all sides to prevent catheter contamination. Gauze dressings are often initially used at time of CVC placement and should be changed within 24 hours to a transparent dressing of a porous synthetic material (Op-Site®). This dressing allows for visualization of the catheter entry site and can be left in place for 7 days as long as it remains dry and occlusive.

Aseptic Maintenance

Aseptic maintenance of the catheter and tubing system cannot be emphasized enough for the safe administration of long-term PN through a CVC. The following precautions should be followed in addition to the techniques mentioned above.

1. Avoid a bulky dressing. A single folded 4 × 4-in. pad should be adequate.
2. Make sure the dressing is occlusive on *all* sides.

3. Tape all connections to avoid accidental disconnection or contamination.
4. Clean all connections, including the catheter–tubing connection, with alcohol or povidone-iodine before any tubing changes are made.
5. Change the catheter dressing if it is wet. If the replaced dressing also becomes damp, then the catheter–tubing junction and exposed catheter should be examined carefully. Under no circumstances should this examination be performed in a casual way without adhering to the usual aseptic technique. If the catheter dressing must be removed, sterile precautions should be taken to avoid accidental contamination of the catheter insertion site.
6. Once infusion from a solution bag is started, the bag should not hang for more than 24 hours so that bacterial growth is minimized.

NUTRIENT REQUIREMENTS DURING PARENTERAL NUTRITION

The calculation of calorie and protein requirements is covered in Chapter 5. Dietary vitamin and mineral requirements are discussed in Chapters 6 and 7. The usual goals for protein, carbohydrate, fat, and fluid intake for adult patients on PN are similar for like patient types not on PN and are presented in Table 11-6 (6,23–25).

Nonprotein Calories versus Total Calories

Total calories are used to determine intake for patients receiving all forms of enteral feeding. However, when administering PN, some clinicians do not count amino acids as a calorie source. This is based on the expectation that some of the amino acids will be incorporated into new protein rather than metabolized. However, this implies that one can direct protein utilization. It may make more physiological sense to include amino acids as a calorie source in the expectation that more will be metabolized than incorporated into new protein (26,27). This assumption helps prevent overfeeding and hyperglycemia.

Fluid Requirements

Fluid requirements will vary depending on the capacity of the patient to excrete an osmotic load and the estimate of fluid losses. Increased losses may occur in patients with fever, open abdomen, high drain or ostomy outputs, frequent emesis, and diarrhea. Electrolyte concentrations in various gastrointestinal fluids are presented in Table 11-7. Understanding of a patient's electrolyte losses will aid in their repletion. In general, the euvolemic patient will require 30 to 40 mL per kg per day. The PN should not be used as the primary source for

TABLE 11-6. Energy and Substrate Guidelines for Adult Patients on Parenteral Nutrition

	Critical care	Acute care
Energy		
Obese (BMI ≥ 30)	15–20 kcal/kg/day	15–20 kcal/kg/day
Nonobese (BMI 15–29)	20–35 kcal/kg/day	25–35 kcal/kg/day
Undernourished (BMI < 15)[a]	35–40 kcal/kg/day	30–40 kcal/kg/day
Protein	1.2–2.0 g/kg/day	0.8–1.0 g/kg/day[b]
Carbohydrate (dextrose)	<4 g/kg/day	<7 g/kg/day
Lipid	<1 g/kg/day	<1–2 g/kg/day
Fluid	Minimum needed to deliver prescribed formula	30–35 mL/kg/day + losses

[a]If refeeding risk starts at 15 kcal/kg.
[b]If patient catabolic increases to 1.2 to 2.0 g/kg/day.

TABLE 11-7. Electrolyte Concentrations of Gastrointestinal Fluids

	Na	K	Cl	HCO_3
	(mEq/L)			
Stomach	65	10	100	—
Bile	150	4	100	35
Pancreas	150	7	80	75
Duodenum	90	15	90	15
Mid-small bowel	140	6	100	20
Terminal ileum	140	8	60	70
Rectum	40	90	15	30

fluid and electrolyte repletion, especially in critically ill patients whose status may change from the time PN is ordered to completion (approximately 36 hours). However, in circumstances where fluid restriction is desired, it may be beneficial to make changes to the PN solution. For example, increase the base component of the PN (i.e., acetate) as opposed to starting a separate sodium bicarbonate infusion in a patient with renal failure and a metabolic acidosis.

Vitamin Requirements

Vitamin requirements during parenteral therapy are uncertain because they are not based on balance studies. Refer to Chapter 6 for a discussion of specific vitamin requirements and monitoring for vitamin deficiencies. The requirements for an adult parenteral multivitamin drug product were last amended by the Food and Drug Administration (FDA) in 2003 (28). They recommended an increase in vitamins B_1, B_6, C, and folic acid to better meet estimated needs and to include 150 μg of vitamin K. The present formulation of the MVI-Adult® (Mayne Pharma, Paramus, NJ) parenteral vitamin is presented in Table 11-8. There is some debate regarding the correct dosing of vitamin D, given the development of metabolic bone disease during long-term PN which appears to

TABLE 11-8. MVI Adult® Daily Parenteral Vitamin Formulation

Vitamin	Amount
Thiamin (B_1)	6 mg
Riboflavin (B_2)	3.6 mg
Pyridoxine (B_6)	6 mg
Cyanocobalamin (B_{12})	5 μg
Niacin	40 mg
Folic acid	600 μg
Pantothenic acid	15 mg
Biotin	60 μg
Ascorbic acid (C)	200 mg
Vitamin A (retinol)	3300 IU
Vitamin D	5 mg
Vitamin E	10 IU
Vitamin K	150 μg

Adapted from Parenteral multivitamin products; drugs for human use; drug efficacy study implementation; amended (21 CFR5.70). *Fed Reg.* 2000;65:21200-21201.

respond to the removal of vitamin D from the solution. However, no change in standard of practice is recommended at this time. Patients with increased oxidative stress benefit from the antioxidant properties of vitamin A, C, and E. The intake of antioxidant vitamins below 66% of RDA leads to worsening in oxidative stress parameters, compared to intake of at least 66% of the RDA (29). Patients at risk of refeeding syndrome (see Clinical Applications of Nutritional Status Assessment in Chapter 5) may also be at risk of thiamine deficiency and may benefit from the addition of 100 mg thiamin to the PN solution for 3 to 4 days (30). Risk factors for folate deficiency in the hospital patient include extensive tissue damage due to sepsis, trauma or surgery, acute renal failure requiring renal replacement therapy, or recent alcohol abuse (31). In a study of the erythropoietin response in critical illness, 13% of patients were found to have iron, B_{12}, folate, or a combination deficiency on admission to the ICU (32). Although information was not provided on the admitting nutritional status of the deficient patients, it may be beneficial to provide an additional 1 mg folate for 3 to 4 days to critically ill patients.

Mineral Requirements

Mineral requirements may vary considerably from patient to patient and for an individual patient during a course of PN therapy. Ranges of major minerals and reasons for adjustments in CPN are listed in Table 11-9. For optimal nitrogen repletion, adequate supplementation of these minerals is required.

Potassium requirements may fluctuate based on the presence of a catabolic state. As a patient's metabolic stress decreases, potassium requirements decrease as well. In addition, potassium requirements may also be affected by certain medications (i.e., diuretics) or changes in renal function of hospitalized patients. If the patient is at risk of refeeding, potassium should be adequately supplemented prior to starting PN.

Phosphate should also be repleted prior to initiating PN. The phosphate required varies with the number of calories provided. In general, the PN solution should be supplemented with 7 to 9 mmol per 1,000 kcal. However, this amount may need to be reduced in patients with renal failure.

Other trace minerals may not need to be supplemented daily in short-term PN. However, syndromes have been caused by the omission of zinc, chromium, and copper from long-term PN. Recommendations for parenteral supplementation of these minerals were established by the ASPEN Nutrition Advisory Group and are listed in Table 11-10 (33). The amounts of trace minerals in commercially available products are listed in Table 11-11.

The acid–base balance of the patient is influenced by the chloride and acetate content of the PN formula. Acetate can be converted to bicarbonate, which raises the pH. In cases of metabolic acidosis, the acetate content of the formula should be increased and the chloride content decreased. Increasing the acetate content of the PN solution is also useful in cases of large bicarbonate loss, as in pancreatic fistula. In contrast, the chloride content should be increased in metabolic alkalosis. The chloride content should also be increased when nasogastric tube drainage results in a significant loss of stomach acid.

Essential Fatty Acids

Essential fatty acids (EFA) must be supplied for all patients receiving PN. This is done with the addition of linoleic and linolenic acid, 18-carbon EFA. Although a large amount of adipose storage fat is linoleic acid (8% to 10%), fatty stores are largely inaccessible during the infusion of concentrated carbohydrate solutions. High plasma levels of insulin, resulting from the infusion of concentrated glucose, prevent the breakdown of stored triglycerides and release of the EFAs into the circulation. Linoleic acid deficiency has been reported in patients on glucose-based PN without lipids for as little as 2 weeks. Currently available intravenous fat emulsions (IVFE) contain approximately one-half to two-thirds of their fatty acids as linoleic acid and approximately 5% to 10% as linolenic acid.

Manifestations of EFA deficiency, which often appears 3 to 4 weeks after the initiation of lipid free PN, include the following:

1. Dry, cracked, scaling skin with impetigo and oozing in intertriginous folds
2. Coarsened hair

TABLE 11-9. Electrolytes Administered via the PN Solution

Suggested electrolytes (per liter)	Conditions that may require alteration of amount provided	Electrolyte carriers
Sodium 60–150 mEq	■ Renal function ■ Fluid status ■ GI losses ■ Traumatic brain injury	Sodium chloride Sodium acetate Sodium phosphate
Potassium 40–120 mEq	■ Renal function ■ GI losses ■ Metabolic acidosis ■ Refeeding	Potassium chloride Potassium acetate Potassium phosphate
Phosphate 10–30 mM	■ Renal function ■ Refeeding ■ Bone disease ■ Hypercalcemia ■ Rapid healing[a] ■ Hepatic function	Sodium phosphate Potassium phosphate
Chloride 60–120 mEq	■ Renal function ■ GI losses (gastric) ■ Acid–base status	Sodium chloride Potassium chloride
Acetate 10–40 mEq	■ Renal function ■ GI losses (small bowel) ■ Acid–base status ■ Hepatic function	Sodium acetate Potassium acetate
Calcium 4.5–9.2 mEq	■ Hyperparathyroidism ■ Malignancy ■ Bone disease ■ Immobilization ■ Acute pancreatitis ■ Renal function	Calcium gluconate Calcium chloride
Magnesium 8.1–24.3 mEq	■ Renal function ■ Refeeding ■ Hypokalemia	Magnesium sulfate

[a] Rapid healing examples being burn, and young trauma patients who have rapid tissue generation.

TABLE 11-10. Recommended Daily IV Delivery of Essential Trace Minerals to Adults

Element	Stable adult	Comments
Zinc	2.5–4.0 mg	Increase dose with catabolic state; increase dose with intestinal fluid losses: 12.2 mg/L small bowel fluid loss 17.1 mg/kg stool/ileostomy
Copper	0.3–0.5 mg	Reduce or hold dose with biliary disease
Chromium	10–15 mcg	Increase dose to 20 μg with intestinal losses, reduce in renal disease
Manganese	60–100 mcg	Reduce dose with biliary disease
Selenium	20–40 mcg	
Molybdenum[a]	20–130 mcg	Reduce dose with renal disease

[a] Molybdenum is not presently included in the combination commercial trace element product.

TABLE 11-11. Commercially Available Intravenous Trace Mineral Products for Adults

Product	Chromium (μg)	Copper (mg)	Manganese (mg)	Zinc (mg)	Selenium (μg)
Multitrace-4	4	0.4	100	1	0
Multitrace-5	4	0.4	100	1	20
Multitrace-4 concentrate	10	1	500	5	0
Mutitrace-5 concentrate	10	1	500	5	60

Amounts of trace elements are for a 1ml dose.
Above products manufactured by American Regent (www.americanregent.com).
Single trace element products are also available for chromium, copper, manganese, zinc, selenium, molybdenum, and iodine.

3. Hair loss
4. Impaired wound healing
5. Alterations in platelet function

Tests for deficiency include measuring the triene:tetraene ratio. Deficiency is present when the ratio exceeds 0.2 and is combined with the before-mentioned clinical manifestations. The ratio of linoleic acid to arachidonic acid also can be measured. Normal values average 1.67 ± 0.62. Ratios of approximately 1.2 are seen in EFA deficiency.

In patients who do not tolerate parenteral lipids, either **cutaneous application of safflower oil** (approximately 3 mg/kg/day) or oral supplementation of 15 ml corn oil or MCT oil may be used to prevent EFAD (34).

DESIGNING THE SOLUTION FOR PARENTERAL NUTRITION

The base solution is the amino acid and dextrose combination to which electrolytes, vitamins, and minerals are added. The dextrose–amino acid combination must be prepared in the hospital pharmacy with sterile technique by combining concentrated dextrose solutions with commercially available amino acid preparations. Characteristics of various commercially available amino acid solutions are given in Tables 11-12, 11-13, and 11-14.

Commercial Amino Acid Solutions

Commercial amino acid solutions may contain various amounts of electrolytes as noted in Table 11-12. This becomes important when the final electrolyte content of combined solutions is calculated. Many of the 3% to 5% solutions are used in PPN. Higher concentrations of electrolytes have been added to these solutions so that they can be ordered without additional electrolyte supplementation. Most of the more concentrated amino acid solutions have a low concentration of electrolytes so that individualized combinations of total daily electrolytes can be prepared. The standard solutions profiles presented in Table 11-13 are based on amino acid concentrations in normal serum with modifications to stimulate anabolism. Disease specific solutions are also available (Table 11-14). In general these solutions should not be used for longer than 2 weeks since they do not provide a complete amino acid profile (34).

Amino acid solutions designed for **patients with renal failure not receiving dialysis** have an increased concentration of essential amino acids (Table 11-14). The benefit of these solutions has not been proven in controlled trials. In addition they are more expensive and are available only in low concentrations which may lead to problems with fluid overload.

TABLE 11-12. Electrolyte and Nitrogen Content of Crystalline Amino Acid Solutions for Parenteral Nutrition

	Sodium (mEq/L)	Potassium (mEq/L)	Magnesium (mEq/L)	Acetate (mEq/L)	Chloride (mEq/L)	Phosphorus (mmol of P per liter)	Nitrogen (g/L)	Osmolarity (mEq/L)	pH
Standard									
Aminosyn 10%	0	5.4	0	148	0	0	15.7	1,000	5.3
Aminosyn 8.5% w/o lytes	0	5.4	0	90	35	0	13.4	850	5.3
Aminosyn 8.5% + lytes	70	66	10	142	98	30	13.4	1,160	5.3
Aminosyn II 10%	45	0	0	72	0	0	15.3	873	5.0–6.3
Aminosyn II 8.5%	33	0	0	61	0	0	13	742	5.0–6.5
FreAmine 10%	10	0	0	89	<3	10	15.4	950	6.5
FreAmine III 8.5%	10	0	0	72	2	10	13.0	810	6.6
Novamine 15%	0	0	0	151	0	0	23.7	1,388	5.2–6.0
Procalamine 3%	35	24	5	47	41	3.5	4.6	735	6.8
Travasol 10%	0	0	0	87	40	0	16.5	1,000	6.0
Travasol 8.5% w/o lytes	3	0	0	73	34	0	9.3	520	6.0
Travasol 8.5% + lytes	70	60	10	141	70	30	14.3	1,160	6.0
Travasol 3.5% M	25	15	5	54	25	7.5	5.9	525	6.0

(*continued*)

TABLE 11-12. Electrolyte and Nitrogen Content of Crystalline Amino Acid Solutions for Parenteral Nutrition (*Continued*)

	Sodium (mEq/L)	Potassium (mEq/L)	Magnesium (mEq/L)	Acetate (mEq/L)	Chloride (mEq/L)	Phosphorus (mmol of P per liter)	Nitrogen (g/L)	Osmolarity (mEq/L)	pH
Catabolic state									
Aminosyn-HBC 7%	7	0	0	70	42	0	NA	665	5.2
BranchAmin 4%	0	0	0	0	0	0	4.43	316	6.0
FreAmine HBC 6.9%	10	0	0	57	<3	0	9.7	620	6.5
Hepatic failure									
HepatAmine 8%	10	0	0	62	<3	10	12.0	785	6.5
Renal failure									
Aminess 5.2%	0	0		50	0	0	6.6	416	6.4
Aminosyn-RF 5.2%		0	0	105	0	0	7.7	475	5.2
Nephramine 5.4%	5	0	0	44	<3	0	6.5	435	6.5
RenAmin 6.5%	0	0	0	60	31	0	10	600	5.0–7.0
Pediatric									
Aminosyn-PF 10%	3.4	0	0	46	0	0	15.2	834	5.0–6.5
Trophamine 10%	5	0	0	97	<3	0	15.5	875	5.0–6.0

Formulations may have changed since the preparation of this table. Consult prescription information.

TABLE 11-13. Amino Acid Profiles of Standard Crystalline Amino Acid Solutions for Parenteral Use[a]

Amino acid	Aminosyn 10%	Aminosyn II 10%	FreAmine III 10%	Novamine 15%	Procalamine 3%	Travasol 10%
Essential amino acids (g/dL)						
Lysine	0.72	1.05	0.75	1.18	0.31	0.58
Tryptophan	0.16	0.20	0.15	0.25	0.05	0.18
Phenylalanine	0.44	0.30	0.56	1.04	0.17	0.56
Methionine	0.40	0.17	0.53	0.75	0.16	0.40
Threonine	0.52	0.40	0.40	0.75	0.12	0.42
Leucine	0.94	1.00	0.91	1.04	0.27	0.73
Isoleucine	0.72	0.66	0.69	0.75	0.21	0.60
Valine	0.80	0.50	0.66	0.96	0.20	0.58
Nonessential amino acids (g/dL)						
Histidine	0.30	0.30	0.28	0.89	0.08	0.48
Glutamate	—	0.74	—	0.75	—	—
Proline	0.86	0.72	0.63	0.89	0.34	0.68
Aspartate	—	0.70	—	0.43	—	—
Serine	0.42	0.53	0.59	0.59	0.18	0.50
Arginine	0.98	1.02	0.95	1.47	0.29	1.15
Alanine	1.28	0.99	0.71	2.17	0.21	2.07
Glycine	1.28	0.50	1.40	1.04	0.42	1.03
Tyrosine	0.04	0.27	—	0.04	—	0.04
Cysteine	—	—	<0.02	—	<0.02	—

Formulations may have changed since the preparation of this table. Consult prescribing information.
[a] Values are given for a single concentrated solution available in each product line.

TABLE 11-14. Amino Acid Profiles of Modified Crystalline Amino Acid Solutions for Specialized Parenteral Use

	Catabolic state			Renal failure				Hepatic failure	Pediatric growth formulas	
Amino acid	Aminosyn-HBC 7%	Branch-Amin 4%	FreAmine HBC 6.9%	Aminess 5.2%	Aminosyn-RF 5.2%	Nephr-Amine II 5.4%	Ren-Amin 6.5%	Hepat-Amine 8%	Aminosyn-PF 10%	Tropha-mine 10%
Essential amino acids (g/dL)										
Lysine	0.25	—	0.41	0.60	0.54	0.64	0.45	0.61	0.47	0.49
Tryptophan	0.09	—	0.09	0.19	0.16	0.20	0.16	0.07	0.12	0.12
Phenylalanine	0.23	—	0.32	0.82	0.73	0.88	0.49	0.10	0.30	0.29
Methionine	0.21	—	0.25	0.82	0.73	0.88	0.50	0.10	0.12	0.20
Threonine	0.27	—	0.20	0.38	0.33	0.40	0.38	0.45	0.36	0.25
Leucine	1.58	1.38	1.37	0.82	0.73	0.88	0.60	1.10	0.83	0.84
Isoleucine	0.79	1.38	0.76	0.52	0.46	0.56	0.50	0.90	0.53	0.49
Valine	0.79	1.24	0.88	0.60	0.53	0.64	0.82	0.84	0.45	0.47
Nonessential amino acids (g/dL)										
Histidine	0.15	—	0.16	0.41	0.43	0.25	0.42	0.24	0.22	0.29
Glutamate	—	—	—	—	—	—	—	—	0.58	0.30
Proline	0.45	—	0.63	—	—	—	0.35	0.80	0.57	0.41
Aspartate	—	—	—	—	—	—	—	—	0.37	0.19
Serine	0.22	—	0.33	—	—	—	0.30	0.50	0.35	0.23
Arginine	0.51	—	0.58	—	0.60	—	0.63	—	0.86	0.73
Alanine	0.66	—	0.40	—	—	—	0.56	0.77	0.49	0.32
Glycine	0.66	—	0.33	—	—	—	0.30	0.90	0.27	0.22
Tyrosine	0.03	—	—	—	—	—	0.04	—	0.04	0.14
Cysteine	—	—	<0.02	—	—	<0.02	<0.02	—	—	<0.02
Taurine	—	—	—	—	—	—	—	—	0.05	0.02

Formulations may have changed since the preparation of this table. Consult prescribing information.

Solutions with **increased branched-chain amino acids (BCAAs)** were developed to be used in patients with increased metabolic stress or hepatic failure with encephalopathy (Table 11-14). Standard amino acid solutions have total BCAA concentrations of 20% to 25%. Again, the high cost of these formulas combined with lack of evidence regarding their benefit outside of patients with encephalopathy limits their usefulness.

During catabolism, intracellular levels of glutamine fall. Animal studies have shown that parenteral nutrition supplemented with **glutamine** decreases intestinal damage and improves survival in sepsis (35). High-dose parenteral glutamine (>0.20 to 0.30 g/kg/day or ≥30 g/day) appears to demonstrate the greatest potential for benefit in critically ill patients. However, decreased mortality has not been confirmed in human trials (36). No evidence of harm has been observed in studies conducted to date. A review of prospective randomized clinical trials of glutamine supplementation in patients with short-bowel syndrome, during cancer chemotherapy and in bone marrow transplantation, and in surgical, burn, and intensive care unit patients was completed and concluded, based on present evidence, that no firm recommendation regarding the use of supplemental glutamine can be made at this time (37) (see Chapter 11 for further discussion of glutamine).

Dextrose

Dextrose is the primary energy source for the human body. The **dextrose monohydrate** used in IV solutions provides 3.4 kcal per gram. The brain, erythrocytes, leukocytes, lens of the eye, and renal medulla exclusively require or preferentially use glucose to meet their needs. Dextrose is available in concentrations of 5% to 70%. The percent concentration is grams of solute per 100 mL of solution. For example, 10% dextrose (D10) contains 10 g dextrose per 100 mL of solution or 100 g per L. The most common concentrations used to compound CPN are 50% and 70% dextrose.

Minimum requirement: 1 mg/kg/min
Maximum tolerated: 4 mg/kg/min in critically ill patients
7 mg/kg/min in stable hospitalized patients

Higher rates are associated with hyperglycemia and fatty liver (3).

Intravenous Fat Emulsions

Intravenous fat emulsions (IVFE) of soybean or safflower oil in combination with glycerol and emulsifiers are available in 10%, 20%, and 30% concentrations. The emulsified particles are about the same size as chylomicrons. The most commonly used in PN solutions are 10% and 20% emulsions which provide 1.1 kcal per mL and 2.0 kcal per mL, respectively. The additional nonfat calories come largely from glycerol. Egg phospholipids are used as an emulsifier. Patients with an egg allergy should not be given lipids. The IVFE should not be given to patients who have triglyceride concentrations of >400 mg per dL. Moreover, patients at risk for hypertriglyceridemia should have serum triglyceride concentrations checked at least once during IVFE infusion to ensure adequate clearance. Characteristics of several commercially available lipid emulsions are given in Table 11-15. Because the emulsions are isotonic, administration together with the base solution reduces the overall osmolarity of the infused fluids, an advantage in PPN. The optimal percentage of calories from fat is not known; however, 20% to 60% of calories from fat have been administered without detrimental effects. Problems (decreased reticuloendothelial system function, impaired immune response, fat overload syndrome) have been associated with very high rates of lipid administration (>1 kcal/kg/hour). *Limiting the rate of lipid administration to 0.03 to 0.05 g/kg/hour has been recommended* (3,38).

Vitamin K is included in most commercial lipid emulsions (Table 11-15). The vitamin K content is affected by the proportion of safflower oil to soybean oil (higher concentration of vitamin K) as well as the lipid concentration, doubling with an increase from 10% to 20% lipid (39).

Lipid emulsions containing **fish oil as a source of omega-3 fatty acids (n-3 lipids)** in addition to a fixed combination of long chain triglycerides (LCT), LCT/medium chain triglyceride mixture, with or without olive oil-based lipid emulsion, are available in the

TABLE 11-15. Characteristics of Lipid Emulsions for Parenteral Use

Product	Parent oil	Average droplet size (μg)	Osmolarity (mOsmol/L)	Caloric content (kcal/mL)	Linoleic acid (% total fat)	Linolenic acid (% total fat)
Intralipid 10%	Soybean oil	0.5	260	1.1	50	9
Intralipid 20%	Soybean oil	0.5	268	2.0	50	9
Intralipid 30%	Soybean oil	0.5	200	3.0	50	9
Liposyn II 10%	Soybean and safflower oils	0.4	320	1.1	66	4
Liposyn II 20%	Soybean and safflower oils	0.4	340	2.0	66	4
Liposyn III 10%	Soybean oil	0.4	284	1.1	54	8
Liposyn III 20%	Soybean oil	0.4	292	2.0	54	8

European market. Emulsions available in the United States are based on soybean oil which is rich in omega-6 fatty acids (n-6 lipids) and are still considered the standard. Concerns regarding the use of n-6 lipids in trauma patients arose after a prospective randomized trial that showed significantly higher rates of infections and pulmonary failure and length of stays for both hospital and ICU in patients receiving n-6 lipids as opposed to no IVFE (40). Furthermore, soybean-based emulsions were found to be potentially harmful in patients with severe pulmonary failure and sepsis (41). It is known that n-6 lipids serve as a precursor of the cyclooxygenase and lipoxygenase pathway for the production of highly inflammatory mediators (prostaglandin E2 and leukotriene B4). Emulsions with n-3 lipids change the synthesis to mediators with less inflammatory potential (prostaglandin E3 and leukotriene B5). The shift in lipid mediator generation and the incorporation of n-3 lipids into cell membrane phospholipids has been confirmed in several studies (42–45).

Several small studies have been completed comparing n-3 lipids to n-6 lipids, primarily in ICU and trauma patient populations (40,46–49). A retrospective study comparing 110 surgical patients on standard emulsion to 139 receiving fish oil-supplemented emulsions demonstrated a significantly reduced length of stay, time on ventilator, and mortality in those patients receiving fish oil (46). In a randomized, controlled, double-blind study of 44 patients who had undergone major abdominal surgery, those who received the emulsions supplemented with fish oil had better postoperative liver and pancreas function parameters (47). A similar study of 20 patients who were randomized either to a standard emulsion or the latest generation of IVAF containing omega-3 fatty acids found the group receiving n-3 lipids did not experience the significant increase in liver enzymes noted in the control group (50).

The lack of adequately powered clinical trials does not allow for a recommendation to change present clinical practice. The Canadian Guidelines recommend considering withholding n-6 lipids to minimize potential risk in critically ill patients in whom PN is required for <10 days (38). However, the data regarding potential harm of omega-6 fatty acids are not strong enough to suggest this become a standard of practice.

Lipid emulsions can be given at different times from the base solution, at the same time as the base solution in a single bag (refer to earlier section on Nutrient Requirements during Parenteral Nutrition), or at the same time as the base solution in a separate bag. In the latter case a Y-tube arrangement of the two bags is used to mix the base solution and lipid emulsion just before they enter the patient. Issues of stability have become more important as home PN has become more common and delays between the preparation and use of PN formulas are longer. In general, admixtures are less stable than base solution and

lipids in separate bags. A new product has the base solution and lipid in separate compartments of one bag. The compartments are separated by a zipper, which is opened just before use.

Total Nutrient Admixture

Total nutrient admixture (TNA), also known as a 3-in-1 PN, provides the lipid emulsion and base solution combined in a single bag. This approach allows a hospital pharmacy to combine all the components of a patient's PN formula for a whole day in a single 3-L bag. Physical manipulation of the central line is reduced, as is the risk for infection. Reduced requirements for nursing time and equipment (bags, tubes) lead to cost savings. However, certain disadvantages and advantages are associated with TNAs as presented in Table 11-16. The emulsion may break down, with fat droplets combining to form larger fat droplets and, if deterioration progresses, the fat and water components separating. The safe use of total nutrient admixtures requires visual inspection for signs of deterioration before administration. Deterioration takes place in stages:

1. **Aggregation—**larger fat droplets form and are distributed throughout the solution; reversible with gentle shaking.
2. **Creaming—**the formation of a thin (1- to 2-cm) layer of aggregated fat droplets on the surface of the solution; reversible with gentle shaking.
3. **Coalescence—**the further fusion of fat drops to create a thicker (10-cm), dense layer at the surface; if coalescence develops, the infusion must be discontinued.
4. **Oiling out—**occurs when fat droplets separate from the solution and appear as a clear layer on the surface; if oiling out is observed, the infusion should be discontinued. The likelihood that a lipid emulsion will deteriorate increases with time and temperature. Total nutrient admixtures should not hang at room temperature for more than 24 hours.

Electrolyte and Trace Mineral Preparations for Parenteral Use

These should be added to base solutions for parenteral nutrition in pharmacy IV additive rooms under controlled, aseptic conditions. The use of laminar flow hoods has reduced the incidence of contaminated fluids.

Electrolyte Additives

Electrolyte additives can be added by specifying the actual additive (e.g., sodium chloride) or ideally by specifying the final content of the individual cations and anions. Electrolyte salts often used in PN solutions, the normal ranges of requirements for the patient receiving

TABLE 11-16. Advantages and Disadvantages Associated with TNA

Disadvantages
- Lipid droplets (0.33 to 0.5 μm) can clog filters, thus a larger filter is needed which may not trap all organisms increasing risk of contamination
- Some medications that are compatible with base solutions are incompatible with TNA (55)
- Lipid emulsions are a good medium for growth of bacteria and fungi
- It is more difficult to see particulates, such as precipitated salts
- The emulsion may break down with the fat and water components separating

Advantages
- Only one bag of solution to compound and administer
- Less manipulation during administration
- Less risk of contamination
- Possible benefit in fluid-restricted patients
- May be more cost-effective overall

PN, and conditions that may require an alteration of the amount provided are listed in Table 11-9. Additional electrolytes may also be needed to compensate for increased losses from wounds, gastric suction, fever, surgical drains, emesis, and diarrhea. Although the approximate electrolyte content of GI losses are known (Table 11-7), if there is any question an aliquot of the output can be sent for analysis.

Vitamins

Vitamins are ordered daily or every other day from the outset of parenteral nutrition therapy. The formulation for the MVI Adult® is presented in Table 11-8. As previously mentioned the present standard MVI preparations contain vitamin K.

Vitamin K was included in the new formulation with the intention of providing the patient with a consistent daily supply. This addition raised concerns regarding the potential impact on patient management. Prior to this change, physicians were prescribing vitamin K separately either as a subcutaneous (SC) or intramuscular (IM) injection. Theoretically the consistent and modest amount of vitamin K added to the new formulation should increase the ease of maintaining a desired level of hypoprothrombinemia in patients on anticoagulant therapy with warfarin (51). However, this may make initial titration of anticoagulant therapy difficult, especially if the patient is receiving vitamin K from other sources (i.e., enteral nutrition, diet) as well. Mayne Pharma manufacturs a product that does not contain vitamin K (MVI-Adult without vitamin K®) if needed. It should also be noted that intravenous fat emulsions contain vitamin K as discussed earlier.

Trace Mineral Supplements

Commercial Trace Metal Solutions. These provide *chromium, copper, zinc, manganese, selenium, iodide,* and *molybdenum* in various combinations to provide the recommended daily adult dose in 0.8 to 3 mL of solution, depending on the manufacturer. The components of commonly used trace elements supplementation for CPN are presented in Table 11-11.

Zinc. Additional zinc may be added as zinc sulfate; however, it should not exceed 10 mg in TNAs. The addition of 5 mg of elemental zinc (commonly found in combination supplements) meets the average daily requirements of most patients who do not have additional intestinal losses.

Iron. Iron deficiency can be corrected with the administration of parenteral iron (e.g., iron dextran) IM or IV (see Chapter 7, under Trace Minerals). The IM administration of iron dextran rarely has been associated with pain, the formation of sterile abscesses, and tissue atrophy. As a result, IV administration is the preferred route. The usual daily requirements are met by the monthly administration of 1 mL of iron dextran (50 mg of elemental iron), which may be added directly to a base solution but not to a TNA. Two other preparations are also available: sodium ferric gluconate and iron sucrose. If abnormal amounts of iron are being lost from the gastrointestinal tract or other sites of bleeding, larger replacement doses are necessary. Iron replacement should be titrated to laboratory indices of iron status. The parenteral administration of iron dextran is associated with anaphylaxis. The precautions to be taken in administering parenteral iron are outlined in Chapter 7, and these must be carefully observed. Because of the large stores of iron and the low rate of turnover in iron-repleted patients, the problems associated with iron administration can be avoided in many cases by not giving parenteral iron at all. Patients with normal iron stores prior to starting PN who require <2 months of therapy will most likely not need supplementation.

Additional Points. **Iodine deficiencies** have been described in infants (52) and adult patients on long-term PN. Iodine must be ordered individually as sodium or potassium iodide; the suggested daily dose is 1.0 μg of iodine per kilogram. There is some concern that the amount of **manganese** added to the standard trace element formulations may lead to toxicity in patients receiving long-term PN. Whole blood manganese levels should be monitored periodically (53). **Molybdenum** (20 μg) also may be provided within the PN for patients on long-term support (54).

Other Additives

Other additives may be included directly in the PN formula or administered safely in piggyback fashion with the base solution or TNA. Compatibility is a complex issue that is influenced by the exact components of the nutrient solution (including electrolytes, vitamins, and minerals), pH, concentration of the additive, and mixing sequence.

Medications. Medications that will come in direct contact with the PN (admixture in container or co-infusion through the same IV tubing), compatibility, and stability of the various components should be known. Otherwise, the medications should be administered separate from the PN. Incompatible medication and PN formulations can lead to precipitates that can obstruct blood flow through the pulmonary capillaries leading to pulmonary embolism. Most pharmacies have a short list of medications that are commonly added directly to PN formulations (histamine$_2$-receptor antagonists, insulin, vitamins). Other additives are better given piggyback fashion. Table 11-17 lists common additives reported to be compatible with base solutions or three-in-one admixtures (55,56). References for the compatibility of specific additives appear in Rombeau and Rolandelli (57) and in Trissel (58).

Insulin. Regular insulin reduces hyperglycemia when added directly to the PN solution. Hypoglycemia is less apt to result from a decrease in the fluid rate or inadvertent interruption of the PN fluid if the insulin is added directly to the fluid rather than given by SC injection. Insulin is not routinely added to all TPN solutions; however, when added, only regular human insulin should be used.

- Insulin-requiring diabetics: add 0.1 unit of insulin for each g of dextrose. For example, if the PN solution contains 250 g dextrose, 25 units of insulin should be added. Supplement with additional SC insulin as dictated by the blood glucose (BG) level.

TABLE 11-17. Medication Compatibilities with PN

Additive	Base solution	TNA	Additive	Base solution	TNA
Albumin	C	I	Hydrocortisone	C	X
Amikacin	C	I	Imipenem	X	X
Aminophylline	C	C	Insulin	C	C
Amphotericin B	I	I	Iron dextran	C	I
Ascorbic acid	C	C	Isoproterenol	C	C
Carbenicillin	C	X	Kanamycin	C	C
Cefazolin	C	C	Lidocaine	C	C
Cefoxitin	C	C	Meperidine	C	X
Cephalothin	C	X	Methicillin	C	X
Cephapirin	C	C	Metronidazole	I	I
Chloramphenicol	C	X	Methyldopate	C	I
Cimetidine	C	C	Mezlocillin	C	X
Clindamycin	C	C	Morphine	C	X
Cyanocobalamin	C	X	Multivitamins	C	C
Cyclosporine	C	X	Nafcillin	C	X
Cytarabine	C	X	Norepinephrine	C	C
Dexamethasone	C	C	Octreotide	I	I
Digoxin	C	C	Oxacillin	C	C
Dopamine	C	C	Penicillin G	C	C
Doxycycline	C	X	Phenytoin	I	I
Erythromycin	C	C	Phytonadione	C	C
Famotidine	C	C	Piperacillin	C	C
Folic acid	C	C	Ranitidine	C	C
Furosemide	C	C	Ticarcillin	C	C
Gentamicin	C	C	Tobramycin	C	C
Heparin	C	C	Vancomycin	C	C

C, compatible; I, incompatible; X, no information.

- On day 2 of PN for insulin-requiring diabetics: increase the added insulin by two-thirds of the additional SC insulin given in the previous 24 hours.
- All patients started on PN should have their BG levels monitored q 4 h while the PN is infusing, covering with SC insulin as needed. Oral hypoglycemics should be discontinued when TPN is initiated.

Heparin. Heparin has been advocated by some as an additive to prevent fibrin plugging of the CVC. Sodium heparin is compatible at all concentrations with the TPN solution but probably is of little benefit and is not currently recommended for routine TPN use.

METABOLIC COMPLICATIONS ASSOCIATED WITH PARENTERAL NUTRITION

The morbidity associated with parenteral nutrition is the greatest deterrent to its use in many institutions. Complication rates are effectively reduced when teams that include physicians, dietitians, nurses, and pharmacists are organized to administer parenteral nutrition (59,60). Serious complications develop in fewer than 5% of patients treated with TPN at institutions where a team approach has been implemented. The complications of parenteral nutrition can be categorized as metabolic or nonmetabolic depending on whether they are related to the nutritional formula or the mechanical technique of delivery. Mechanical or nonmetabolic complications were addressed earlier in this chapter.

Hyperglycemia and Hyperosmolarity

A common complication resulting from the delivery of concentrated dextrose, hyperglycemia is more likely to develop during periods of intense catabolic stress. Hyperglycemia can adversely affect fluid balance, immune function, inflammation, and outcome; glucose control has been shown to lessen these effects (61). Because this appears to be true for patients with and without a known diagnosis of diabetes, hyperglycemia should be aggressively treated in all patients (62). The ability to handle the glucose load may improve as PN continues. Hyperosmolarity results from the insufficient administration of free water or from persistent glycosuria and free water diuresis. The insidious development of hyperglycemia and glycosuria during an apparently stable course of PN can indicate the onset of a new catabolic stress, such as catheter sepsis. Hyperglycemia secondary to insulin resistance is often seen in the stressed hospital patient as well. Overfeeding (receiving more calories than needed) will cause hyperglycemia as well. Short-term overfeeding causes hyperglycemia; long-term overfeeding causes fatty liver and can result in impaired immune function. Overfeeding with resultant hyperglycemia is one of the most common and most serious problems associated with PN (63). The concern for the metabolic complications of overfeeding has led to growing support for hypocaloric feeding (64). Many protocols now exist to aid with glycemic control of the hospitalized patient (65). There remains debate regarding the desired target BG range for different patient populations; however, the majority agree BG levels should be maintained $<$150 mg/dL.

Abnormalities of Serum Electrolyte Concentration

Abnormalities of any serum electrolyte concentration can develop during PN; requirements vary considerably from patient to patient and during an individual patient's course of therapy. Potassium requirements may be high initially because of fluxes from the extracellular to intracellular space (secondary to insulin and glucose administration) and because of reversal of the catabolic state. This initially high requirement is likely to decrease during the course of PN. Hyperchloremic acidosis was once a frequent complication of parenteral nutrition because of the high chloride content of early amino acid solutions. Currently available solutions are low in chloride, and this complication is now less frequent. Still, one should *keep the chloride content equal to or below the sodium content in the daily prescription to prevent hyperchloremia* unless unusual chloride losses are occurring. Phosphorus requirements increase with the initiation of protein anabolism. Inadvertent omission of phosphate results in hypophosphatemia shortly after PN is initiated. The PN formula should not be used as the "repletion" route for low electrolyte levels due to the

rate of infusion. For example, a PN formulation containing 80 mEq of potassium given over a 24-hour period would only provide 3.3 mEq per hour. This may be too long to delay repletion. In general, patients should be given an IV piggyback supplementation, with the amount in the PN adjusted to reflect what has been given with the goal of maintenance as opposed to repletion.

Bone Disease/Liver Dysfunction

Complications of long-term PN include metabolic bone disease and liver dysfunction. These are discussed in detail later in this chapter.

ORDERING AND INITIATING PARENTERAL NUTRITION FOR CENTRAL VENOUS CATHETER

The decision to begin PN need never be made in haste. PN should be initiated under controlled conditions and according to a defined protocol (Table 11-18). Orders must be carefully written because of the multiple additives needed on a daily basis. A special order form is recommended to avoid transcription errors and accidental omission of important nutrients. Figure 11-1 is an example of a CVC PN order form that offers four different TNAs based on amino acid content, and the option to provide only a base solution of amino acid/dextrose with separate or no lipid emulsion. The TNAs provide percent calories for all macronutrients within recommended ranges. According to this order form, PN bags are sequentially numbered throughout a patient's course of therapy. Note that all the additives are ordered on the same order form so that the daily prescription of nutrients can easily be seen.

TABLE 11-18. Calculation of Macronutrient Additives for TPN

1. Calculate patient's caloric and protein needs:

70 kg × 25 kcal/kg = 1,750 calories
70 kg × 1.2 g pro/kg = 84 g protein

2. Determine amino acids first:

84 g = 336 calories
10% amino acid solution = 10 g/100 mL of solution
12.5 % = 12.5 g/100 mL
8% = 8 g/100 mL

Example: 10 g/100 mL = 84 g/? mL

$$\frac{84\text{ g} \times 100\text{ mL}}{10\text{ g}} = \text{? mL of 10\% amino acid solution}$$

$$= \textbf{840 mL of 10\% amino acid solution}$$

3. Determine dextrose requirements next:

Assume patient is a nondiabetic = 55% calories from carbohydrate
1,750 × .55 = 962 calories
962 calories ÷ 3.4 (kcal/kg dextrose) = 283 g dextrose

Based on 70% dextrose base: 70 g/100 mL = 283 g/? mL

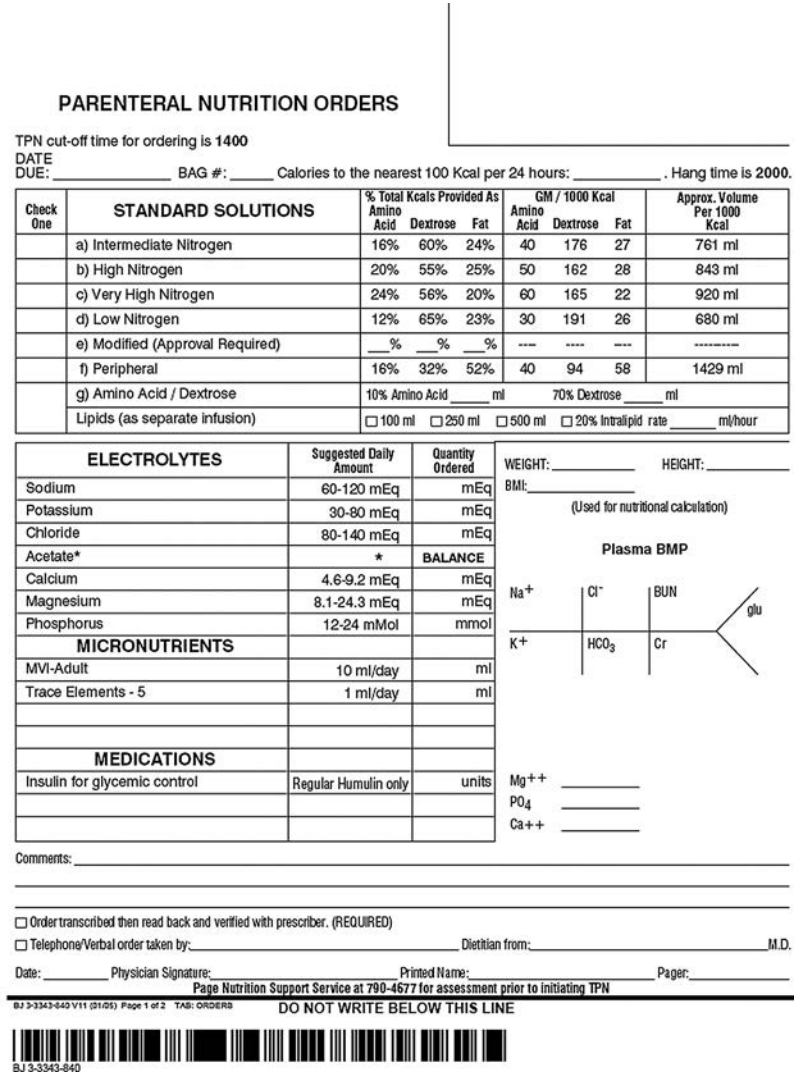
$$\frac{283\text{ g} \times 100\text{ mL}}{70\text{ g}} = \text{? mL of D70}$$

$$= \textbf{404 ml of D 70 (70\% dextrose) solution}$$

4. Leftover calories as lipid (or withhold these calories if lipids to be held)

1,750 calories − (336 protein calories + 962 dextrose calories) = 452 calories

10% lipid emulsion = 1.1 kcal/ mL 452 ÷ 1.1 = **411 mL 10% lipid solution**
20% lipid emulsion = 2.0 kcal/ mL 452 ÷ 2.0 = **226 mL 20% lipid solution**



PARENTERAL NUTRITION ORDERS

TPN cut-off time for ordering is 1400

DATE DUE: _____ BAG #: _____ Calories to the nearest 100 Kcal per 24 hours: _____. Hang time is 2000.

Check One	STANDARD SOLUTIONS	% Total Kcals Provided As Amino Acid	Dextrose	Fat	GM / 1000 Kcal Amino Acid	Dextrose	Fat	Approx. Volume Per 1000 Kcal
	a) Intermediate Nitrogen	16%	60%	24%	40	176	27	761 ml
	b) High Nitrogen	20%	55%	25%	50	162	28	843 ml
	c) Very High Nitrogen	24%	56%	20%	60	165	22	920 ml
	d) Low Nitrogen	12%	65%	23%	30	191	26	680 ml
	e) Modified (Approval Required)	__%	__%	__%	---	----	---	----------
	f) Peripheral	16%	32%	52%	40	94	58	1429 ml
	g) Amino Acid / Dextrose	10% Amino Acid _____ ml			70% Dextrose _____ ml			
	Lipids (as separate infusion)	☐ 100 ml	☐ 250 ml	☐ 500 ml	☐ 20% Intralipid rate _____ ml/hour			

ELECTROLYTES	Suggested Daily Amount	Quantity Ordered
Sodium	60-120 mEq	mEq
Potassium	30-80 mEq	mEq
Chloride	80-140 mEq	mEq
Acetate*	*	BALANCE
Calcium	4.6-9.2 mEq	mEq
Magnesium	8.1-24.3 mEq	mEq
Phosphorus	12-24 mMol	mmol
MICRONUTRIENTS		
MVI-Adult	10 ml/day	ml
Trace Elements - 5	1 ml/day	ml
MEDICATIONS		
Insulin for glycemic control	Regular Humulin only	units

WEIGHT: _____ HEIGHT: _____

BMI: _____

(Used for nutritional calculation)

Plasma BMP

Mg++ _____

PO4 _____

Ca++ _____

Comments: _____

☐ Order transcribed then read back and verified with prescriber. (REQUIRED)

☐ Telephone/Verbal order taken by: _____ Dietitian from: _____ M.D.

Date: _____ Physician Signature: _____ Printed Name: _____ Pager: _____

Page Nutrition Support Service at 790-4677 for assessment prior to initiating TPN

BJ 3-3343-840 V11 (01/05) Page 1 of 2 TAB: ORDERS

DO NOT WRITE BELOW THIS LINE

BJ 3-3343-840

FIGURE 11-1. Sample parenteral nutrition ordering form, page 1.

1. **Review patient assessment and baseline labs (Table 11-19).**
2. **Determine patient's caloric and protein requirements as previously outlined (Table 11-6).**
3. **Determine which standard formula would come closest to meeting the patient's estimated needs.** On the example form, the grams of each macronutrient per 1,000 calories are provided. For example, if it is determined the patient requires 1,500 calories (1.5 × 1,000 calories): 1,500 calories of the Intermediate Nitrogen solution will provide 60 g protein (40 g × 1.5 = 60), whereas 1,500 calories of the High Nitrogen solution will provide 75 g protein. Therefore, the practitioner would decide if the patient would benefit more from 60 or 75 g protein per day.

TABLE 11-19. Monitoring the Acute Care Patient on PN

Parameter	Baseline	Initiation period	Critically ill	Stable patient
Vitals, temp	Yes	q 6 h	q 8 h	q 12 h
Weight	Yes	3 times per day	Daily	3 times per week
Intake/Output	Yes	Daily	Daily	As indicated
Blood glucose	Yes	q 4 h	q 1–4 h based on control	q 4–72 h based on control
CBC	Yes	Daily	2 times per week	Weekly
Basic metabolic profile (Na, K, Cl, CO2, BUN, Creat, Glu, Ca)	Yes	Daily	Daily	2–3 times per week
Mg, PO_4	Yes	Daily	3–4 times per week	Weekly
Triglyceride	Yes	Day 1–2	As needed	As needed
LFTs – ALT, AST, ALP, total bilirubin	Yes	Day 1–2	Weekly	Monthly
Line site	Yes	Daily	Daily	Daily
Dressing change		Day 1–2 post-line placed, replace gauze with Transparent dressing	Transparent dressing q week or if nonocclusive	Transparent dressing q week or if nonocclusive

4. **Whether or not to start at full calories is based on patient tolerance.** Patients who have poor glycemic control, are critically ill, or at risk of refeeding syndrome should be started with 100 to 200 g or 10% to 15% dextrose. If BG levels remain <200 and electrolytes are within normal limits, the dextrose concentration should be advanced to goal over 1 to 2 days. If the patient is critically ill or septic, consideration should be given to withholding the lipids for the first 7 to 10 days. Although it is unproven that withholding n-6 lipids in these patients will improve outcomes, it will allow for increased medication compatibility with Y-site administration in patients often plagued with limited IV access. In this case the base solution formula would be used. The example presented in Table 11-18 demonstrates how to determine the milliliters needed from each macronutrient solution.
5. **Begin electrolytes, MVI, and trace elements based on the patient's lab values and general requirements as outlined in Tables 11-8 to 11-10.** The breakdown of the electrolyte salts used and MVI and trace element formulations, in addition to the intrinsic electrolytes included in the amino acid solution as they appear on the back of the sample order form, are presented in Figure 11-2.
6. **Recommendations for monitoring patients on PN are presented in Table 11-19.** Metabolic complications occur frequently, and the results of routine monitoring should be used not only to adjust the PN formula but also to regulate the frequency of monitoring. Thus, if a patient is found to be hypokalemic on routine monitoring, the appropriate response is not only to increase the potassium content of the PN formulation, but also to monitor the serum potassium level more frequently.
7. **The appropriate protocol for discontinuing PN** has been controversial, and practice patterns vary from hospital to hospital. Some investigators have recommended infusing 10% dextrose to avoid hypoglycemia if PN is interrupted and slow tapering of PN solutions to avoid hypoglycemia when PN is discontinued. In these circumstances, the potential for hypoglycemia is thought to be related to the continued secretion of insulin when the infusion of high-glucose solutions is stopped. Others have noted there was no symptomatic hypoglycemia, and glucose profiles returned to a similar baseline level in those whose PN was abruptly stopped when compared with those in the tapered group (66).
8. **Cycling PN** is a method of parenteral nutrition in which the base solution or TNA is infused over a 12- to 16-hour period, usually at night. One guideline for deciding the

Salts Used
Sodium chloride, Sodium acetate, Sodium phosphate
Potassium chloride, Potassium acetate, Potassium phosphate
Calcium gluconate
Magnesium sulfate

Trace Elements-5	Amount per 1 ml
Zinc	5 mg
Copper	1 mg
Manganese	0.5 mg
Chromium	10 mcg
Selenium	60 mcg

MVI-Adult	Amount per 10 ml
Ascorbic acid (Vitamin C)	200 mg
Retinol (Vitamin A)	1 mg
Ergocalciferol (Vitamin D)	5 mcg
Thiamine (Vitamin B_1)	6 mg
Riboflavin (Vitamin B_2)	3.6 mg
Pyridoxine (Vitamin B_6)	6 mg
Niacinamide	40 mg
d-Panthenol	15 mg
Vitamin E	10 mg
Biotin	60 mcg
Folic acid	0.6 mcg
Cyanocobalamin (Vitamin B_{12})	5 mcg
Phylloquinine (Vitamin K_1)	150 mcg

Travasol 10%-Intrinsio Electrolytes	Amount per 1 liter
Acetate	87 mEq
Chloride	40 mEq

FIGURE 11-2. Sample parenteral nutrition ordering form, page 2.

duration of the infusion during cycling is that the patient should not receive more than 0.5 g of glucose per kilogram of body weight per hour. Cycling has no physiologic disadvantage over continuous infusion and may actually be better. The fluids are discontinued in the morning so that the patient is free to perform his or her usual daily activities. This method of PN delivery is used for patients who will ultimately be sent home on PN and is also suitable for selected patients expected to undergo long courses of PN in the hospital (e.g., patients receiving bone marrow transplantation). Cyclic PN may not be suitable for patients with diabetes, especially those requiring insulin, because of the risks for hypoglycemia. Cyclic PN also may be unsuitable for patients with heart failure, who cannot tolerate the higher rates of fluid administration.

- **A period of stability** (>24 hours) on conventional PN therapy (24-hour infusions) should be demonstrated prior to initiating cyclic PN.
- **The use of a volumetric infusion pump** is required. Cyclic PN is facilitated by using a single 2- or 3-L bag for the entire night's infusion. The TNA system is ideal for cyclic infusion if lipid emulsions are required.
- **Blood glucose levels should be checked while the infusion is running and 1 to 2 hours postcompletion.** Given the half-life of regular insulin the effects of any insulin in the PN may be seen for 1 to 2 hours postcompletion. The goal should be to keep BG levels >70 mg/dL when the patient is off the PN. Cycling is not advisable for patients who are persistently hyper- or hypoglycemic or who have erratic insulin requirements.
- **Use sterile technique each time the catheter is handled** to connect or disconnect the tubing. A sterile cap should be placed over the catheter tip when it is not in use. Be certain to clamp the catheter before disconnecting it from the solution tubing.
- **Flush the catheter port with heparinized saline solution** immediately before beginning an infusion and when discontinuing the infusion. We use 1:100 heparinized saline solution

for permanent catheters and 1:10 for temporary catheters. The volume of the flush varies from 1 to 5 mL and is determined by the length and internal diameter of the catheter.

ORDERING AND INITIATING PERIPHERAL PARENTERAL NUTRITION

General Principles

Providing PN through a peripheral vein is more difficult than through a central vein because peripheral veins tolerate concentrated hypertonic solutions poorly. Daily volume limitations in combination with the requirement for less concentrated solutions may prevent delivery of the desired number of calories. However, protein, vitamin, and mineral requirements can usually be met. In most institutions, CPN is viewed as the procedure of choice for almost all patients requiring PN; however, some investigators advocate supplemental PPN in elderly patients with poor intake and intolerance to short-term feeding tubes (67,68). Need to change access site and phlebitis were noted as downsides to this approach. Pre-made PPN formulations (e.g., ProcalAmine®) are available on the market, lessening the labor cost and concerns for incompatibilities.

Basic Rules for Planning Peripheral Parenteral Nutrition

1. Keep the osmolarity of the final infusate below 800 to 900 mOsmol/L and the dextrose concentration at 10% or less (Table 11-20).
2. Utilize lipid emulsions to increase the nonprotein calories delivered per day and decrease the osmolarity of the final infusate. An example of a standard PPN formula is a TNA with a caloric distribution of 32% dextrose, 16% protein, and 52% fat and a caloric density of 0.7 cal per mL. Three liters of this TNA contain 2,100 calories and 84 g of protein. Possible immunosuppressive effects have been associated with formulations in which lipids provide such a high portion of the calories.
3. Do not allow fats to provide more than 60% to 70% of the total daily nonprotein calories (>2.5 g/kg of body weight per day).
4. Make sure that both the physician and the pharmacist understand the electrolyte content of the ordered solution. Many of the 3.0% to 3.5% amino acid solutions for peripheral venous administration contain significant amounts of electrolytes. The ordering physician should be aware of the electrolyte content before adding additional electrolytes to the daily parenteral nutrition prescription (Table 11-12).
5. Change the IV infusion site regularly and at the first sign of thrombophlebitis.
6. The osmolarity of PPN solutions may be calculated as follows:

$$\text{Osmolarity (mOsm/L)} = (\text{grams dextrose/L}) \times 5 + (\text{grams amino acid/L}) \times 10 + (\text{grams lipids/L}) \times 0.67 + (\text{mEq cations/L}) \times 2$$

TABLE 11-20. Osmolarity and Caloric Content of Concentrated Dextrose Solutions

Dextrose concentration (wt/vol)	Osmolarity (mOsmol/L)	Caloric content[a] (kcal/dL)
5%	250	17
10%	500	34
20%	1,000	68
50%	2,500	170
70%	3,500	237

[a] Based on the caloric value of dextrose monohydrate used in commercial preparations (3.4 kcal/g).

HOME PARENTERAL NUTRITION

Home parenteral nutrition (HPN) allows for the increased survival of patients with diseases prohibiting adequate intake and absorption of nutrients via the oral or enteral route. Primarily this includes patients with short bowel syndrome, cancer (causing obstruction or malabsorption), or severe inflammatory bowel disease. According to the Oley Foundation, a nonprofit organization supporting home PN and EN patients (http://oley.org/index.html), in 2003 approximately 7,000 people in the United States were receiving HPN (69). The first patient discharged home on PN was in the late 1960s (70). While many patients have been on HPN over 10 years, a few are nearing 30 years. The underlying diagnosis is the single most important factor with regard to outcome. For example, a cancer patient has a >70% mortality rate per year, while a Crohn patient has 4% mortality rate per year. While some factors are absolute, such as diagnosis, length of remaining bowel, and patient's age, others are not, such as use of narcotics and sedatives, treatment by multidisciplinary professionals with experience in HPN, adequate patient/caregiver training, and participation in a HPN support group (71). Regardless, a long-term patient accrues a 10% to 15% chance of dying from a complication of the HPN.

COMPLICATIONS ASSOCIATED WITH LONG-TERM HOME PARENTERAL NUTRITION

Line Sepsis

Line sepsis is the most common cause of fever in a HPN patient. In general, HPN patients have an episode of line or catheter sepsis once every 2 to 3 years (71). An outcome analysis in 50,470 patients with central venous access found that the most common catheter complications, in descending order, were catheter dysfunction (primarily thrombotic occlusion), catheter site infections, and bloodstream infections. The least number of complications were associated with a chest port followed by tunneled catheter. Midline and nontunneled catheters were associated with increased complications (72).

Metabolic Bone Disease

In some patients receiving long-term CPN (>2 to 3 months), severe pain develops in the periarticular regions, lower extremities, and back despite apparent improvement in the overall nutritional status. Bone biopsies reveal patchy osteomalacia and decreased mineralization, although serum levels of calcium, phosphorus, parathyroid hormone, and total 25-hydroxyvitamin D are normal. Low serum levels of 1,25-dihydroxyvitamin D have been reported in patients on long-term CPN; thus, an altered vitamin D metabolism may be involved in the pathogenesis of the syndrome. Symptoms resolve and 1,25-dihydroxyvitamin D levels normalize after CPN is discontinued. Abnormalities have also been found in the bone biopsy specimens of asymptomatic patients. A study that evaluated 943 bone mass scans (spinal, hip, and forearm) in 75 patients on HPN found a statistically significant decline over time ($p < 0.005$) (73). However, the decline was not significantly different than that of healthy well-matched controls for age and sex. Other factors contributing to bone disease include hypercalciuria during the CPN infusion (likely related to glucose loading or an increased burden of organic sulfate) and possibly improper administration of trace minerals.
Detection. The pathogenesis is not well understood; no good serum marker is available at this time. Symptoms usually include pain in the periarticular regions, lower extremities, and back. Bone mineral density is required for diagnosis.
Treatment. Temporary or permanent discontinuance of CPN and potentially the removal of vitamin D from the solution are the only currently known therapies.

Liver Dysfunction

Liver dysfunction in patients receiving CPN ranges from mild complications such as elevated transaminases (aspartate aminotransferase, alanine aminotransferase) to steatosis, cholestasis,

cirrhosis, liver failure, and even death (74). The mild complications seen in short-term CPN generally resolve with the discontinuation of CPN and rarely lead to severe abnormalities (75). Delayed elevations or persistent elevations (>20 days) of enzymes may represent toxic hepatitis, thought to be related to the amino acid infusion (possibly from products of tryptophan degradation). A reduction in liver enzyme levels has been reported with the use of metronidazole. A retrospective review also suggested that liver enzymes are less likely to be elevated in patients receiving metronidazole (76). This effect is possibly related to a reduction in the anaerobic bacterial overgrowth in the small bowel that occurs during CPN. Such organisms may produce hepatotoxic substances, for example, endotoxins, or lithocholic acid. In some patients, elevated liver enzymes and painful hepatomegaly result from acute fat accumulation during carbohydrate feeding. The administration of glucose at rates above 7 mg per kg per minute is associated with the development of fatty liver. A recent study of liver disease in patients on HPN found high rates of liver disease (77). Chronic cholestasis developed in 65% of patients after an average of 6 months of HPN. The prevalence of complicated liver disease was 26% after 2 years of HPN and 50% after 6 years.

Detection. Liver disease is detected by regular monitoring of common liver function tests (76) (Table 11-19).

Treatment. Focus should be on prevention of CPN-associated liver disease by avoiding overfeeding (specifically glucose and lipids). Steatosis, fatty liver, often resolves with a reduction of the total calories provided. In addition, lipid intake of greater than 1 g per kg per day has been associated with CPN-induced liver disease (78). Elevated liver enzymes *per se* are not an indication for discontinuation of CPN. Cycling of the CPN formula over 12 to 14 hours is associated with a decreased metabolic load to the liver. In a study of 65 patients with impaired liver function, cycling was beneficial in those with mild to moderate disease (bilirubin 0.5 to 1 mg/L), but not those with bilirubin greater than 1.5 mg per L (79). The onset of hepatic encephalopathy requires a reduction in protein delivery and possibly discontinuance of amino acid infusion if significant hepatic toxicity is suspected.

References

1. Lipman TO. The chicken soup paradigm. *JPEN J Parenter Enteral Nutr.* 2003;27:93–99.
2. Dudrick SJ, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. *Surgery.* Jul 1968;64(1):134–142.
3. American Society of Parenteral and Enteral Nutrition. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr.* 2002;26(1 supplement):1S.
4. Detsky AS and Veterans Affairs TPN Cooperative Study Group. Parenteral nutrition - is it helpful? *N Engl J Med.* 1991;325:573.
5. Howard L, Ashley C. Nutrition in the perioperative patient. *Annu Rev Nutr.* 2003;23:263–282.
6. Madsen H, Frankel EH. The hitchhiker's guide to parenteral nutrition management for adult patients. *Practical Gastroenterol.* 2006(July):46–68.
7. Klein S. Influence of nutrition support on clinical outcome in short bowel syndrome and inflammatory bowel disease. *Nutrition.* 1995;11(Suppl 2):233.
8. Lloyd DA, Gabe SM, Windsor AC. Nutrition and managment of enterocutaneous fistula. *Br J Surg.* 2006; 93:1045–1055.
9. Hollington P, Mawdsley J, Lim W, et al. An 11-year experience of enterocutaneous fistula. *Br J Surg.* 2004; 91:1646–1651.
10. Jeejeebhoy KN. Management of short bowel syndrome: avoidance of total parenteral nutrition. *Gastroenterology.* Feb 2006;130(2 Suppl 1):S60–66.
11. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2004;28:S39–S70.
12. McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med.* 2003;348:1123–1133.
13. Vanek VW. The ins and outs of venous access: Part 1. *Nutr Clin Pract.* 2002;17:85–98.
14. Klein S, Taylor B, Rubin D. Nutritional support in the patient with gastrointestinal disease. In: Therapy of Digestive disorders 2nd ed. Wolfe MM ed. *Digestive Diseases*; Saunders/Elsevier, Philadelphia; 2006: 41.
15. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systemic review of 200 published prospective studies. *Mayo Clin Proc.* 2006;81:1159–1171.
16. Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA.* 2001;286:700–707.
17. Moretti EW, Ofstead CL, Kristy RM, et al. Impact of central venous catheter type and methods on catheter-related colonization and bacteraemia. *J Hosp Infect.* 2005;61:139–145.
18. Raad II, Hohn DC, Gilbreath BJ, et al. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol.* 1994;15:231–238.

19. Zakrzewska-Bode A, Muytiens HI, Liem KD, et al. Mupirocin resistance in coagulase-negative staphylococci, after topical prophylaxis for the reduction of colonization of central venous catheters. *J Hosp Infect.* 1995;31:189–193.
20. McLaws ML, Berry G. Nonuniform risk of bloodstream infection with increasing central venous catheter-days. *Infect Control Hosp Epidemiol.* 2005;26:715–719.
21. Fraenkel D, Rickard C, Thomas P, et al. A prospective, randomized trial of rifampicin-minocycline-coated and sliver-platinum-carbon-impregnated central venous catheters. *Crit Care Med.* 2006;34:668–675.
22. Malach T, Jerassy Z, Rudensky B, et al. Prospective surveillance of phlebitis associated with peripheral intravenous catheters. *Am J Infect Control.* 2006;34:308–312.
23. Merritt R, ed. *The ASPEN Nutrition Support Practice Manual.* 2nd ed. Silver Spring, MD: ASPEN; 2005.
24. Klein S, Taylor B, Rubin D. Nutrition support in the patient with gastrointestinal disease. In: Wolfe MM, ed. *Therapy of Digestive Disorders*. 2nd ed. New York: Saunders; 2005.
25. Frankenfield D. *Energy and Macrosubstrate Requirements*. Dubuque, IA: Kendall/Hunt Publishing; 2001.
26. Van Way CA. Total calories vs nonprotein calories. *Nutr Clin Pract.* 2001;16:271–272.
27. Miles JM, Klein J. Should protein calories be included in caloric calculations for a TPN prescription? Point-counterpoint. *Nutr Clin Pract.* 1996;11:204–206.
28. Parenteral multivitamin products; drugs for human use; drug efficacy study implementation; amended (21 CFR5.70). *Fed Reg.* 2000;65:21200–21201.
29. Abiles J, de la Cruz AP, Castano J, et al. Oxidative stress is increased in critically ill patients according to antioxidant vitamins intake, independent of severity: a cohort study. *Crit Care.* 2006;10:R146.
30. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. *Nutrition.* 2001;17:632–637.
31. Geerlings SE, Rommes JH, van Toorn DW, et al. Acute folate deficiency in a critically ill patient. *Neth J Med.* 1997;51:36–38.
32. Rodriguez RM, Corwin HL, Gettinger A, et al. Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness. *J Crit Care.* 2001;16:36–41.
33. Safe practices for parenteral nutrition formulations. National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition. *JPEN J Parenter Enteral Nutr.* 1998;22:49–66.
34. Gasser E, Parekh N. Parenteral nutrition: macronutrient composition and requirements. *Support Line.* 2005;27:6–22.
35. Ardawi MSM. Effect of glutamine-supplemented total parenteral nutrition on the small bowel of septic rats. *Clin Nutr.* 1992;11:207.
36. Ockenga J, Borchert K, Stuber E, et al. Glutamine-enriched total parenteral nutrition in patients with inflammatory bowel disease. *Eur J Clin Nutr.* 2005;59:1302–1309.
37. Alpers DH. Glutamine: do the data support the cause for glutamine supplementation in humans? *Gastroenterology.* 2006;130(2 Suppl 1):S106–S116.
38. Heyland DK, Dhaliwal R, Drover JW, et al. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr.* Sep-Oct 2003;27(5): 355–373.
39. Fogle P. Vitamin K and lipid emulsions. *Support Line.* 2001;23:3–8.
40. Battistella FD, Widergren JT, Anderson JT, et al. A prospective randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J Trauma.* 1997;43:52–58.
41. Suchner U, Katz DP, Furst P, et al. Impact of sepsis, lung injury, and the role of lipid infusion on circulating prostacyclin and thromboxane A(2). *Intensive Care Med.* 2002;28:122–129.
42. Morlion BJ, Torwesten E, Lessire H, et al. The effect of parenteral fish oil on leukocyte membrane fatty acid composition and leukotriene synthesizing capacity in patients with postoperative trauma. *Metabolism.* 1996;45:1208–1213.
43. Koller M, Senkal M, Kemen M, et al. Impact of omega-3-fatty acid enriched TPN on leukotriene synthesis by leukocytes after major surgery. *Clin Nutr.* 2003;22:59–64.
44. Senkal M, Haaker R, Linseisen J, et al. Preoperative oral supplementation with long-chain omega-3-fatty acids beneficially alters phospholipid fatty acid patterns in liver, gut mucosa and tumor tissue. *JPEN J Parent Enteral Nutr.* 2005;29:236–240.
45. Grimm H, Mertes N, Goeters C, et al. Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. *Eur J Clin Nutr.* 2006;45:55–60.
46. Tsekos E, Reuter C, Stehle P, et al. Perioperative administration of parenteral fish oil supplements in a routine clinical setting improves patient outcome after major abdominal surgery. *Clin Nutr.* 2004;23: 325–330.
47. Heller AR, Rossel T, B G, et al. Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients. *Int J Cancer.* 2004;111:611–616.
48. Heller AR, Fischer S, Rossel T, et al. Impact of n-3 fatty acid supplemented parenteral nutrition on haemostasis patterns after major abdominal surgery. *Br J Nutr.* 2002;87(Suppl 1):S95–S101.
49. Tappy L, Berger MM, Schwarz JM, et al. Metabolic effects of parenteral nutrition enriched with n-3 polyunsaturated fatty acids in critically ill patients. *Clin Nutr.* 2006;25:588–595.
50. Antebi H, Mansoor O, Ferrier C, et al. Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. *JPEN J Parent Enteral Nutr.* 2004;28:142–148.

51. Helphingstine CJ, Bistrian BR. New Food and Drug Administration requirements for inclusion of vitamin K in adult parenteral multivitamins. *JPEN J Parenter Enteral Nutr.* 2003;27:220–224.
52. Ibrahim M, de Escobar GM, Visser TJ, et al. Iodine deficiency associated with parenteral nutrition in extreme preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2003;88:56–57.
53. Van Gossum A, Neve J. Trace element deficiency and toxicity. *Curr Opin Clin Nutr Metab Care.* 1998;6: 499–507.
54. Sardesai VM. Molybdenum: an essential trace element. *Nutr Clin Pract.* 1993;8:277–281.
55. Trissel LA, Gilbert DL, Martinez JF, et al. Compatibility of medications with 3-in-1 parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1997;23:67–74.
56. Trissel LA, Gilbert DL, Martinez JF, et al. Compatibility of parenteral nutrient solutions with selected drugs during simulated Y-site administration. *Am J Health Syst Pharm.* 1997;54:1295–1300.
57. Rombeau JL, Rolandelli RH, eds. *Clinical Nutrition: Parenteral Nutrition*. Philadelphia: Saunders; 2000.
58. Trissel LA. *Handbook on Injectable Drugs*, 13th ed. Bethesda, MD: American Society of Hospital Pharmacists; 2005.
59. Shang E, Hasenberg T, Schlegel B, et al. A European survey of structure and organisation of nutrition support teams in Germany, Austria and Swizerland. *Clin Nutr.* 2005;24:1005–1013.
60. Martinez MJ, Martinez MA, Montero M, et al. Hypophosphatemia in postoperative patients with total parenteral nutrition: influence of nutritional support teams. *Nutr Hosp.* 2006;31:657–660.
61. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;345:1359–1367.
62. Rady MY, Johnson DJ, Patel BM, et al. Influence of individual characteristics on outcome of glycemic control in intensive care unit patients with or without diabetes mellitus. *Mayo Clin Proc.* 2005;80:1558–1567.
63. McMahon MM. Management of parenteral nutrition in acutely ill patients with hyperglycemia. *Nutr Clin Pract.* 2004;19:120–128.
64. Boitano M. Hypocaloric feeding of the critically ill. *Nutr Clin Pract.* 2006;21:617–622.
65. Whitehorn J. A review of the use of insulin protocols to maintain normoglycaemia in high dependency patients. *J Clin Nurs.* 2007(16):16–27.
66. Nirula R, Yamada K, Waxman K. The effect of abrupt cessation of total parenteral nutrition on serum glucose: a randomized trial. *Am Surg.* 2000;66:866–869.
67. Thomas DR, Zdrodowski CD, Wilson MM, et al. A prospective randomized clinical study of adjunctive peripheral parenteral nutrition in adult subacute care patients. *J Nutr Health Aging.* 2005;9:321–325.
68. Schoevaerdts D, Gazzotti C, Cornette P, et al. Peripheral parenteral nutrition in geriatric wards. *Acta Clin Belg.* 2006;61:170–175.
69. Wilson E. The Oley Foundation celebrates 20 years. *Support Line.* 2003;25:6–10.
70. Shils ME, Wright WL, Turnbull A, et al. Long term parenteral nutrition through external arteriovenous shunt. *N Engl J Med.* 1970;283:341–344.
71. Howard L, Ashley C. Management of complications in patients receiving home parenteral nutrition. *Gastroenterology.* 2003;124:1651–1661.
72. Moureau N, Poole S, Murdock MA, et al. Central venous catheters in home infusion care: outcomes analysis in 50,470 patients. *J Vasc Interv Radiol.* 2002;13:1009–1016.
73. Haderslev KV, Tjellesen L, Haderslev PH, et al. Assessment of the longitudinal changes in bone mineral density in patients receiving home parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2004;28:289–294.
74. Buchman AL. Complications of long-term home total parenteral nutrition: their identification, prevention and treatment. *Dig Dis Sci.* 2001;46:1–18.
75. Grant JP, Cox CE, Kleinman LM, et al. Serum hepatic enzyme and bilirubin elevations during parenteral nutrition. *Surg Gynecol Obstet.* 1977;145:573–580.
76. Lambert JR, Thomas SM. Metronidazole prevention of serum liver enzyme abnormalities during total parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 1985;9:501.
77. Cavicchi M, Beau P, Crenn P, et al. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. *Ann Intern Med.* 2000;132:525.
78. Hamilton C, Austin T. Liver disease in long-term parenteral nutrition. *Support Line.* 2006;28:10–18.
79. Hwang T, Lue M, Chen L. Early use of cyclic TPN prevents further deterioration of liver functions for the TPN patients with impaired liver function. *Hepato-Gastroenterol.* 2000;47:1347–1350.
80. Lochs H, Meryn S, Marosi L, et al. Has total bowel rest been a beneficial effect in the treatment of Crohn's disease? *Clin Nutr.* 1983;2:61.
81. Jones VA. Comparison of total parenteral nutrition and elemental diet in induction of remission of Crohn's disease. *Dig Dis Sci.* 1987;32(Suppl 12):1008.
82. Greenberg GR, Fleming CR, Jeejeebhoy KN, et al. Control trial of bowel rest and nutritional support in the management of Crohn's disease. *Gut.* 1988;29:1309.
83. Wright RA, Adler EC. Peripheral parenteral nutrition is no better than enteral nutrition in acute exacerbation of Crohn's disease: a retrospective trial. *J Clin Gastroenterol.* 1990;12:396.

12 USE OF DIETS AND DIETARY COMPONENTS IN CLINICAL PRACTICE

GENERAL PRINCIPLES

In many diets useful in managing disease, a particular element (e.g., fat or lactose) is *restricted*. In such cases, care must be taken to ensure that a balanced diet providing all the major required macronutrients and micronutrients is offered. Sometimes, supplements must be added to a restrictive diet (e.g., calcium to a low-lactose diet). In other diets, a nutrient that may be required in larger amounts than can be obtained from a usual, well-balanced diet (e.g., protein or calcium) is *added*. Finally, in some cases, either the *consistency* of a diet or the content of indigestible residue or fiber is *altered*. The availability of required nutrients is not changed in a major way, but such diets are useful in the treatment of certain intestinal disorders. This chapter begins with a review of the components of a usual, well-balanced diet because many patients do not maintain such diets, either through ignorance or a wish to avoid certain foods that seem to cause symptoms. Useful source books for information on diets are available (1,2).

Normal Diet

To obtain all the essential nutrients, foods from each of the five major groups—dairy products, meat (including nuts), cereals and grains, fruits, and vegetables—should be included in the diet. Macronutrients are required for different reasons. Protein is needed to supply essential amino acids (see Chapter 5 for a discussion of requirements). The essential amino acid content of plant proteins is lower than that of animal proteins. To obtain a mix of essential amino acids comparable with that in animal proteins, protein from various sources must be consumed (Table 12-1). Fats are needed to supply essential fatty acids (see Chapter 11) and vary the flavor of food. When fat is cooked, chemical changes occur that markedly affect food palatability.

Carbohydrates are needed to provide texture and blandness, which offset the stronger flavors of protein and fats to make food pleasant-tasting. However, no carbohydrate is essential for the maintenance or growth of tissue. The distribution of macronutrients in some common foods is listed in Table 12-2. The values in the table refer to unprepared foods. Cooking can modify the components of food greatly (e.g., fried foods) or not at all (e.g., milk).

Micronutrients are distributed widely among the major food classes, but the distributions differ for the individual vitamins and minerals. The food sources for each micronutrient are covered in Chapters 6 and 7, and the information is summarized in Tables 12-3 and 12-4. The content of vitamins and minerals is often higher in more brightly colored fruits and vegetables. For example, vitamin A and carotenoids are more abundant in bright orange vegetables and fruits and in dark green leafy vegetables. Fortified foods are enriched with some micronutrients.

Occasionally, certain foods that are sources of nutrients have special features that must be considered when the foods are used to maintain a balanced diet. For example, grapefruit juice (but not other citrus juices), a good source of vitamin C, contains furanocoumarins (psoralens) that are competitive and mechanism-based inhibitors of the cytochrome P-450 isoform, CYP3A4, and enhances the effect of some medications by down-regulating the intestinal cytochrome P-450 system, thereby increasing their bioavailability (3). Other citrus fruits also contain furanocoumarins, including pummelos and Seville oranges. Grapefruit juice also inhibits the drug transporter P-glycoprotein, but by a

TABLE 12-1. Use of Vegetarian Sources to Provide Adequate Essential Amino Acids

Group	Major components	Limiting amino acids	Other group needed for complete proteins
A[a]	Whole grains, cereals	Lysine, threonine, tryptophan (sometimes)	B or D ± C
B	Legumes, including peanuts	Methionine, tryptophan	A
C	Nuts and seeds, except peanuts	Lysine	A + B or D
D	Vegetables, especially potato	Methionine	A

[a] Also provides iron and riboflavin.
Modified from *Mayo Clinic Diet Manual,* 6th ed. Toronto: BC Decker, 1988.

different mechanism. Other foods suspected to inhibit or induce intestinal CYP3A4 include red wine, broccoli, brussels sprouts, watercress, and cabbage (4). In general, ingestion of 200 to 250 mL of juice taken over a few days is needed to decrease enterocyte CYP3A4 activity, and this effect is greater in African-Americans than in Caucasians (4). A partial list of medications that interact with grapefruit juice include:

- Calcium channel blockers: felopidine, nimodipine, nisoldipine, pranidipine
- Protease inhibitors: saquinavir
- Antihistamines: ebastine, loratadine, terfenadine
- Calcineurin antagonists: cyclosporine, tacrolimus
- HMG-CoA reductase inhibitors: atorvastatin, lovastatin, simvastatin
- Neuropsychiatric: buspirone, carbamazepine, clomipramine, diazepam, methadone, sertraline, trazolam, zaleplon
- Other: sildenafil, losartan

In another example, avocados provide fiber, folate, potassium, vitamin C, and vitamin B_6 in good amounts, but each ounce contains about 50 kcal and 5 g of fat (5). Both of these foods are excellent components of a balanced diet, but the special features of each should be noted. The common macronutrients, vitamins, and minerals contained in foods are listed in Table 12-5, which provides guidelines for maintaining a balanced diet.

Food Guide Pyramid

An alternate method for educating consumers about a balanced diet was devised by the U. S. Department of Agriculture and introduced in 2005 as "MyPyramid,"a personalized approach to healthy eating and physical activity (6). Unlike the previous pyramids that layered nutrients horizontally, the most recent version uses vertical colored bands representing the five food groups (grains, vegetables, fruits, milk, meat and beans) plus oils, to show that foods from all groups are needed each day for good health. The pyramid also emphasizes moderation, and links the ingestion of more added sugars and solid fats with increased activity. Individuals are encouraged to use the website to determine the proportion of various food groups that are important for them (Figures 2-1 and 2-2). In the pyramid, meals are based on grains, fruits, and vegetables, which are supplemented with low-fat milk products and meat, poultry, fish, beans, and nuts.

In practice, the food pyramid corresponds to the basic five food groups plus oils. Depending on age, sex, and degree of daily physical activity, MyPyramid constructs a plan for recommended servings from each group. Table 12-6 provides a few examples of suggested food distribution at three different levels of caloric intake, assuming 30 to 60 minutes of active exercise daily. A variety of vegetables are suggested weekly including (for the

TABLE 12-2. Food Sources of Macronutrients

Food group	Serving	Approximate content			
		Protein (g)	Carbohydrate (g)	Fat (g)	kcal
Dairy					
Milk					
Whole	1 cup	8.5	12	8.5	160
2% with nonfat milk solids	1 cup	10	15	5	145
Skim	1 cup	9	12	0.2	88
Ice cream	1 cup	6	27	14	287
Butter	1 tsp	—	—	5	45
Cream, coffee	2 tbs	1	1.0	6	64
Cheese, slice	1 oz	8	0.5	8	105
Meat, fish, peanut butter					
Chicken, turkey	3 oz	21	—	15	220
Fresh fish	3 oz	21	—	15	220
Lean meats	3 oz	21	—	15	220
Egg	1	7	—	5	75
Shrimp, medium	3 oz	21	—	—	124
Tuna	3 oz	21	—	15	220
Peanut butter	1 oz	7	—	5	75
Cereals and grains					
Bread	1 slice	2	15	—	70
English muffin	1	2	15	—	70
Bagel	1/2	2	15	—	70
Unsweetened cereals	3/4 cup	2	15	—	70
Pasta, cooked	1/2 cup	2	15	—	70
Rice, cooked	1/2 cup	2	15	—	70
Cooked hot cereal	1/2 cup	2	15	—	70
Fruits and vegetables					
Potato chips	1 oz	2	15	12	170
Corn	1/2 cup	2	15	—	70
Peas, beans, lentils (dried and cooked)	1/2 cup	2	15	—	70
Potatoes, baked	1	2	15	—	70
Squash, baked	1/2 cup	2	15	—	70
Other vegetables	1/2 cup	2	15	—	70
Fruit juices					
Apple, grapefruit, orange	1/2 cup	—	10	—	40
Apricot, cranberry, grape Hi-C, prune juice	1/4 cup	—	10	—	40
Berries, melon	1 cup	—	10	—	40
Orange, peach, pear, apple	1 (medium)	—	10	—	40
Grapefruit, banana	1/2	—	10	—	40

2,200 kcal diet) 3 cups of dark green vegetables, 2 cups of orange vegetables, 3 cups of dry beans and peas, 6 cups of starchy vegetables, and 7 cups of other vegetables. In addition, it is suggested that half of the grains ingested be whole grains. The use of whole grain foods is essential to realize the distribution recommended by the food pyramid. Packaged foods with a high content of whole grains are those that list *first* among their ingredients one of the following: whole barley, cornmeal, oats, rye, wheat, brown rice, bulgur, cracked wheat, graham flour, or oatmeal. Enriched grains have for years contained added thiamine, riboflavin, niacin, and iron. Whole grain foods contain folate, but folic acid is now added to some grain products (mainly ready-to-eat cereals) to reduce the risk for certain serious birth defects.

TABLE 12-3. Food Source of Vitamins

Vitamin	Meat/fish/ eggs	Grains	Vegetables/ fruits	Dairy	Nuts/beans	Comments
B_1	+	++	+	++	+	Grain products enriched
B_2	++	+	+	+	+	Especially organ meats
Niacin	++	+	+	—	—	Grain products enriched
B_6	+	++	+	+	—	Produced by bacteria
Folate	+	+	++	+	++	Especially green leafy vegetables, organ meats, eggs, whole grains, dried beans
B_{12}	++	—	—	++	—	Foods of animal origin only
C	—	—	++	—	—	Especially citrus fruits, green vegetables
A	++	—	++	+	—	Especially liver, pigmented vegetables, fruits
D	++	—	—	++	—	Milk enriched; made in skin; high levels in liver, fish, and eggs
E	++	—	++	+	+	Only in animal or vegetable fat
K	+	—	++	—	—	Especially green leafy vegetables; made by enteric bacteria

Estimates of content refer to raw food. Water-soluble vitamins are extracted into the cooking water. +, present in appreciable amounts; ++, daily portion contains about 25% of RDA.

Plant whole foods are very important in the diet, but these foods contain a variety of components including fiber, proteins, lipids, vitamins, minerals, antioxidants, and a variety of anticarcinogenic chemicals (7). Thus, it is difficult to know which vegetables should comprise the portions of food groups that include plants (grains, fruits/vegetables, beans). Should they contain roots or stalks? Should they be red, green, or yellow? Should they be eaten raw or cooked? A list of examples of foods offered as part of each of these food groups in the MyPyramid website is given in Table 12-7.

One can obtain a meal tracking worksheet for each individual plan. In this most recent version of MyPyramid, allowance is made for ingesting some oils and sugars, and somewhat fewer servings of the other food groups. In the last iteration of MyPyramid, the recommendations were provided as servings, creating difficulty in defining one serving. The definitions were generally clear in principle, but often hard to follow in practice. The advantage of the current food pyramid is that it is more practical than before, and is individualized and interactive on the website.

Every adult and child should ingest a diet balanced with components from each of the major food groups. Individual items may be eliminated because of intolerance, but

TABLE 12-4. Food Source of Minerals

Mineral	Meat/fish/eggs	Grains	Vegetables/fruits	Dairy	Nuts/beans	Comments
Na	+	+	—	++	+	Especially processed food
K	++	+	++	+	+	Especially meat, milk, fruits
Ca	+	—	+	++	++	Especially dairy, meat, fish
P	+	+	+	+	+	Widely distributed
Mg	+	+	+	+	+	Widely distributed
Fe	++	—	+	—	++	Heme iron best
Zn	++	+	—	—	—	Complexes in grain less bioavailable
I	++	—	—	+	—	Seafood best, salt enriched
Cu	++	—	+	—	++	Shellfish, organ meats best
Mn	+	++	+	—	++	Organ, not muscle meats
F	+	+	+	+	+	Drinking water enriched
Cr	+	+	+	+	+	Widely distributed
Se	++	+	—	—	—	Especially organ meats, fish

+, present in appreciable amounts; ++, daily portion contains about 25% of RDA.

all macronutrients and micronutrients essential for tissue maintenance and growth should be consumed. When an entire food group is eliminated (e.g., dairy products for lactose intolerance or meat for an ovo-lacto-vegetarian diet), the nutrients supplied by that group (e.g., calcium or protein) must be obtained from other food groups (Table 12-5).

The need to maintain adequate nutrition in children is even more pressing than in adults. Undernutrition in 62,000 children from many nations, aged 6 to 72 months, was a cause of increased mortality associated with diarrhea, pneumonia, malaria, and measles (8). In 24,396 children less than 3 months of age from India, wasting, stunting, or underweight were risk factors in developing diarrhea or acute respiratory infection (9).

Vegetarian Diets

The vegetarian diets include strict vegan (without milk or eggs), lacto-vegetarian, ovo-vegetarian, and lacto-ovo-vegetarian. The strict vegan diet compared to an omnivore diet contains lower fat, less saturated fat, a high polyunsaturated/saturated fat ratio, no cholesterol, about 50% to 100% more fiber, and somewhat less protein (10). A lacto-ovo-vegetarian diet contains intermediate ranges of these components. The more milk and cheese is ingested, the higher the animal fat and cholesterol content. But all vegetarian diets contain more plant foods, bringing with them higher intake of fiber, folate, antioxidants, and phytochemicals. These components are thought to account for many of the lower risks that have been observed for developing cancer (especially colon and lung), obesity, heart disease, type 2 diabetes, hypertension, constipation, and gallstones (11). The risks of vegetarian diets are mostly seen with strict vegan diets, and include osteopenia from low calcium intake, vitamin B_{12} deficiency, and impaired growth from low energy intake. Vegetarian diets are now considered to offer more health benefits than risks (11).

TABLE 12-5. Distribution of Nutrients among Food Groups for Balanced Meals

Food group	Major nutrients	Minimum recommended number of servings[a]					
		Child	Teenager	Adult	Pregnant woman	No meat	No milk
Dairy products	Calcium, vitamin D,[b] protein, vitamins B_1 and B_2, vitamin A[b]	3	4	2	4	4	0
Meat and meat alternates (beans, nuts, peas)	Protein, Zn, Fe, vitamins B_1, B_2, B_6, and B_{12}, folate, niacin	1–1 1/2	2	4	3	3 (legumes)	6 (2 legumes)
Fruits and vegetables[c]							
Vitamin A-rich	Vitamin A, Mg, vitamins C and B_6, folate	1/2	1	1	1	1 1/2	3
Vitamin C-rich	Vitamins C and A, niacin, folate, carbohydrate	1/2	1	1	1	3	3
Others	Vitamin B_6, folate, niacin, K, carbohydrate	2	2	2	2	0	0
Enriched or whole-grain cereals and breads	Vitamins B_1[b] and B_2,[b] niacin,[b] protein, carbohydrate, Fe,[b] Mg	4	4	4	4	6	3
Oils and fats	Essential fatty acids, vitamins E and A[b]	Depends on caloric need					

[a] A serving equals 1 cup milk or milk products; 3 oz meat, poultry, or fish; 3/4 cup cooked legumes; 1 oz nuts; 3/4 cup cooked or 1 cup raw vegetables or fruit; 1 oz dry cereal; 1/4 cup cooked cereal or pasta; 1 slice bread; 1 tbs oil.
[b] Often fortified in the food.
[c] Representative fruits and vegetables: vitamin A—broccoli, green peppers, collards, carrots, spinach, sweet potato, cantaloupe, plums, squash; vitamin C—citrus fruits and juices, tomatoes, strawberries, green pepper, watermelon, brussels sprouts; other—banana, apple, pear, grapes, potatoes, corn, peas, green beans.

TABLE 12-6. Examples of MyPyramid Plan

Daily intake Appropriate groups	1,600 calories[a] Children 6–8 years, women, some older adults	2,200 calories[a] Older children, teenage girls, active women, most men	2,800 calories[a] Teenage boys, active men
Grains (oz)	5	7	10
Vegetables (cups)	2	3	3.5
Fruits (cups)	1.5	2	2.5
Milk, yogurt, and cheese (cups)	3[b]	3[b]	3[b]
Meat poultry, fish, dry beans, eggs, nuts & beans (oz)	5	6	7
Oil (tsp)	5	6	8
Sugar and fat limit (kcal)	130	240	425

[a] These are the calorie levels if you choose low-fat, lean foods from the five major food groups, use foods from the fats, oils, and sweets group sparingly, and perform 30 to 60 minutes of physical activity daily.
[b] Women who are pregnant or breast-feeding, teenagers, and young adults to age 24 need three servings.
Adapted from U.S. Department of Agriculture, *MyPyramid.gov, 2005.*

TABLE 12-7. Examples of Foods within the Five Major Food Groups Suggested by *MyPyramid.gov*

Whole grains, including the whole kernel (bran, germ, and endosperm): whole-wheat flour, bulgur, oatmeal, whole cornmeal, brown rice, whole wheat cereals, popcorn, amaranth, millet, quinoa, sorghum, triticale. Check ingredient list for the words "whole grain or whole wheat."
Refined grains, milled to remove bran and germ along with dietary fiber, iron, and many B vitamins: white flour, white bread, white rice, degermed cornmeal, most of the following; cornbreads, corn tortillas, flour tortillas, crackers, grits, noodles, pasta, breakfast cereals. Products with added bran are not necessarily whole grain products.
Vegetables:
Dark green: bok choy, broccoli, collard greens, kale, mesclun, romaine lettuce, spinach, turnip greens, watercress
Orange: acorn/butternut/hubbard squashes, carrots, pumpkin, sweet potatoes
Dry beans and peas: beans (black, garbanzo, kidney, lima, navy, pinto, white), lentils, black-eyed or split peas
Starchy: corn, green peas, lima beans, soy beans, potatoes
Others: artichokes, asparagus, beets, brussels sprouts, cabbage, cauliflower, celery, cucumber, eggplant, green beans, green/red peppers, lettuces, mushrooms, onions, tomatoes, turnips, zucchini
Fruits: apples, apricots, avocado, bananas, berries, cherries, grapefruit, grapes/raisins, kiwifruit, lemons, limes, mangoes, melons, nectarines, oranges, peaches, pears, papaya, pineapple, plums/prunes, tangerines, 100% fruit juices
Milk, yogurt, and cheese: All fluid milks, flavored milks, lactose-reduced or free milks, milk based desserts (ice milk, frozen yogurt, ice cream, puddings), cheese (hard, soft, or processed), all yogurt
Meat, poultry, fish, dry beans, eggs, and nuts (meat & beans): Lean cuts of beef, ham, lamb, pork, veal, rabbit, venison, lean ground meats, lean luncheon meats, liver, poultry, eggs, dry beans (see list under vegetables), nuts and seeds, all fish, all shellfish, canned fish. If higher fat choices of meat or poultry are selected, or if solid fat is used in the cooking, that fat counts as part of the discretionary calorie allowance for sugar and fat. Fish rich in omega-3 fatty acids include salmon, trout, and herring especially. Egg yolks and organ meats are high in cholesterol. Processed meats are high in sodium and often in fat. Nuts and seeds are high in vitamin E.
Oils: All liquid oils (canola, corn, cottonseed, olive, safflower, soybean, sunflower), natural foods high in oil (nuts, olives, some fish, avocados), foods that contain mainly oils (mayonnaise, some salad dressings, soft margarine, all solid fats (butter, tallow, suet, lard, chicken fat, stick margarine, shortening)

Practical Aspects

Food should be consumed as three daily meals. This practice avoids periods of great hunger with subsequent overeating and provides energy for tasks to be performed throughout the day.

Snacks can certainly be a part of the diet and can include foods from any of the major groups. *Junk* or *fast foods* also can be included in a balanced diet. It is only when most of the daily calories are derived from these foods that they pose a problem. Fast foods often contain many calories in the form of fat and carbohydrates, with lesser amounts of protein. Moreover, they usually do not include fruits and vegetables and so do not provide all the micronutrients needed.

The term *empty calories,* which has been used to describe the nutritive value of these foods, is a poor one. The caloric value of fast foods is as real as that of any other foods because all calories are equal. The foods lack many of the other nutrients, but the caloric value is the same.

The best way to entice a patient to follow a *balanced diet* is to review food lists, identify the perceived problems in the intake of all foods, and provide specific recommendations for foods in each major group. In addition, the health care provider must discover what behavioral patterns accompany the abnormal or irregular intake of food if an attempt to correct the diet is to be made.

The average *hospital house diet* is balanced as far as nutrients are concerned, although the palatability is not always good because the flavors are usually quite bland. The hospital diet provides each day between 2,000 and 2,500 kcal, 60 to 80 g of protein, 2.5 to 3.5 g of sodium, 3.5 to 4.5 g of potassium, 1.0 to 1.3 g of calcium, 1.1 to 1.5 g of phosphorus, 300 to 400 mg of magnesium, 7 to 9 mg of iron, and 13 to 14 mg of zinc. However, many teaching hospitals do not design house diets to meet nationally recognized dietary recommendations (12). Moreover, they do not always provide enough information for the patients to select appropriate and healthful choices.

Dietary Guidelines for Americans

Many guidelines have been developed to provide a diet to minimize the risks for major chronic conditions, such as heart disease, cancer (see Chapter 15), stroke, diabetes, hypertension, dental caries, alcoholism, and obesity. With all diets, the following measures are recommended: achieving and maintaining a desirable body weight, decreasing total lipid intake to 30% of total caloric intake, decreasing saturated fatty acid to less than 10% of total calories, decreasing cholesterol intake to less than 300 mg per day, increasing complex carbohydrate and fiber intake, and decreasing salt intake. All these recommendations are included in *Nutrition and Your Health: Dietary Guidelines for Americans, 2000* and are discussed in detail in Chapters 2 and 3 and other chapters as noted.

1. Eat a variety of foods (see Chapter 12).
2. Maintain ideal weight (see Chapter 14).
3. Avoid excess fat (total and unsaturated) and cholesterol (see Chapter 13).
4. Eat foods with adequate dietary fiber (see Chapter 12).
5. Avoid excess sugar (see Chapter 13).
6. Avoid excess salt (see Chapter 7).
7. Recognize protein sources for vegetarian diets. *Lacto-ovo:* dairy and egg products provide complete protein. *Vegan:* A full complement of protein is provided by a variety of grains, legumes, vegetables, seeds, and nuts. Many grains contain approximately 3 to 8 g protein per portion, legumes provide 12 to 18 g per portion, and nuts provide 4 to 7 g per portion (10). Soybeans match human needs for essential amino acids, and so are a complete protein source.

The results of the National Research Council study on diet and health are available to patients in a user-friendly guide (13). Vegetarian diets achieve many of these objectives because they reduce the risks for hypertension, coronary artery disease, diabetes (type 2), and gallstones (10,11). Diets designed to prevent cancer or heart disease are based on similar recommendations. The dietary recommendations outlined above and discussed in

Chapters 2 and 3 are intended for general populations in the United States. However, some special considerations should be emphasized for African-Americans and other minority groups. The diets of middle-aged African-Americans may be lower in calcium, magnesium, iron (for women), folacin, and zinc. Obesity is more prevalent in African-American women than in white women, and it may be more difficult for them to achieve a desirable weight. Hispanic-Americans tend to consume a diet higher in fiber and with less animal fat. Overweight has been a greater problem in Hispanic-Americans than in Anglo-Americans. The diet of Asian/Pacific-Americans is generally higher in fish, shellfish, and fruits and vegetables but lower in dairy products and calcium. As these populations become more assimilated into Anglo-American societies, group differences may diminish.

The American Heart Association has issued its revised diet and lifestyle recommendations, designed to reduce the risk of cardiovascular disease (14). However, these recommendations are very similar to all other evidence-based healthy diets. Because they are the most recently published (2006), they are highlighted here. Recommendations include the suggestions to:

- Achieve and maintain a healthy body weight (body mass index [BMI] 18.5 to 24.9)
- Consume a diet rich in vegetables and fruits (especially those that are deeply colored)
- Select whole-grain, high-fiber foods (half of grain intake should be whole-grain)
- Consume fish at least twice a week (especially oily fish rich in omega-3 fatty acids)
- Limit intake of saturated fat to <7% of calories, *trans* fat to <1% of calories, and cholesterol to <300 mg per day by selecting lean meats, skim and low-fat dairy products, and minimizing intake of partially hydrogenated fats by substituting solid margarines with liquid vegetable oils
- Minimize intake of beverages and foods with added sugars (especially sucrose and corn syrup)
- Choose and prepare foods with little or no salt (limit to 2.3 g of sodium per day)
- Consume alcohol in moderation (less than two drinks per day for men, one drink per day for women)

Alcohol

Alcohol is a component of many diets, and the carbohydrate and caloric load should be appreciated, as these can be considerable (Table 12-8).

TABLE 12-8. Nutritional Composition of Alcoholic Beverages

Beverage	Serving size (oz)	Alcohol (% vol)	Calories (kcal)	Carbohydrate (g)
Beer	12	4–5	140–150	10–11
Light beer	12	~4.3	~110	6–7
Wine, red	5	11.7	105	2.5
Wine, dry white	5	11.7	94	1.3
Gin & tonic	7	13.8	190	15.5
Martini	2	40.7	119	0.1
Bloody Mary	4.6	15.7	120	4.5
Frozen daiquiri	4.7	19.3	190	15.5
Manhattan	2.3	38.2	137	3.4
Margarita	3.5	41.4	221	11.3
Pina colada	6	24.1	644	91.8
Screwdriver	7	13.8	208	16.1

Mixed drink source: www.drinkmixer.com; wine data source: USDA Nutritional Database SR17, 2004; calorie and carbohydrate source: Borushek A, *The Doctor's Calorie Fat and Carbohydrate Counter*, Family Health Publications, 2004.

Taste and Smell

One major factor in maintaining an adequate oral intake is the presence of normal taste and smell. It is now clear that the gustatory system, unlike other sensory systems, is comprised of many (~50) different receptors concentrated in only a few cell types, providing clues to perceive thousands of different smells by a combination of receptor activation (15). Thus, sensing sweet, salty, bitter, and amino acids is probably coordinated within the brain. This unusual sensory architecture may be the reason why people lose smell and taste acuity as they age, and this change is associated with poorer appetite and food intake (16). In addition, many elderly people are unaware of this impairment in smelling acuity. Other important causes of altered taste and smell include depression, the postmenopausal state, and many medications, particularly halide salts that are concentrated in salivary secretions.

DIETS OF ALTERED CONSISTENCY

Clear Liquid Diet

A clear liquid diet meets the daily requirement for water but minimally stimulates the gastrointestinal tract. This effect is achieved at the cost of minimal ingestion of protein and fat—macronutrients that are potent stimuli of gastric and pancreatic secretions and gastrointestinal motility. In addition, the diet is low in fiber. Because few unabsorbed components are provided, fecal weight and bacterial mass are decreased.

A clear liquid diet is used in the following cases: To treat dehydration resulting from excessive diarrhea or vomiting (if the vomiting has ceased), in mild or moderate pancreatitis as a prelude to introducing full feeding, to decrease output from enterocutaneous fistulae, to manage diarrhea resulting from inflammatory bowel disease (IBD), to maintain nutrient intake during chemotherapy or radiation therapy for cancer, and to prepare a patient for bowel surgery or for colonoscopic examination (17). In the surgical setting, a clear liquid diet is useful in the recovery phase of abdominal or other surgery when partial ileus is present. This restriction may not be applicable to patients after gastrointestinal surgery once bowel sounds have been heard. Early refeeding by tube or per os of either liquid or solid food has been used successfully after gastrointestinal surgery and may be beneficial for reducing hospital stay and complications (18). There seems to be no clear advantage to withholding feeding from patients following lower bowel surgery, and perhaps even after upper abdominal surgery. A clear liquid diet may be useful preoperatively as well, as some data suggest that preoperative fasting has adverse consequences for the patient, especially insulin resistance (19). No studies are available demonstrating an effect of preoperative fasting on differences in morbidity and mortality.

Increased intake of calorie-containing beverages (150 to 300 kcal per day) has been associated with an increase in weight in the United States. A Beverage Guidance Panel was organized and has issued a report (20). This panel concluded that drinking water should be the preferred beverage to fulfill daily water needs, followed by tea and coffee, low fat and skim milk, noncalorically sweetened beverages, beverages with some nutrients (juices, whole milk, alcohol, and sport drinks), and least of all calorically sweetened but otherwise nutrient-poor beverages. The clear liquid diet designed for medical purposes needs to use caloric beverages, but it is worth remembering that in other circumstances, it is better to drink calorie-poor beverages, mainly water.

The clear liquid diet is largely water and sugar and provides few other nutrients unless supplements are added. Without supplements, the diet provides about 1,200 kcal per day (300 g of carbohydrates) along with 1.0 g of sodium, 50 to 60 mg of calcium and magnesium, 2,000 to 2,500 mg of potassium, less than 100 mg of phosphorus, 1.2 mg of iron, and only 0.33 mg of zinc. To obtain even this supply of nutrients, one must ingest about 1,500 mL of strained fruit juice, 600 mL of gelatin or fruit ice, and 30 g of sugar added to coffee or tea. Intake of these volumes can be achieved by healthy or younger patients.

The diet of an elderly or ill patient may be even more restricted because intake is smaller. *Patient information on this topic is available in Appendix D.*

Multiple vitamin and iron supplementation is suggested if the patient is to be on the diet for more than 3 weeks, or sooner if deficiency is present when the diet is initiated. If the diet is to be continued beyond 3 days or if fluid intake is limited, it can be supplemented with carbohydrate and a small amount of protein in addition to some micronutrients. Table 12-9 lists these modifications. The supplemented clear liquid diet provides about half the daily adult protein allowance, and it meets or exceeds allowances for vitamins E and C, folic acid, thiamine, riboflavin, niacin, vitamins B_6 and B_{12}, and iron. Vitamin A, calcium, and phosphorus are provided at about 60% of the daily allowance. Carbonated beverages can be substituted for Polycose as a source of carbohydrate, but they have many fewer calories. The use of supplements depends on the acceptability of fruit juices and gelatins as the major caloric source for the patient. Foods allowed include coffee, tea, carbonated beverages, broth, bouillon, strained fruit juices, gelatin, sugar, and sugar candies. Side effects do not develop if supplements are provided. Calories, protein, vitamins, and minerals are needed in the usual circumstances during long-term use.

Caffeine

It is generally agreed that the caffeine content of various beverages alters certain aspects of gastrointestinal function (e.g., transit time is shortened), and causes unwanted alertness and a jittery feeling. For this reason, the inclusion of caffeinated beverages may not be desirable in other diets. However, these drinks are usually included in a clear liquid diet. Table 12-10 lists the caffeine content of some foods and drugs. *Patient information on this topic is available in Appendix D.*

The caffeine content of beverages depends on the amount of water used, method of brewing, and type of coffee or tea. Because caffeine is water-soluble, the longer the exposure to hot water, the greater the extraction of caffeine. Coffee is a complex mixture of

TABLE 12-9. Nutritive Value of Clear Liquid Diets

Diet	Protein (g/d)	Fat (g/d)	Carbohydrate (g/d)	Total calories per day
No supplements (~2.5 L intake)	12	0	300	1,200
No supplements (<1 L intake)	6	0	74	320
+ Ensure (three 8-oz servings) (Ross)	32	26	167	1,040
+ Polycose (three 4-oz bottles) (Ross)	6	0	254	1,040
+ Citrotein (three 8-oz servings) (Sandoz Nutrition)	29	1	144	700
Vivonex Plus (with flavor pack, four 300 mL servings) (Novartis)	54	8	228	1,200
Enlive (four 240 mL servings) (Ross Laboratories)	40	0	260	1,200
RESOURCE fruit beverage (four 240 mL servings) (Novartis)	36	0	214	1,000
NuBasics Juice Drink (four 250 mL servings) (Nestle Clinical Nutrition)	39.6	0.6	208	1,000

Vivonex Plus, Enlive, RESOURCE, and NuBasics Juice Drink are commercially available clear liquid supplements that are intended to serve as the total daily nutritional provision. They contain varying amounts of sodium (183, 65, <80, and 77 mg per serving, respectively) and potassium (317, 40, <20, and 77 mg/serving, respectively), and all are hyperosmolar (650, 840, 750, and 1,000 mOsm/kg of water, respectively).

TABLE 12-10. Caffeine Content of Foods and Drugs

Food	Unit	Caffeine content[a] (mg/unit)
Prepared coffee	**6-oz cup**	
Instant, freeze-dried		61–72
Percolated		97–125
Drip		137–174
Starbuck's Coffee Grande[b]	16-oz cup	259
Decaffeinated coffee	**6-oz cup**	
Ground		2–4
Instant		0.5–1.5
Tea, bagged or loose	**6-oz cup**	**15–75**
Black, 5-min brew		40–60
Green, Japan, 5-min brew		20
Iced	12-oz cup	67–76
Cocoa beverages	**6-oz cup**	**10–17**
Chocolate		
Chocolate milk	8 oz	2–7
Milk chocolate	1 oz	1–15
Semi-sweet	1 oz	5–35
Baker's	1 oz	26
Syrup	1 oz	4
Bar	One	60–70
Carbonated drinks	**12-oz can**	
Colas[c]		45–55
Diet colas		0.3
Root beer, citrus		0
Ginger ale, tonic, other nondiet		0–22
Drugs	**Tablet**	
Cold tablets		30–32
Alertness tablets		100–200
Weight control tablets		140–200
Pain relief OTC		32–65
Prescription pain tablets		30–100
Dietary supplements[c]	**Capsule/powder**	**100–200**
Sport drinks[c]		
AMP energy	8.5 oz	75
Full Throttle	16 oz	144
Red Bull	8.5 oz	80
SoBe No Fear	16 oz	158

[a] The ranges represent the range of figures from the literature because the method of preparation affects caffeine content of some beverages.
[b] Data from Mayo Clinic Diet Manual (www.mayoclinic.com/health/caffeine), Adapted from Nagy M. Caffeine content of beverages and chocolate. *JAMA* 1974;29:337, and from Bunker ML, McWilliams M. Caffeine content of common beverages. *J Am Diet Assoc* 1979;74:28.
[c] Data from Haller A, Juan M, Benowitz NL, Jacob P. Concentrations of Ephedra alkaloids and caffeine in commercial dietary supplements. *J Analytical Toxicol* 2004;28:145. Supplements include Diet Fuel, Dymetradine Xtreme, Metabolift, Metacuts, Ultra Ripped, Hydroxycuts, Ripped Fuel, and Ripped Force.

chemicals and provides more than caffeine alone. Unfiltered coffee contains the diterpenes cafestol and kahweol that have been implicated in elevating cholesterol (21).

Low doses (<50 mg per day) probably have little effect on gastrointestinal function. The actual caffeine content of cocoa is not certain because of the wide variation in reported figures and the fact that most hospitals and homes now use instant cocoa mix, a prepared

product. Theobromine, not caffeine, is the major methylxanthine stimulant in cocoa (~250 mg per cup) and chocolate. Caffeine is also a component of some over-the-counter analgesics and of many dietary supplements. These sources should be considered when caffeine intake seems important.

The health consequences of caffeine ingestion are not severe (22). For those patients with hypertension or hyperhomocysteinuria, or for groups that might be more vulnerable to the effects of caffeine (elderly, children, adolescents), limiting intake may be helpful. A subset of patients with restless leg syndrome may have attacks triggered by caffeine (23). No consistent epidemiologic evidence has been found of an effect on birth-related outcomes, including low birth weight, prematurity, spontaneous abortion, and congenital anomalies. However, many studies have not been controlled for smoking, alcohol, or medication. In one case–control study, more spontaneous abortions occurred in nonsmoking women who ingested more than 100 mg of caffeine a day when the fetus had a normal karyotype (24). The risk was proportional to the dose of caffeine ingested. Considering the mixed results of earlier studies, one could cautiously recommend reducing caffeine intake during early pregnancy, limiting coffee consumption to 3 cups per day (21). The hypercalciuric effect of 300 mg of caffeine has been well established in women with a diet low in calcium (<600 mg per day), but the mechanism is not clear. However, no effects have been noted on bone health, and caffeine is not considered an important risk factor for osteoporosis, except possibly when used on a long-term basis by persons with a dietary calcium deficiency. The pharmacologic effects on the cardiovascular, renal, respiratory, gastrointestinal, and central nervous systems have been studied extensively (22). Consumption of up to 500 mg of caffeine does not cause arrhythmias, but some patients may be especially sensitive to caffeine and should limit their intake. Although data have been reported on both sides of the issue, it does not appear that caffeine causes hypertension or coronary artery disease, nor are the data convincing that caffeine causes hyperlipidemia or fibrocystic breast disease.

Although habituation to caffeine is common, it is not considered a drug of abuse, and it does not fulfill the Diagnostic and Statistical Manual-IV criteria for psychoactive substance dependence. Headache is a frequent withdrawal symptom. Because coffee contains many more chemicals than caffeine, studies of coffee intake have shown some interesting differences from that of caffeine alone. Coffee ingestion is associated with a lower risk of type 2 diabetes, but prospective studies are needed to confirm the relationship (25). Coffee intake does not seem to increase the risk of heart disease or cancer, and 3 to 4 cups per day (300 to 400 mg caffeine) appear not to carry any long-term health risk (21). Although no increased risk of colon and rectal cancer was seen with ingestion of caffeinated coffee or tea, ingestion of >2 cups of decaffeinated coffee was associated with a decreased risk of rectal cancer (26). Tea ingestion may improve endothelium-dependent vasodilation. A meta-analysis of prospective cohort studies concluded that an increase in tea consumption of 24 oz per day was associated with an 11% decrease in myocardial infarction (27). But the results of subsequent studies have been inconsistent, and firm conclusions cannot be made (20).

Full Liquid Diet

The full liquid diet is designed to provide adequate nourishment in a form that requires no chewing. Such a diet can also be useful when the esophagus is narrowed and solid food cannot pass. The full liquid diet (or mechanical soft diet) is indicated for patients who cannot chew properly or who have esophageal or stomach disorders interfering with the normal digestion of solid foods. Liquid supplements (500 kcal) given to patients postoperatively after major abdominal surgery led to improved weight (28). This diet can be used in conjunction with dilation in the management of esophageal stricture. Available methods for dilation include bougienage with mercury-weighted rubber catheters or with metal (olive) dilators.

The diets in which table foods are used can be maintained for long periods only when appropriate supplementation is provided or when all allowed food groups are included. Otherwise, this diet can be nutritionally incomplete. Alternatively, commercially available

liquid diets can be used alone (see Chapter 10). However, long-term acceptability is greater when table foods are used as the major source of nutrition.

Full liquid diets can be given through a gastrostomy tube to bypass esophageal obstruction. In such cases, enteral supplements that supply all nutritional needs may be preferred (see Chapter 10) because taste is no longer a factor. Full liquid diets can be helpful temporarily after many types of surgery for debilitated patients who may not have recovered sufficient strength to chew food. Usually, this phase of recovery lasts no more than a few days, except after laryngectomy, when soreness and swelling are present and a new swallowing technique must be learned. In such instances, the use of creamier foods and thicker liquids makes it easier for patients to relearn how to swallow.

Practical Aspects

Certain characteristics of this diet should be kept in mind, especially for successful long-term use:

1. Foods need not be bland.
2. Milk-based foods form an important part of the diet. Lactose intolerance presents a problem when this diet is used, but many milk substitutes are now available, based on either corn syrup or soy.
3. Flavoring is helpful for some milk-based liquids, but natural or vanilla flavor is best tolerated for long-term use.
4. Caloric intake should be maintained near the estimated requirement.
5. Medications should be given in liquid form if possible.
6. Table foods allowed on a full liquid diet include all beverages, broth, bouillon, strained cream soups, poached or scrambled eggs, cereal (e.g., cream of wheat, farina, strained oatmeal), strained fruit juices, ice cream, sherbet, gelatin, custards, puddings, tapioca, yogurt without fruit, margarine, butter, cream, and all spices.
7. The full liquid diet easily provides adequate calories, protein, and essential fatty acids but not certain vitamins, notably ascorbic acid and thiamine, unless fruit juices and cereals are routinely included. The average hospital full liquid diet provides 1,900 to 2,000 kcal per day, along with 40 to 50 g of protein, 3 to 4 g of sodium, 3 to 4 g of potassium, 1.8 g of calcium, 1.3 g of phosphorus, 200 to 300 mg of magnesium, 3 mg of iron, and 8 to 9 mg of zinc.

Side Effects

The diet can be boring, and it is wise to include some items from the mechanical soft diet. If lactose intolerance is present, diarrhea may result, and milk substitutes can be used. If meat soups or brewer's yeast are not used, the diet will be deficient in folic acid, iron, and vitamin B_6.

Supplements Required

No supplements are required if all food groups are used. However, a multiple vitamin and mineral preparation, preferably liquid, is not unreasonable if this diet is to be used for a long time.

Mechanical Soft Diet

The mechanical soft diet is designed to provide a greater variety of foods than the full liquid diet for patients who find it difficult to chew or have an anatomic stricture. Patients with dysphagia may require a liquid or soft solid diet. A history of coughing or choking during meals, prolonged eating time, hoarseness after eating, regurgitation of liquid or food into the nose, frequent drooling, recurrent respiratory infections, and weight loss should lead to an evaluation of oral or pharyngeal swallowing problems. The diet must be planned individually depending on the reason for the restriction. The entire range of solid and liquid foods is used so that the diet is nutritionally balanced. One attempts to provide easily masticated foods. Because texture is an important part of taste, patients must choose the foods that they tolerate best and are most acceptable to them.

A mechanical soft diet is indicated for patients who have difficulty chewing because of advanced age or infirmity, postoperative weakness, or dental problems. It is also indicated for patients with anatomic strictures of the esophagus, especially those caused by carcinoma. For patients with strictures in other parts of the intestinal tract, such as the duodenum in active Crohn's disease, only certain restrictions may be necessary because gastric grinding/mixing softens food.

Practical Aspects

Spices (except hot peppers) are allowed and are in fact desirable to make food more palatable. Food thickeners, largely gums and modified starches, are available as an aid in swallowing to avoid aspiration. Patients with oral or pharyngeal dysphagia should eat slowly, sit up as straight as possible, keep their head in an optimal position for swallowing (as determined by swallowing studies), and ingest small amounts at any one time.

1. **Foods allowed on a mechanical soft diet.** All beverages and soups are allowed. Whole tender meat is permissible, as is ground or puréed meat, but not fibrous meat. Eggs and cheese are permissible. Melted cheese or nonfat dry milk can be used to increase protein content. All potatoes and starches are allowed. Breads and cereals are acceptable, except for high-fiber cereals and hard, crusty breads. Cooked or refined ready-to-eat cereals are often better. Vegetables can be included if they are well cooked or puréed, but raw vegetables must be shredded or chopped. Foods that are hard to chew must be chopped, ground, or blended. Canned or fresh fruits without skin or seeds are acceptable, but not other fresh or dried fruits. Nuts are not allowed. Desserts are acceptable if they do not contain nuts.
2. The bland diet is often combined with a mechanical soft diet and has been used for years in the treatment of ulcer disease. However, no evidence has been found of the value of a bland diet that restricts spices or coarse foods.
3. Some dietary maneuvers have been helpful in the past in the management of acid peptic disease, such as the use of small, frequent feedings to minimize acid secretion after a meal and the avoidance of snacks before bedtime to prevent acid stimulation during sleep. Other dietary modifications in peptic disease have included the elimination of alcoholic and caffeine-containing beverages and smoking. However, with the current availability of potent acid-suppressing medications, these restrictions are now usually unnecessary.
4. Certain dietary restrictions also may benefit patients with gastro-esophageal reflux disease (GERD). Foods that increase lower esophageal sphincter pressure include tomatoes and tomato juice, citrus fruits, chocolate, peppermint, and very fatty foods. However, the value of restricting fatty foods in the treatment of GERD has been questioned (29).

Side Effects

No side effects have been associated with this diet.

Supplements Required

Supplements are not required.

Modified-Fiber Diets

Dietary fiber is not one chemical substance, nor is it completely indigestible. It is a component of the diet that either by itself or through its metabolites produces certain physiologic effects in humans, although the nature and importance of these effects are as yet poorly delineated. *Fiber* is not the same as *residue*. The latter term refers to all stool solids that result from the ingestion of any given diet. In addition to fiber, residue includes bacteria, exfoliated cells, and mucus. A full or clear liquid diet is best for minimizing fecal residue.

Definition

The accepted definition of dietary fiber by the American Association of Cereal Chemists (2000) is "the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Dietary fiber includes polysaccharides, oligosaccharides, lignin, and

associated plant substances. Dietary fibers promote beneficial physiological effects including laxation, and/or blood cholesterol attenuation, and/or blood glucose attenuation" (30). About the same time as the AACC document was prepared, the Institute of Medicine (IOM) prepared a volume on dietary reference intakes that included fiber, recognizing that nondigestible carbohydrates could be isolated and when added to products might produce a health benefit (31). Thus, the IOM definitions are as follows: "Dietary fiber consists of non-digestible carbohydrates and lignin that are intrinsic and intact in plants. Functional fiber consists of isolated, nondigestible carbohydrates that have beneficial physiological effects in humans. Total fiber is the sum of dietary fiber and functional fiber."

Fiber Content

The fiber content of foods is most commonly based on the rather indirect and imprecise measurement of *crude fiber*—the residue of food that remains after sequential acid and alkali treatment. The relationship between the measurement (of the residue that escapes digestion) and the physiologic role of the residue is confusing. A proposal for a definition of methods of analysis has been made by the Codex Committee on Nutrition and Foods for Special Dietary Uses (32). This group has stated that nondigestible material is composed of carbohydrate polymers with a degree of polymerization >3, and that these polymers can be present in food when raw or prepared, or added back as synthetic polymers. Furthermore, dietary fiber that is not digested or absorbed in the small intestine should result in increased stool bulk, reduced blood total or LDL cholesterol, or reduced postprandial blood glucose or insulin levels. All these definitions and inclusions have caused a major issue with regulators and consumers (33). The division of fiber into dietary and functional fiber has created much of this confusion. Although U.S. labeling does not distinguish dietary from functional fiber, many products called functional fiber are on the market. Canadian regulators have concluded that a synthetic or "novel" fiber, when produced and added back to food, can be included in the total for dietary fiber if it meets the accepted definitions (is not digested and is polymerized enough) and has a proven physiological function (34). However, this is a difficult hurdle, as only four novel fibers have been approved since 1985 (ground bleached oat hulls, soy cotyledon, sugar beet fiber, and psyllium seed husk) (33). For an understanding of the uses of altered-fiber diets, the definition, measurement, metabolism, and possible functions of dietary fiber and functional fibers should be considered.

Classes of Fiber

The major chemical classes of dietary and functional fiber are cellulose, noncellulose polysaccharides, and lignin (Table 12-11). These are all included in the category of nonstarch polysaccharides (NSP), referring to the naturally occurring cell-wall material in plant foods. Although the NSP content of cereals is high, the ratio of NSP to dry matter (DM) is much greater in fruits and vegetables than in cereals (35). The total fiber content of plants, as exemplified by their content of NSP, is what has been considered the factor leading to health benefits, rather than individual components of NSP. Cereals and grains are rich in arabinoxylans (xylose polymers), cellulose (β-glucans/glucose polymers), and polymers of arabinose, mannose, and galactose. Fruits and vegetables are rich in pectins (uronic acid polymers), cellulose (glucose only), and polymers of rhamnose and fucose in addition to the other polymers found in cereals. The fiber components that are not found in the cell wall (gums, fructo-oligosaccharides, resistant starch) are the major sources of fiber that are added to foods and called "functional" fiber. Because of this label it is often assumed that they are more beneficial than plant wall-derived fiber, but this is not the case. Most health benefits have been shown to be due to the use of whole plants in the diet, and it is not possible to make independent claims for most of the components of dietary fiber (35).

Cellulose. Cellulose is a straight-chain polymer of glucose with a β-1,4 linkage. It is not digested by pancreatic or small-bowel enzymes. Cellulose is a major structural component of cell walls but rarely accounts for more than 20% of total polysaccharides. It is highly represented in wheat bran, apple and pear skin, and strawberries.

TABLE 12-11. Properties of Components of Dietary Fiber

Component	Plant function	Major food sources	Effects
Cellulose	Cell wall structure	Bran, whole wheat/other flours, legumes, root vegetables, apples	↑ Fecal bulk, ↓ transit time, ↓ micronutrient absorption (? impact), binds bile salts
Noncellulose polysaccharides (hemicellulose)	Cell wall stability	Bran, cereals, whole grains	Same as cellulose
Pectins[a]	Cell wall stability	Citrus fruits, berries, apples, bananas, carrots, potatoes	Alters food consistency, ↓ cholesterol absorption, ↑ fecal water, ↓ gastric emptying
Gums and mucilages [a] (psyllium, guar gum)	Secretions	Oatmeal, dried legumes, used in food industry (baking, dressings, juice stabilizers)	↓ Cholesterol absorption, ↑ fecal water, ↓ vitamin/mineral absorption
Lignins	Cell wall strength	Old/tough vegetables, wheat	↑ Fecal bulk, ↓ transit time
Fructo-oligosaccharides, polydextrose [a]	Cell structure, secretions	Onions, bananas, tomatoes, honey, barley, garlic, wheat	Prebiotic, alters fecal flora, ↑ SCFAs, ? prevents colon cancer
Resistant starch	Storage form	Processed grains, flours	? ↓ Glycemic index, ? ↓ colon cancer

SCFA, short-chain fatty acid.
[a] Included in the category of functional fiber.

Hemicelluloses. Hemicelluloses are linear and highly branched polysaccharides of xylose, arabinose, mannose, and glucuronic acid. They act as plasticizers and intertwine with lignin between the cellulose fibers of the cell wall. *Nonstructural polysaccharides,* including pectins, gums, and mucilages, are branched polymers containing many uronic acids that hold water and form gels. They are highly branched in growing plants and become less branched as the support structure becomes more developed. They act as adhesives and are insoluble in unripe fruit, becoming soluble only as the fruit matures. Thus, the amount extracted may vary with the age of the fruit.

Polyphenols (Especially Flavonoids) and Other Cell Wall-Associated Nonpolysaccharide Substances. Polyphenols, products of plant metabolism, range from phenols to highly polymerized compounds, such as tannins and lignins. Distinctions are made according to the number of phenol rings they contain, leading to classification as phenolic acids (one ring), stilbenes and lignans (two rings) and flavonoids (three rings) (36). These chemicals include isothiocyanates and indoles in cruciferous vegetables, genistein in soybeans and tofu, saponins in many legumes, and lycopene in tomatoes.

Fruits and beverages (e.g., tea, red wine) provide the main sources of dietary polyphenols, but in most cases the mix of polyphenols is complex and poorly characterized. The food content is greatly affected by climate, soil type, rainfall, and other environmental factors. Polyphenols are easily oxidized, so food content is affected by storage and food preparation. For example, onions and tomatoes lose about three-quarters of their initial quercitin content after boiling for 15 minutes. Most of them are not currently included in the determination of dietary fiber, but lignin is the exception. *Lignin* is not a carbohydrate and constitutes about 12% of plant organic compounds. It comprises a

group of phenyl propane polymers of varying sizes because polymerization continues as the plant ages. It reinforces the cellulose support structure and inhibits microbial cell wall digestion. Thus, lignin is variably degraded by anaerobic digestion systems and is only partially metabolized in the colon, as are the cell wall polysaccharides. It represents only a small part of the human diet (~0.2%).

Phenolic acids and aldehydes, such as vanillin, are common, but the most common of the plant phenolics are the flavonoids, which consist of two aromatic rings linked through three carbons that form an oxygenated heterocyclic ring (36). Flavonoids and other polyphenols are ubiquitous in plants and beverages. They are found in tea and contribute to the bitterness of that and other beverages (37). Polyphenols usually account for less than 1% of the dry matter of plants, but they can reach concentrations of 4,000 to 7,000 mg per mL in red wines and fruit juices (36). The dietary intake of polyphenols in the United States is 1 to 1.1 g per day, with flavonoids accounting for about 4% of the total.

Like other components of fiber, polyphenols are degraded and absorbed in the colon, but the effect of these compounds on short-chain fatty acid production and microflora depends on the type of compound and the microorganisms present. Polyphenols bind proteins and precipitate in the intestinal lumen, and they can increase the fecal excretion of nitrogen and fat. They also inhibit iron absorption. Most recently, the antioxidant effects of polyphenols have been of interest, particularly as they relate to carcinogens and low-density lipoproteins (LDLs). Some evidence suggests that a moderate consumption of tea, a rich source of flavonoids, may provide protection against several forms of cancer, cardiovascular diseases, and kidney stones (37). The blacker the tea, the greater the degree of oxidation of the polyphenols and the weaker the possible effects of these compounds. Herbal teas are not true teas (*Camellia sinensis*), and their flavonoid content is much lower. Tea contributes more than 60% of dietary flavonoids and onions about 13%; grapes, apples, red wine, and dairy products provide most of the rest. The consumption of 1 to 2 cups of tea per day has been associated with health benefits in epidemiologic studies (37). Drinking tea has been as reported to decrease mortality from stroke in men by 50%, and from cancer of the mouth, pancreas, colon, esophagus, skin, lung, prostate, and bladder by 20% to 40%.

These data show only associations, not causation. Moreover, phenolics can under some conditions act as pro-oxidants (38). Their antioxidant effects depend on solubility and chelating potential, among other properties. Thus, it is not possible to recommend the consumption of large amounts of phenolics as foods or supplements until more data are available.

Resistant Short-Chain Carbohydrates (RSCCs). These include those nonglycemic carbohydrates that are soluble in 80% ethanol, other than highly polymerized sugar alcohols. The RSCC fraction includes carbohydrates otherwise referred to as nondigestible oligosaccharides, and includes inulin, fructo-oligosaccharides, polydextrose, methylcellulose, and resistant maltodextrins.

Resistant Starches. Resistant starches are defined as starches that enter the colon. RS1 is physically inaccessible because of its particle size or entrapment in food. RS2 and RS3 resist amylase action because of their compact (unbranched) structure; RS2 is unbranched and RS3 is retrograded (i.e., altered during processing) (41). Some starches are relatively resistant because they become available slowly in the intestinal lumen. Most resistant starches are produced during food preparation, a process that can either increase or decrease the amount of RS. The food properties that determine whether or not carbohydrate is digestible are determined *in vitro* by measuring the release of rapidly and slowly available glucose (RAG/SAG); what is left is RS (35). Cereals and bakery products have lower SAG values than do pasta and whole grains. The intake of such starches in a Western diet is estimated at 5 to 10 g per day.

Measurement

Four methods for measuring dietary fiber have provided enough data to be useful in assessing the fiber content of foods.

Crude Fiber. Crude fiber is the residue of plant food left after sequential extraction with solvent, dilute acid, and dilute alkali. Early chemists thought that residue resisting alkali and acid treatment was indigestible. The crude fiber procedure was developed in the 19th century and was favored because of the purity of the residue, which was low in ash and nitrogen content. Extraction and loss of hemicelluloses (>80%) and lignin (50% to 90%) are a consequence of solubility at acid and alkaline pH. All components of dietary fiber are at least partially soluble in these solutions. However, the degree of extraction varies with food preparation, particle size, and presence of other fiber components. Crude fiber is still the measure of fiber reported in some food tables and was the original basis for all altered-fiber diets. However, it provides an incomplete and inaccurate assessment of fiber because hemicellulose and lignin are extracted more than cellulose. Crude fiber is slowly being replaced by other methods. The relation of crude fiber to plant cell wall polysaccharide content depends on the proportions of pectins, cellulose, and hemicelluloses, which vary among vegetables and fruits. Monocotyledons in general are high in hemicelluloses and lignin and low in crude fiber. Legumes are higher in lignin but low in hemicelluloses and are intermediate for crude fiber. Dicotyledonous nonlegume vegetables have the highest proportion of cellulose and crude fiber.

Neutral Detergent Residues. These were developed by Van Soest and McQueen (42) and refined further by Englyst et al. (43) and Anderson and Bridges (44). Neutral detergent fiber or residue results from extraction with boiling sodium lauryl sulfate and ethylenediaminetetraacetate (EDTA) and is nonhydrolytic. Pectins and mucilages are removed completely, and the residue contains cellulose, lignin, and hemicelluloses (i.e., the cell wall components of fiber). This residue contains other nonlignin components that are not polysaccharides. Because neutral detergent residue includes all the major plant cell wall components, it continues to be used to assess the dietary fiber content of foods.

The Method of Southgate (45). This method is the most complex but probably the most accurate because it measures both soluble polysaccharides (mucilages, gums, and pectins) and cell wall components. A series of extractions with organic solvents and acids is followed by enzymatic treatment and hydrolysis. Data derived by this method or a modification of the method are recorded as "total dietary fiber," which includes noncellulose polysaccharides (hemicelluloses, gums, mucilages, and pectins) and lignins.

Association of Official Analytical Chemists (AOAC) Method. In the AOAC method enzymes and gravimetry are used. After fat is extracted from food, dried samples are gelatinized and then digested with protease and amyloglucosidase to remove protein and starch. The soluble dietary fiber is precipitated with ethanol, dried, and ashed. Total dietary fiber equals ethanol-precipitated residue weight minus ashed residue weight. This is the method now used by the U.S. Department of Agriculture for its tables of food fiber content (see *www.usda.gov*).

The "correct" assessment of fiber content cannot be made from these data because the physiologic importance of each component is not known. In addition, the preparation of food may alter the measurements by removing soluble and loosely bound components. Thus, fiber supplements should be offered with an understanding of the nonequivalent nature of the product sources.

Fermentation of Fiber

Variations in Degradation. The proportion of cellulose digested in the colon varies widely, from 47% to 80%. Purified cellulose is handled differently from dietary cellulose and is less degraded, about 25% (46). Bran cellulose is less degraded, perhaps because of its high lignin content. Cellulose metabolism is increased by slow transit, as in the elderly. Noncellulose polysaccharides are in general more completely degraded. Wheat bran is among the most poorly digested sources of dietary fiber, for reasons not related solely to its chemical composition. The digestion of nonstarch polysaccharides is variable and unpredictable. Most freshly cooked foods and uncooked cereals contain a high percentage

of readily digested starch. However, a cooled, cooked potato is less digestible than a freshly cooked one. Thus, it is not true that starch is completely digested and absorbed in the small intestine. Moreover, the fermentation products of starch and nonstarch polysaccharides differ in the large intestine. Factors that affect starch digestibility in humans include (besides the physical form) transit time, food processing, and the presence of amylase inhibitors, lectins, or phytates (47). In a Western-type diet, the amount of fermentable carbohydrate entering the colon includes, on average, 12 g of nonstarch polysaccharides and a variable amount of starch.

Volatile Fatty Acids. Volatile fatty acids are probably the main product of fiber polysaccharides and are well absorbed by the human colon. Thus, some of the nutritive value of dietary fiber is recovered by the absorption of fermentation products. It has been estimated that from 20 g of dietary fiber, 100 mEq of volatile fatty acids is produced, of which about 20% is excreted and the rest absorbed or used by bacteria.

Fermentation. The overall fermentation process as it is now understood can be defined quantitatively. Fermentation of resultant soluble hexoses is about 60%. Hydrogen produced in large amounts is converted to methane in the ruminating animal. Of humans, only 30% to 40% produce methane, so that hydrogen gas is excreted in large amounts. The gas by-products of carbohydrate fermentation are odorless but carry with them the more noticeable by-products of protein breakdown (putrefaction). The volatile fatty acids (acetate, propionate, and butyrate) are available in part as energy sources. Some of the available energy supports bacterial growth. It has been estimated that fermentation of 100 g of carbohydrate supports the growth of 30 g of bacteria. The effect of bacterial growth on other colonic functions has not been determined.

Functions of Dietary Fiber

A high-fiber diet increases stool bulk, produces more frequent stools, and decreases transit time through the intestine. Fecal bile acids appear to be increased when fiber is included in the diet. Table 12-11 reviews the properties of fiber components that may be responsible for the (known and postulated) effects of dietary fiber. However, the intake of fiber must be adequate if the potential benefits are to be realized. Intake in the United States remains lower than the recommended 25 g per day, averaging 17 g per day in the third National Health and Nutrition Examination (NHANES III) (48).

Factors Related to Increased Stool Weight. Even when a function of dietary fiber has been established (water-holding capacity), that function does not necessarily correlate with the crude fiber or total dietary fiber content of foods (Table 12-12). Moreover, the increment in stool weight is not linearly related to either the *in vitro* water-holding capacity or the water content of the food. It is possible that more than one factor (e.g., volatile fatty acid production in addition to water-holding capacity) is responsible for the observed result—an increase in stool weight. The practical aspect of this information is that not all fiber sources are alike, and the effect of a high-fiber diet may depend on the exact mixture of foods used.

Possible Additional Clinical Effects of a High-Fiber Diet. The following effects are associated with increased fiber intake.

Decreased intake of food. Obesity is rare in populations that consume a high-fiber diet, possibly because of a lower caloric intake or increased satiety (49). Dietary fiber intake is lower for obese subjects and BMI is lower in subjects who have higher fiber ingestion (50). Supplementing 14 g per day of fiber is associated with modest weight loss (1.9 kg over 3.8 months), but decreased intake was found mostly in obese subjects (51). The mechanism for this weight loss is unclear but might include satiation, altered glycemic responses, decreased energy absorption, altered gastric emptying, or decreased food intake at a later meal (50). Convincing evidence for most of these mechanisms is lacking. Supplements proposed to work by increasing satiety have shown some effect (glucomannan, guar gum) or no effect (psyllium), but the positive trials showed only modest results in small numbers of subjects (52). Intervention studies show that only a

TABLE 12-12. Water-holding Capacity of Various Foods

Food	Crude fiber content (g/100 g of raw food)[a]	AOAC fiber content (g/100 g of raw food)[a]	Capacity of fiber in 100 g of raw vegetables to absorb water (g)[b]	Moisture (g/100-g edible portion)[a]
Potato, fresh	0.5	1.5	41	75.4
Tomato	0.5	1.3	71	94
Cucumber	0.4	1.0	77	96
Celery	0.6	1.6	97	94.7
Lettuce	0.6	1.0	99	95.7
Pear	1.4	2.6	113	83.8
Orange	0.5	2.4	122	86.8
Corn	0.7	3.7	129	69.6
Apple	0.6	2.2	177	83.9
Carrot	1.0	3.2	208	87.8
Wheat bran	9.4	35.3	447	2.9

AOAC, Association of Official Analytical Chemists.
[a] McConnell AA, Eastwood MA, Mitchell WD. A comparison of methods of measuring "fiber" in vegetable material. *J Sci Food Agric* 1974;25:1457.
[b] Human Nutrition Information Service, U.S. Department of Agriculture. *Provisional table on dietary fiber content of selected foods,* HNIS/PT-106, 1988, and updated *Appendix* Tables 8-19, 1991; and 8-20, 1989.

very large amount of fiber (~30 g per meal) is needed to decrease energy intake taken after the fiber-containing meal, but this is much beyond what most subjects could tolerate (31).

Coronary heart disease. Coronary heart disease has been inversely related to fiber intake, e.g., in the Nurses' Health Study, in which each increase of total daily dietary fiber of 10 g was associated with a relative risk reduction of 0.81 (53). Of the various sources of dietary fiber, only cereal fiber was strongly associated with a reduced risk for coronary heart disease (relative risk reduction of 0.63 per 5 g daily). There are no epidemiologic studies that link functional fiber (mostly soluble fibers) with the risk of coronary artery disease (31). However, prospective population studies (e.g., Wolk [53]) show a strong relationship between total food-derived fiber intake and coronary heart disease (54).

Diabetes. Fiber ingestion by diabetic patients leads to some delay in gastric emptying, improvement in glucose tolerance, and reduction of hyperinsulinemia and hyperlipidemia (55). The diet used for this study contained 25 g each of soluble and insoluble fiber, and the effect was greater than that seen when the American, British, and Canadian Diabetes Association recommendations were used (8 g of soluble and 16 g of insoluble fiber per day). Total fiber intake may decrease the risk of diabetes and improve postprandial glucose responses, although it may be difficult to separate any positive effect from an improvement in weight (56).

Mineral availability. Binding by fiber of minerals and trace elements has been shown consistently *in vitro,* but has not been consistently reported in clinical studies. When a wide variety of food is available and ingested, it is not known whether fiber intake affects mineral availability, and micronutrient supplements are not needed when fiber intake is increased. In fact, oligofructans have been reported to improve calcium absorption and calcium balance in experimental models (39).

Colonic disorders. The evidence for the inverse association of dietary fiber with diverticular disease, cancer of the colon, and irritable bowel syndrome is incomplete, and

TABLE 12-13. Adequate Intake Values (g/day) for Total Fiber

Life stage (year)	Male	Female
1–3	19	19
4–8	25	25
9–13	31	26
14–18	38	26
19–50	38	25
51–>70	30	21
Pregnancy/lactation		28/29

Source: Food and Nutrition Board, Institute of Medicine, *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (*Macronutrients*). Washington DC: National Academies Press, 2005.

much of it is based on epidemiologic data (31). In one prospective study, a low intake of fiber (13 g per day) was associated with an increase in the relative risk for the development of symptomatic diverticular disease of 2.35 (57). Some data suggest that a fiber intake of 30 to 35 g per day is inversely related to the risk for colon cancer (see references 58 and 59 for reviews of case–control studies), but the data do not unequivocally support a protective role for fiber. The data from the Nurses' Health Study, a cohort study, do not support a protective effect against either colon cancer or adenoma (60). However, the highest quintile of fiber intake averaged only 24 g per day, not quite the recommended 25 g per day. Thus, it is possible that higher levels of fiber intake would have shown a preventive effect against colon tumors. Two subsequent studies have suggested a protective role for fiber against colorectal cancer (61) and against colorectal adenomas (62–64). When other dietary risk factors (smoking, alcohol, folate, red meat, total milk, and total energy) are accounted for in prospective cohort studies, the significance of the association disappeared (65). Because it is difficult to single out one dietary component in relation to cancer prevention (see also Chapter 14), it is not possible to make a recommendation for altering fiber content at this time, except to suggest that the DRI of fiber be followed (Table 12-13).

Lowering cholesterol levels. Soluble gel-forming fiber (β-glucans, pectins, guar gum) decreases serum total and LDL cholesterol concentrations and improves insulin resistance (54).The effect may be mediated by cholesterol binding, altered gastric emptying, or both. Sources of insoluble fiber (wheat bran, cellulose) have no effect. Rice bran lowers cholesterol, but the effects appear to be produced by nonfiber components. The cholesterol-lowering effect is small but within the practical range of intake. For example, 3 g of soluble fiber from oatmeal (84 g) decreases total and LDL cholesterol by about 0.13 mmol per L (66). The addition of psyllium supplements (10.2 g per day) to a prudent American Heart Association diet can lower total cholesterol by about 5% and LDL cholesterol by 8.6% (67). Although a decreased intake of saturated fat is the most important dietary factor in lowering serum cholesterol, the effect of soluble fiber is comparable with decreasing dietary cholesterol to below 200 mg per day and with a weight loss of 5 kg (68).

Treatment of inflammatory colitis. Some products of the fermentation of fiber (especially short-chain fatty acids, primarily butyrate) are an important energy source for colonic mucosal cells. Infusions of sodium butyrate (100 mmol per L) in the form of enemas may relieve ulcerative colitis and diversion colitis, but the data are not consistent, and a strong recommendation cannot be made with current information (69).

Indications for Modified-Fiber Diets

Current Consumption Levels. Total dietary fiber intake has been only about half of the recommended intake in recent decades in the United States, estimated as 11 to

13 g per day in NHANES II (1976–1980) (58) and as 10 to 14 g per day in NHANES III (1988–1991) (48,70). Fewer grain products are consumed on average than in the 1930s and 1940s, but more fresh fruits and vegetables are now consumed throughout the year than previously.

Recommended Intake. The recommendations of the Institute of Medicine committee on macronutrients considered the availability of food fiber and added (or functional) fiber, as well as the amount of fiber needed to deliver possible health benefits when estimating the dietary recommended intake for fiber. Not enough data were available to provide an estimate average requirement (EAR), so an adequate intake (AI) was used to meet the average needs of a healthy population (Table 12-13).

Low-Fiber Diet. This diet is indicated whenever decreased fecal bulk is desired, as during preparation for barium studies or intestinal surgery, although a clear liquid diet is often preferred in such cases. A low-fiber diet may be used in *acute diarrheal illnesses,* such as gastroenteritis and ulcerative colitis, and in *short-bowel syndrome* when the colon is still present. This diet is not indicated for the long-term treatment of diverticular disease or irritable bowel syndrome. In patients with diverticulitis presenting with a chronic partial obstruction of the colon, a low-fiber diet may be used temporarily. *Partial obstruction of any part of the intestinal tract* (e.g., pylorus, colon) may be managed either by mechanical softening of foods (more useful for upper intestinal obstructions) or by a low intake of fiber (more useful for lower intestinal obstructions).

Partial Low-Fiber Diet. Sometimes, a diet with only a moderate restriction of fiber is indicated. When an ileal segment is very narrow in a patient with *Crohn disease,* only the most indigestible of the fiber sources need be eliminated (bran buds, corn, nuts); the other fiber-rich foods often can be consumed in moderation. *Gastric phytobezoars* can be treated initially with a full low-fiber diet; however, to prevent recurrences, the elimination of pulpy fruits (citrus fruits, pears) and persimmons from the diet is sometimes sufficient. Alternatively, a modified low-fiber diet can be used, in which only the foods highest in fiber (Table 12-13) are avoided. Examples include fruits (oranges, grapefruits, prunes, raisins, figs, cherries, persimmons, apples, grapes, berries); vegetables (celery, pumpkin, sauerkraut, lettuce, broccoli, brussels sprouts, potato skins); and others (bran, coconut, peanut, popcorn, kidney beans).

High-Fiber Diet. A high-fiber diet is used in the long-term treatment of recurrent diverticulitis (not simple diverticulosis) and irritable bowel disease when altered bowel habit is a major symptom. A high-fiber diet is not essential for every healthy adult who is ingesting the recommended amount of dietary fiber per day (Table 12-13). It is sometimes used nonspecifically in the treatment of chronic diarrhea to produce semiformed, less liquid stools, especially as a fiber-supplemented enteral formula (71). However, the effect is often produced at the expense of an increase in the number or volume of stools. Moreover, if a high-fiber supplement is administered to a patient through a small-bore tube, the tube may become obstructed. For these reasons, a high intake of fiber must be used cautiously in most cases of diarrhea. When the diarrhea results from a motility disorder (irritable bowel syndrome [IBS]), a high intake of fiber may be used more successfully in controlling symptoms.

Polyphenols/Flavonoids. Data have been accumulating on potential benefits of polyphenols, including some flavonoids and isoflavones. There are no extensive food composition tables to allow observational epidemiologic studies, and the claims for these compounds have been limited to small interventional studies. There are not enough data to make recommendations for general use for total flavonoids or for specific foods. But the diet should contain a wide variety of flavonoid-rich foods (fruits, vegetables, and beverages like tea) as part of a balanced healthy diet. Recommendations for intake of specific compounds vary from the companies selling the supplements. Some recommend 50 mg per day of isoflavones or 100 to 300 mg per day of grape seed extracts rich in proanthocyanidins, in order to approximate the intake derived from

ingestion of soy products in Japan, or in grapes or wine in European nations (36). Other avalailable tablets or capsules contain much more of this type of compound, amounting to ~100 times the polyphenol intake in a Western diet (72). Examples would include one to six doses per day of quercitin 300 mg, citrus flavonoids 1 g, or resveratrol 20 mg. Ingestion of excess polyphenols may not be without risk, as potential hazards identified from the oxidative products of these compounds include carcinogenicity or teratogenicity, thyroid toxicity, estrogenic activity of isoflavones, inhibition of nonheme iron, and interactions with pharmaceuticals (72).

Menopause. Botanical compounds and dietary supplements (e.g., black cohosh, red clover, soy products) are often used by patients to control symptoms of menopause. Phytoestrogen extracts, including soy foods and red clover, do not seem to have much effect, although they appear to have positive effects on plasma lipid concentrations (73). Black cohosh does seem to be safe and to alleviate hot flashes.

Oxidation of low-density lipoprotein particles (ox-LDL). Ox-LDL may play a significant role in atherogenesis, and has been identified as a risk factor for cardiovascular disease. However, flavonoid-rich foods (e.g., olive oil, tea, red wine, soy) have not been shown to have a consistent effect on this risk factor (74). The combination of these products along with fruits, vegetables, and omega-3 polyunsaturated fatty acids does appear to decrease the rate of oxidation of LDL. It is possible that the lack of effect of flavonoid supplements might be due to the variety and quantity used of the supplements or compounds. Nonetheless, the data do not currently justify use of these products for prevention of heart disease.

Chocolate. Chocolate and cocoa powder contain flavanols and procyanidins that can be metabolized to strong antioxidants. Dark chocolate contains about three times the amount of polyphenols as milk chocolate (185 mg versus 64 mg per 40 g serving), and white chocolate contains none, as it has no cocoa powder (75). Cocoa products decrease ox-LDL production but do not alter biomarkers of inflammation in humans (76). Short-term administration of dark chocolate increases insulin sensitivity and decreases blood pressure in healthy persons (77). No recommendations about the use of chocolate for prevention of heart disease can be made at this time.

Practical Aspects

A clear liquid diet may be substituted for a low-fiber diet, but only for a short time because caloric intake is insufficient. Alternatively, commercially prepared liquid diets can be used (see Chapter 10). Table 12-14 lists total dietary fiber per average serving. Both high-fiber and low-fiber diets can be derived from such tables. Low-fiber diets are adequate in protein and fat. If dairy products are eliminated from the diet because of lactose intolerance, protein and calcium intake from other sources should be increased.

Commercial Psyllium Powders. These powders contain about 3.4 g of psyllium mucilloid per teaspoon (Table 12-15). Some plants (e.g., plantago) are very rich in psyllium, which comprises 10% to 12% of soluble fiber. The exact conversion of grams of psyllium to total dietary fiber is uncertain, but a 1:1 equivalence is practical and probably nearly correct.

Sources of Fiber. High-fiber diets can be based on foods with moderate or high amounts of fiber. Commercial psyllium seed may be used instead of, or in addition to, a high-fiber diet or a bran preparation, but this is not recommended for increasing fiber intake in healthy populations. The type of fiber is different in each source, and the effects are occasionally additive. Most often, however, a patient responds to one or another source of fiber. The psyllium seed preparations are easy to take, their effects are reproducible, and they eliminate the need to use a special diet. However, in some instances, they are ineffective, whereas other types of fiber relieve symptoms. Most dietary fiber in a Western-type diet comes from fresh fruits, vegetables, and cereals. Usual servings of fruits, vegetables, and cereals contain 2 to 4 g of dietary fiber (Table 12-14).

TABLE 12-14. Fiber Content/Serving of Commonly Used Foods

Total dietary fiber 5 g
Baked beans (1/4 cup)
Split peas (1/2 cup)
Chick peas, kidney beans, lentils (1/2 cup)
Butter beans, cooled (1/2 cup)
Blackberries (1/4 cup)
Grapes, white (12)
Raspberries (1/2 cup)
Bran wheat (1/4 cup)
All-Bran, raisin bran (1/3 cup)
Shredded Wheat (2 biscuits)
Almonds (15)
Grapenuts (1 cup)
Prunes, stewed (1/2 cup)

Total dietary fiber ~4 g
Peas, fresh or canned (1/2 cup)
Turnip greens (1/2 cup)
Broccoli (1 cup)
Cranberries (1 cup)
Prunes, dried (3)
Pear with skin (1 medium)
Apricots (5)
Apple (1 large)
Figs, dried (2)

Total dietary fiber ~3 g
Beets, boiled (1/2 cup)
Potato with skin, baked (one 2 1/2-in diameter)
Rye crackers (4)
Fruit pie (9-in diameter, 1/6 of pie)
Corn flakes (1 cup)

Total dietary fiber ~2 g
Banana (1 small)
Peach (1 medium)
Potato (1 medium with skin)
Corn on cob (small ear)
Carrot (1 medium)
Cabbage, boiled (1/2 cup)
Tomato (1 medium)
Turnips (2/3 cup)
Cauliflower, raw (1 cup)
Rhubarb (1/4 cup)
Strawberries (10 large)
Plums (2 medium)
Orange (flesh) (1 small)
Tangerine (1 large)
Cherries (15)
Puffed wheat (1 cup)
Corn flakes (1 cup)
Flour, whole-meal (3 tbs)
Peanut butter (2 tbs)
Bran, powdered (1 tbs)
Rye bread (1 slice)
Whole wheat bread (2 slices)

Total dietary fiber ~1 g
Onion (1 small)
Cauliflower, boiled (1/2 cup)
Celery, raw (1/2 cup)
Potato, boiled, no skin (1 medium)
Asparagus, boiled (4 spears)
Cucumber, raw (2 cups)
Rice Krispies (3/4 cup)
Special K (3/4 cup)
White bread (1 slice)
Popcorn (1 cup)
Raisins (1 tbs)
Nectarines (1 medium)
Melon, all types (1/4 melon)
Pineapple, fresh (1/2 cup)
Grapefruit (1/2)
Rice, boiled white (1/2 cup)
Flour, white (3 tbs)
Peanuts (12)

Total dietary fiber <0.2 g
Fruit juices, strained (1 cup)
Sugar, white (1 tbs)
Mayonnaise (1 tbs)
Fruit jellies (1 tbs)
Fats (2 tbs)
Milk (1 cup)
Egg (1 medium)
Meat, fish, poultry (3 oz)
Coffee, tea, soda (1 cup)

High-Fiber Diet. *Patient information on this topic is available in Appendix D.* High-fiber diets should aim to add the equivalent of at least 10 g of total dietary fiber to the diet. This increment may be accomplished by adding a normal distribution of fiber-containing foods to the previous diet, or the use of a single, concentrated source of fiber may be required. The importance of obtaining a dietary history is obvious. Psyllium seed provides 6 to 7 g of fiber in a dosage of 2 tsp per day; All-Bran cereal contains 11.2 g of dietary fiber in each cup; wheat bran contains about 5 g of dietary fiber in each tablespoon. Table 12-15 outlines many of the available nonfood sources of fiber. In general, ingestion of two to three doses per day provides 10 g of additional dietary fiber. Keep in mind that not all sources of fiber produce the same effect (Table 12-11). Thus, it is best to increase foods containing dietary fiber. If added (or functional) fiber is used, it may be necessary to try different types of fiber before finding one that improves symptoms or is well tolerated.

TABLE 12-15. Fiber Content of Commercial Supplements

Fiber component/product	Formulation	Daily dose (adults)[a]	Fiber content (g/unit)
Psyllium			
Alramucil	Effervescent powder	1 packet 1–3×/day	3.6 g/packet
Correctol	Powder	1 tsp	3.5 g/tsp
Effersyllium	Effervescent powder	1 packet 1–3×/day	3.6 g/packet
Fiberall	Powder	1 rounded tsp 1–3×/day	3.5 g/tsp
Hydrocil	Powder	1 tsp 1–3×/day	3.5 g/tsp
Konsyl	Powder	1 packet or rounded tsp 1–3×/day	6 g/packet or tsp
Konsyl D	Powder	1 tsp 1–3×/day	3.4 g/tsp
Genfiber	Powder	1 tsp 1–3×/day	3.4 g/tsp
Metamucil	Powder	1 tsp or packet 1–3×/day	3.4 g/tsp or packet
	Wafer	2 wafers 1–3×/day	1.7 g/wafer
	Capsule	4–6 capsules 1–3×/day	0.525 g/capsule
Natural vegetable fiber (many brands)	Powder	1 tsp 1–3×/day	3.4 g/tsp
Perdiem fiber	Granules	1–2 tsp 1–2×/day	4.0 g/tsp
Reguloid	Powder	1 tsp 1–3×/day	3.4 g/tsp
Serutan	Toasted granules	1 tsp 1–3×/day	2.5 g/tsp
	Powder	1 tsp 1–3×/day	3.4 g/tsp
Syllact	Powder	1 tsp 1–3×/day	3.4 g/tsp
Ca polycarbophil			
Equalactin	Tablet	1–2 tablets 1–2×/day	0.5 g/tablet
Fiberall	Tablet	2 tablets 2–3×/day	1.0 g/tablet
Fibercon	Tablet	2 tablets 1–3×/day	0.5 g/tablet
Fiberlax	Tablet	2 tablets 1–3×/day	0.5 g/tablet
Konsyl fiber	Tablet	1 tablet 1–4×/day	0.5 g/tablet
Other			
Wheat bran	Powder	1 tsp 1–3×/day	1.6 g/tsp
Citrucel (methylcellulose)	Powder	1 tbs 1–3×/day	2.0 g/tbs
Fiber10 (fiber blend)	Packet	1 packet 2–3×/day	10.0 g/packet
Fibermed (grain and fruit fiber blend)	Biscuit	1–2 biscuits 2×/day	5 g/biscuit
Maltsupex (barley malt extract)	Tablet	4 tablets 2–4×/day	0.5 g/tablet
	Powder	1 scoop 1–2×/day	8.0 g/scoop

All doses should be taken with 8 oz of water.

Prebiotics are an increasingly common source of fiber that are available over the counter. The major sources of prebiotics available in Europe and the United States are inulin (derived from chicory roots), fructo-oligosaccharides or oligofructose (derived from the hydrolysis of chicory inulin or synthesized from sucrose), galacto-oligosaccharides (synthesized from lactose), and soybean oligosaccharides (extracted from soybeans). The average chain lengths of most of these are quite short, with only three to four residues, except for inulin, which has an average of 10 residues, and they comprise the classification of resistant short-chain carbohydrates (RSCC) (35). They are used as fat or sugar replacements and to add body to a variety of products, including dairy products, breakfast cereals, baked goods and breads, chocolate and confections, dietetic products, table spreads and salad dressings, and meat products. These supplements should be included on the label of the food products to which they are added, although the amount added may not be specified.

Low-Fiber Diet. Allowed foods are mainly animal foods (eggs, meats, milk), fats, white bread or rice, strained juices, and low-fiber fruits and vegetables, such as peaches without skin and peeled cucumber. *Patient information on this topic is available in Appendix D.*

Side Effects

An excess of fiber can increase the frequency of stools in the absence of constipation or worsen the symptoms of chronic constipation. Thus, fiber should be used cautiously to treat constipation as an isolated symptom. Excess fiber may obstruct a structural narrowing of the intestinal tract. When a low-fiber diet is used inappropriately to treat diverticulitis or irritable bowel disease, symptoms may worsen.

Supplements Required

A strict low-fiber diet containing 3 cups of milk per day and some meat servings is adequate for all nutrients except vitamin A (unless liver is eaten) and iron (for female patients). The caloric intake also may be inadequate, depending on the patient. In most cases, the diet is used only for a short time, and nutritional deficiency is not a problem.

DIETS THAT RESTRICT OR SUPPLEMENT INDIVIDUAL COMPONENTS

Low-Available-Carbohydrate Diet

Principles

When gastric emptying is rapid or when food enters the small intestine at an unregulated rate, the presence of small-molecular-weight foodstuffs is to be avoided. Because it is permeable in both directions, the upper small bowel rapidly corrects hypertonic or hypotonic luminal contents to isotonicity. Most meals are hypertonic, so that a net loss of fluid into the lumen of the intestine leads to a decreased plasma volume and distention of the upper intestine. The decrease in plasma volume and corresponding increase in intestinal distention accounts for many of the symptoms associated with the dumping syndrome.

Small-molecular-weight soluble substances exert a greater osmotic pressure than do macromolecules. The low-molecular-weight dietary components present in high concentrations are monosaccharides and disaccharides (e.g., dextrose, lactose, sucrose). Free amino acids or dipeptides are rarely encountered in the stomach. Therefore, a diet designed to decrease the osmolarity of ingested food is one low in the type of carbohydrate that is readily available for absorption. Of course, starch can be digested rapidly to maltose and glucose, and so starch also contributes to luminal osmolarity. Because milk sugar is a disaccharide, a low-available-carbohydrate diet is also a low-lactose diet. However, within a given range of osmolarity for liquid solutions such as oral rehydration solutions, it is the carbohydrate content rather than the osmolarity that determines the rate of gastric emptying (78). In people with normal stomachs, high carbohydrate content decreases gastric emptying, but when the stomach delivers food more rapidly after gastric resection, the mechanism by which carbohydrate regulates gastric emptying is lost, and increased carbohydrate is delivered to the duodenum where it generates increased osmotic pressure.

Different starchy foods are digested at different rates. Moreover, simple sugars vary in their effect on blood glucose levels. Glucose produces a greater effect than sucrose or fructose. Some starches produce a greater effect on blood glucose than do some simple sugars. Factors that affect starch digestibility include particle size, nature of the starch, processing of the starch, presence and type of fiber, and starch–protein–fat interactions (79,80). Because of the difficulty in predicting the effects of starchy or sugar-containing foods on blood glucose levels, the glycemic index was developed. The glycemic index is defined as follows:

$$[\text{Area under the 2 h glucose curve for food} \div \text{area under the 2 h glucose curve for an equivalent weight of reference sugar}] \times 100$$

The original reference sugar was glucose, but bread baked from flour of known composition has proved a better standard. A lower mean glycemic load in the diet (glycemic index of food times total daily carbohydrate intake) was associated with a twofold lower risk for the development of diabetes and cardiovascular disease in the large Nurses' Health Study (53). In the larger NHANES III sample, a lower glycemic index was a predictor of higher levels of high-density lipoprotein (HDL) cholesterol (81). But a meta-analysis of 15 randomized controlled trials using low glycemic index diets showed only a weak effect on reducing coronary heart disease, and none on LDL or HDL cholesterol (82). It is not clear what role various factors play in modifying the glycemic potency of foods, and its use in routine clinical management is still controversial.

Indications

Dumping Syndrome. The low-available-carbohydrate diet is useful after vagotomy with or without a drainage procedure because many patients have vasomotor and abdominal symptoms of the dumping syndrome (postprandial nausea, vomiting, weakness, dizziness, cramping, diarrhea, flushing, palpitations) during the early postoperative period (83). The rate of gastric emptying of fluids is enhanced at this time. However, the rate eventually returns to normal and the symptoms subside. Only a few patients must maintain the full diet on a long-term basis, although a large number may remain on a somewhat restricted diet. Some of the symptoms associated with dumping occur 1 to 3 hours after a meal; these may be caused by reactive hypoglycemia (see below). The diet also diminishes such symptoms by decreasing the carbohydrate load. The anatomic configuration of patients who have undergone *gastric bypass* for obesity (not gastroplasties) is associated with the dumping syndrome because the fundus of the stomach is anastomosed to the jejunum, and such patients often must remain on a low-available-carbohydrate diet.

Reactive Hypoglycemia. This occurs rarely in the absence of gastric surgery, sufficient in degree to produce symptoms (dizziness, hunger, weakness, sweating, palpitations). However, these symptoms are nonspecific and often related to anxiety. The true incidence of reactive hypoglycemia is probably much lower than the frequency of the diagnosis suggests. The definitive diagnosis requires the production of typical symptoms during a 5-hour glucose tolerance test, accompanied by a low plasma glucose level ($<$50 mg per dL). When reactive hypoglycemia is present, the low-carbohydrate diet is helpful.

Short Bowel Syndrome without a Colon. Although it is not widely accepted that an increased intake of fat may be indicated therapeutically, a few reports suggest the possible usefulness of such a maneuver. The rationale is that fat delays gastric emptying and prolongs small-bowel transit time via a humorally mediated mechanism termed the ileal brake (83). A high-fat diet has been used in some cases of short bowel syndrome (84). The rationale is that in a person with a short bowel and no colon, the importance of unabsorbed fatty acid derivatives as colonic secretagogues is limited. Thus, water secretion is regulated by the osmolarity of the diet, which is lower with a low intake of complex carbohydrate and a high intake of fat. Gastric emptying may also be delayed by a high fat meal, preventing too rapid presentation of calories to the remaining small intestine, but the same effect probably occurs with high complex carbohydrate diets.

Sucrase–Isomaltase Deficiency. For infants with sucrase-isomaltase deficiency, glucose or fructose may be added to formulas that contain no carbohydrate (see Chapter 10). Sucrose is added to many commercial baby foods, especially puréed fruits. Labels should be read carefully. Older children with this disorder become more tolerant to sucrose, and the diet is less necessary. An unsupplemented low-sucrose diet may be limited in ascorbic acid and folic acid, and perhaps also iron, thiamine, and niacin. An oral solution is available containing sucrase from *Saccharomyces cerevisiae* (Baker's yeast), marketed as Sucraid (sacrosidase) by Orphan Medical (*www.orphan.com*). The usual dose is 1 to 2 mL per meal. About three-fourths of treated patients can be reasonably

asymptomatic while ingesting sucrose. The most common side effects are abdominal pain, vomiting, and allergic reactions.

Low-Carbohydrate Diet for Obesity and Cardiovascular Disease. The basis for the low-carbohydrate diet for metabolic disorders remains unproven. It is clear that weight loss can occur, but the effect is not long lasting (87), and it could be due to a decrease in food intake, secondary to limited food choices that achieves portion control in a manner that is not specific to meal content. In fact, a review of low-carbohydrate diets found that it is the duration of diet and restriction of energy intake, not restriction of carbohydrates, that leads to weight loss (88). Intervention studies with low glycemic index diets show only a weak effect on the risk of developing coronary artery disease (82). With current information, a low-carbohydrate diet cannot be recommended to decrease weight long term or to decrease the risk of metabolic disorders.

Low-Carbohydrate Diet Postoperatively Following Bariatric Surgery That Includes Gastric Bypass. When a gastric bypass is created, food from the small fundic pouch moves directly into the jejunum, creating an anatomical situation that produces dumping syndrome. The diet is restricted in volume, but also avoids concentrated sugars and alcohol (89). Patients should eat and drink slowly, take small bites, and chew well to avoid distending the gastric pouch or producing staple dehiscence.

Practical Aspects

Patient information on this topic is available in Appendix D.

1. **Timing.** Food should be taken as six dry meals per day. Because liquids leave the stomach faster than solids, it is better to allow solid foods, with a potentially high osmotic load, to liquefy slowly and be diluted with endogenous secretions. Liquids should be taken 30 to 45 minutes after solids and limited to 1 cup per meal.
2. Milk in all forms, including ice cream and other frozen desserts, should be avoided. Even lactose substitutes contain high concentrations of monosaccharides, disaccharides, or both. Only calorie-free beverages should be consumed.
3. Sugar, sweets, candy, syrup, chocolate, and gravies should be avoided.
4. The stomach should not be overloaded.
5. Foods likely to be high in sugars have the following listed as the first or second ingredient: brown or invert or table sugar, corn sweetener, corn syrup, dextrose, fructose, fruit juice concentrate, glucose, high-fructose corn syrup, honey, lactose, maltose, malt syrup, molasses, sucrose, or syrup.
6. Patient education materials on a diet for dumping syndrome are also available on the internet from the University of Pittsburgh Medical Center (http://patienteducation. upmc. com) and from the University of Virginia (http://www.healthsystem.virginia.edu/internet/digestive-health/nutrition/patientedu.cfm).
7. **Osmolarity of foods.** Simple sugars and low-molecular-weight carbohydrates, in addition to electrolytes and amino acids, all contribute to the osmolarity of food, either as a preformed liquid or after liquefication in the intestinal lumen. Dietary fats are relatively water-insoluble and do not increase osmolarity significantly.

   One major aim of a low-available-carbohydrate diet is to reduce the osmolarity of ingested foods. This diet eliminates foods with a sugar content likely to increase the osmolarity of the gastric contents. The osmolarity of the gastric contents is usually hypertonic after a meal, but iso-osmolar liquids are emptied most efficiently by the stomach. A diet low in available carbohydrate is used to lower the gastric and intestinal osmolarity as much as possible.

   In acute disorders such as gastroenteritis, in which gastric emptying is impaired, or in chronic disorders such as diabetic gastroparesis, the use of iso-osmolar foods is helpful. Unfortunately, such a diet may be low in calories because it is the calorie-containing components of food that contribute most to osmolarity. Moreover, fat decreases the rate of gastric emptying, so that low-fat liquids are needed for rapid gastric emptying. During acute illnesses, however, iso-osmolar low-calorie liquids can be used for short periods alone.

Nearly all liquid or semisolid foods are hyperosmolar (1):

Food	mOsmol/L	Food	mOsmol/L
Gatorade	330	Eggnog	695
Ginger ale	510	Apple juice	683
Gelatin dessert	735	Orange juice	614
Tomato juice	595	Malted milk	940
7-Up	640	Ice cream	1,150
Coca-Cola	680	Grape juice	863
Sherbet	1,225		

When nausea or vomiting is among the symptoms to be treated, the use of these fluids should be modified so that appropriate dilutions decrease the osmolarity to about 280 to 300 mOsmol per L.

8. Foods allowed include those containing protein, fat, or complex polysaccharides.

Foods containing simple sugars should be avoided. Table 12-16 lists the fructose, glucose, sucrose, and starch contents of many foods. In this table, foods are ranked in decreasing order of simple sugar content—that is, monosaccharides and disaccharides. Foods high in simple sugars should be avoided or taken in small amounts. Fructose in excess of glucose is the main determinant of fructose malabsorption and diarrhea. This excess is seen especially in honey, apples, and pears. However, the largest source of dietary fructose is as a sweetener in dietetic foods and soft drinks and in corn syrups (~50% fructose) (90). The mean daily intake of free fructose in the United States is 20 g. Sorbitol is ingested in fruits along with fructose, and as a sweetener in candy, mints, "sugarless" chewing gum, and dietetic foods. As much as 2 g of sorbitol can be contained in one stick of gum. The decreased carbohydrate absorption of fruit juices in young children is related to the sorbitol content of the juice (91). The lactose contents of milk products are listed in Table 12-17, and these should also be limited. In congenital sucrase–isomaltase deficiency, a rare disorder, only foods containing little sucrose can be ingested. As seen in Table 12-16, this diet eliminates many fruits and vegetables and most sweets.

Most beverages contain available sugars and should be limited. These include beer, sodas, and iced tea or lemonade made with sugar. Canned fruits often contain extra sugar in the packing fluid; if these are used, the fluid should be drained away before the fruits are eaten.

9. **Fructose** has been singled out as an important component of available carbohydrate in the diet. Average consumption of fructose in the United States is ~30 g per year, half from sucrose and half from high fructose corn syrup. Fructose enters the glycolytic pathway at the level of triose phosphates, thus bypassing the major control point at which glucose enters, i.e., phosphofructokinase. Fructose can serve, therefore, as an unregulated source of acetyl CoA for hepatic lipogenesis. Fructose has been shown in short-term studies to increase energy intake and body weight, to decrease insulin sensitivity, and to increase postprandial plasma triglyceride levels (92). A low-carbohydrate diet should also be low in fructose.

10. **Sweeteners**. The U.S. Food and Drug Administration has approved four sugar substitutes—*saccharin, aspartame, acesulfame-K,* and *sucralose.* Other sweeteners are under review (*http://vm.cfsan.fda.gov/~dms/fdsugar.html*). The American Dietetic Association Position Paper on Sweeteners concludes that these substances can be safely ingested as part of a diet, if general guidelines for individual health goals are followed, as exemplified in the Dietary Reference Intakes (93).

Saccharin (*Sweet and Low, Sweet Twin*). Despite the concerns about saccharine as a carcinogen, it remains on the market; it is 300 times sweeter than sugar and has been used safely for decades, and the dose required to see tumors in laboratory animals is huge. The Saccharine Study and Labeling Act requires the label to read "Use of this product may be hazardous to your health," but the moratorium on a final decision has been extended until 2002.

TABLE 12-16. Carbohydrate Content of Selected Foods

Food	Fructose[a]	Excess free fructose[b]	Glucose	Sorbitol	Reducing sugars[c]	Maltose	Sucrose	Starch	Total simple sugars[d] (g/100-g portion)
	(g/100-g edible portion)								
Fruits									
Figs, dried	30.9	—	40	—	—	—	0.1	—	73
Dates, dried	—	—	—	—	16.2	—	45.4	—	61.6
Banana, ripe	2–4	0	4.5	—	—	—	11.9	—	19.9
Grapes, white	8.0	0	8.1	0.2	—	—	0.2	—	16.1
Cherries	5–7	0	4.7	1.4–2.1	12.5	—	0.1	—	12.6
Apple juice	6–8	2–7	1–4	0.3–1.0	8.0	—	4.2	—	12.2
Plums, sweet	1–4	0	4.5	0.3–2.8	7.4	—	4.4	—	11.8
Apple	6–8	2–7	1.7	0.2–1.0	8.3	—	3.1	0.6	11.4
Banana, green	—	—	—	—	5.0	—	5.1	—	10.1
Peaches	1.6	—	1.5	—	3.1	—	6.6	—	9.7
Orange	2.7	0	2.5	—	5.0	—	4.6	—	9.6
Pears	5–9	3–8	2.5	1.2–3.5	8.0	—	1.5	—	9.5
Watermelon	—	—	—	—	3.0	—	4.9	—	7.9
Apricots	0.4	—	1.9	—	—	—	5.5	—	7.8
Orange juice, frozen	2–6	0	—	—	4.6	—	3.2	—	7.8
Melon, cantaloupe	0.9	—	1.2	—	2.3	—	4.4	—	6.7
Strawberries	2.3	0	2.6	—	—	—	1.4	—	6.3
Grapefruit	1.2	—	2.0	—	—	—	2.9	—	6.1
Prunes	15	0	30	9.4–18.8	—	—			
Vegetables									
Beets, sugar	—	—	—	—	—	—	12.9	—	12.9
Onions	1	0	2	—	—	—	0.1	—	8.3
Carrots, raw	1	0	1	—	5.8	—	1.2	—	7.9
Peas, green	<0.1	0	<0.1	—	—	—	5.5	4.1	5.5
Potatoes, sweet	0.3	—	0.4	—	0.8	1.6	4.1	16.5	4.9

Cauliflower	—	—	2.8	—	—	—	0.3	—	3.1
Beans, green	1–1.5	0–1	0.5–1	—	1.7	—	0.5	2.0	2.2
Potatoes, white	0.1	—	0.1	—	0.8	—	0.1	17.0	0.9
Squash, summer	0.2	—	0.1	—	—	—	0.4	2.6	0.7
Cucumber	—	—	0.5	—	—	—	0.1	—	0.6
Dry legumes									
Beans, soy	—	—	—	—	1.6	—	7.2	1.9	8.8
Lentils	—	—	—	—	—	—	2.1	28.5	2.1
Beans, navy	—	—	—	—	—	—	—	35.2	—
Nuts									
Peanuts	—	—	—	—	0.2	—	4.3	4.0	4.5
Almonds	—	—	—	—	0.2	—	2.3	—	2.5
Peanut butter	—	—	—	—	0.9	—	—	5.9	0.9
Cereals									
Wheat flour	—	—	—	—	2.0	—	0.2	34.7	2.2
Rice, polished	—	—	2.0	—	—	—	0.4	72.9	0.4
Oats	—	—	—	—	—	—	—	56.4	—
Sweets									
Honey	40.5	7	34.2	—	—	—	—	1.9	88.6
Maple syrup	—	—	—	—	1.5	—	62.9	—	64.4
Molasses	6.8	—	6.8	—	26.9	—	36.9	—	63.8
Jellies	—	—	—	—	—	—	—	40–65	40–65
Chocolate, sweet, dry	—	—	—	—	—	—	56.4	—	56.4
Corn syrup	—	—	21.2	—	—	26.4	—	34.7	47.6

Foods are listed with groups according to their monosaccharide and disaccharide content per 100-g edible portion. Thus, the total sugar added to the diet must take into account the size of the portion. See also *Sugar content of selected foods,* Report No. 48. Human Nutrition Information Service, U.S. Department of Agriculture.

[a] Adapted from Rumessen JJ. *Scand J Gastroenterol* 1992;27:819. Mainly monosaccharides plus maltose and lactose.

[b] Free fructose as monosaccharides in excess of free glucose.

[c] Adapted from Hardinger MG, Swarner JB, Crooks H. *J Am Diet Assoc* 1965;46:197.

[d] Total "simple" sugars equals reducing sugars plus sucrose; where total reducing sugar content is not available, the sum of the published figures for fructose, glucose, and/or maltose has been substituted.

Aspartame (*NutraSweet, Equal*) is a dipeptide (phenylalanine–aspartic acid) that is 180 times sweeter than sugar. The Food and Drug Administration (FDA) has reviewed more than 100 toxicologic and clinical studies that attest to its safety, although claims continue to arise regarding its possible role in causing various diseases. The very small number of patients who have phenylketonuria should not use this compound, but otherwise it appears to be safe. Urticaria has been reported with aspartame and confirmed by rechallenge (94). It is postulated that the product of degradation may form amide bonds with proteins and act as an antigen.

Aspartame is one of only a few food additives for which there are any substantial human trial data for safety. However, setting acceptable dietary intakes (ADIs) for food additives is a daunting job. The amounts of any one additive ingested are small, exposure may occur over a lifetime, synergism in toxic effects is not known between the hundreds of additives permitted, and postmarketing adverse reaction reporting is difficult because of the presence of additives like aspartame in many foods. Thus, most data on toxic effects of additives come from animals (mostly rodent). The statement that approved additives have been "proven to be safe" is superficially correct based on the available data, but the statement needs to be accepted with some qualification.

Acesulfame potassium (*Sunett, Sweet and Safe, Sweet One*) is approved for use in baked goods, frozen desserts, candies, and beverages. It is 200 times sweeter than sugar and is often combined with other sweeteners. It is not degraded when cooked or baked. No evidence of toxicity has been reported.

Sucralose (*Splenda*) is 600 times sweeter than sugar and is approved for use as a table sweetener and in baked goods, nonalcoholic beverages, chewing gum, frozen dairy desserts, fruit juices, and gelatins. It is now approved as a general-purpose sweetener for all foods. It tastes like sugar because it is made from sucrose, but it cannot be digested. It is considered safe to use.

11. **Sugar alcohols** are not technically considered artificial sweeteners, but they do not promote tooth decay or raise blood sugar, as sugar does. They include sorbitol, xylitol, lactitol, mannitol, and maltitol. Sugar alcohols are used to sweeten "sugar-free" candies, cookies, and chewing gums. Fructose is also often added to foods because, like sugar alcohols, it is less sweet than dextrose. However, these sugars are absorbed less efficiently, and ingestion of more than 10 g can produce diarrhea, gas, bloating, and cramps. Fructose is a major ingredient of soft drinks (about 40 g in a 16-oz cola). Sorbitol is added to diet gums (up to 2 g per stick) and processed apple juice (up to 0.7 g per 3 oz). Labels should be read carefully for the content of these sweeteners if symptoms occur regularly after ingestion of sweetened processed foods.
12. **The glycemic index** (GI) has been recommended as an alternative way to classify carbohydrate-containing food. If this were practical, it would have a major effect on the development of a low-carbohydrate diet for any individual. Most grains and potatoes are rapidly hydrolyzed and have a high GI, but nonstarchy vegetables, fruits, legumes, and nuts have a low GI. Glycemic load (GL) has been defined as the arithmetic product of GI and carbohydrate content. Extensive articles and diet books have been published on this topic, and extensive lists of GI and GL values of common foods have been published (79). In general, the factors that affect the glycemic response include the amount of carbohydrate, the nature of the starch (amylase, amylopectin, resistant starch) or monosaccharide components (glucose, fructose, galactose), the food processing (particle size, chemical modification, resistant starch content), and other factors such as dietary fiber content (56). Examples of GI and GL include baked potato (GI 85, GL 20.3 g for 110 g serving), white bread (GI 70, GL 21 g for 2 slices), spaghetti (GI 41, GL 11.8 g for 110 g serving), lentil beans (GI 29, GL 5.7 g for 110 mL cooked serving), and skim milk (GI 32, GL 4.2 for 225 mL) (95). Despite much controversy, the effects of low GI diets on insulin resistance and risks of cardiovascular disease are small (82,95). Moreover, the diets are complicated, and low energy diets probably accomplish as much. The concept of GI fits with the food pyramid and healthy diet recommendations for the United States, but whether a low GI diet has a role in improving insulin sensitivity or hyperlipidemia is not known.

Side Effects

A low-lactose diet may be low in calcium. If the diet is severely limited in fruits and vegetables, vitamin supplements, especially ascorbic acid and folic acid, may be necessary. Such severe restriction is only rarely, if ever, indicated with this diet. Because the diet is high in protein and fat, care should be taken to avoid increasing serum lipid levels in susceptible persons.

Supplement Required

If the diet is used on a long-term basis, 0.5 to 1.0 g of elemental calcium should be given daily.

Low-Lactose Diet

Principles

Most Caucasians are lactose tolerant, but the other peoples of the world are largely lactose intolerant. To avoid symptoms of flatulence, bloating, cramps, and diarrhea, a low-lactose diet is indicated. However, most people who have low levels of lactase are not lactose intolerant (96). African-Americans, a population thought to often be symptomatic from lactose intolerance, can usually tolerate ingesting 1 cup of milk without developing symptoms, even though they can be shown by specific testing to maldigest lactose (97). This situation arises because of differences in rates of gastric emptying and intestinal transit, composition of ingested food, capture of lactose fermentation products by colonic absorption, and perhaps individual tolerance. However, there are patient populations who develop lactose intolerance fairly consistently, including patients with active celiac sprue, those with short bowel syndrome, and following acute gastroenteritis. The diagnosis is usually made either by a trial of lactose elimination or by administering a hydrogen breath test after lactose ingestion (98).

Lactose is commonly used as a sweetening agent in prepared foods because it is inexpensive to prepare and its taste is not excessively sweet. Thus, it is difficult to devise a diet completely free of lactose. In most cases, complete elimination of lactose is unnecessary because symptoms, when they occur, are dose related. Each person has a threshold dose below which few symptoms occur.

Lactose, or milk sugar, is contained in human, cow, and goat's milk and in milk products. The whey contains all the lactose; any lactose in the curds represents contamination by whey. Whey is now added to more foods than before because large amounts of whey are available as a by-product of cheese production. Milk is a remarkable food that contains more than lactose. Many nutrients are lost from the diet when lactose is restricted; however, except for calcium, most of them are readily provided by the rest of a balanced diet.

Indications

Patients with symptoms of *lactose intolerance* are candidates for the diet. Because only 50% of lactose-intolerant persons have a history of intolerance, a useful first step is to place the patient suspected of being lactose intolerant on a low-lactose diet for 3 to 4 days. If the response is uncertain, challenge tests can help to diagnose lactose intolerance.

A positive lactose tolerance test result is defined as a rise in blood sugar of less than 20 mg per dL after a lactose load of 50 g per m^2 in children or 50 g in adults. The hydrogen breath test is a better means of diagnosis. It is more sensitive than the oral lactose tolerance test and can detect malabsorption of as little as 2 g of lactose. Thus, a lower test dose (12.5 g) can be used, an amount equal to the lactose content of one glass of milk. A rise of less than 20 ppm is consistent with lactose intolerance. More recent criteria suggest a 6 ppm rise at 6 hours after the carbohydrate load, or >15 ppm over a 2-hour period from 5 to 7 hours after ingestion of carbohydrate (99). Certain pitfalls are encountered in interpreting the results of a hydrogen breath test. A small percentage of normal persons do not produce hydrogen gas, oral antibiotics can suppress hydrogen-producing bacteria, and smoking causes an increase in breath hydrogen concentration that is unrelated to carbohydrate intake.

The low-lactose diet is also appropriate for *patients requiring a low-available-carbohydrate diet* after gastric surgery or during the course of an intestinal disorder.

A low-lactose diet is used during the acute phase of *diarrheal illnesses,* when intestinal transit is rapid and transient lactase deficiency can develop. These illnesses include acute gastroenteritis, ulcerative colitis, and Crohn disease. However, it is not necessary to restrict lactose from the diet in all such cases. In *sprue,* the enzyme lactase is decreased before treatment, and a low-lactose diet is helpful in the initial phase of therapy until the normal enzyme level is restored. However, restoration to normal levels may take many months.

Galactosemia is the only indication for very severe restriction of lactose. Virtually all dietary galactose is derived from lactose, and in galactosemia, small amounts of galactose cause symptoms. Thus, adherence to the diet must be complete.

Supplemental milk is offered in schools in the United States, even when the racial mixture includes a large proportion of children who would be expected to have lactase deficiency. Tolerance to a small amount of milk, such as part or even all of the cup offered with school lunches, is quite good, and the Committee on Nutrition of the American Academy of Pediatrics supports the use of milk as a good food supplement even in areas of the world where the incidence of lactose intolerance is high (100).

Practical Aspects

Patient information on this topic is available in Appendix D.

Management of lactose intolerance need not include a generalized low lactose diet, as many patients can tolerate small amounts of lactose (~4 g), such as contained in aged cheese or milk chocolate. When small amounts are ingested along with other foods or ingredients, the rate of gastric emptying is decreased and symptoms are less likely to occur. This is the rationale for the use of chocolate milk in small amounts.

1. **Milk and liquid milk products** should be avoided or used sparingly. Milk or cream should not be used in cooking. Small amounts of cheese and butter may be tolerated. Table 12-17 lists the major dietary sources of lactose in milk products.
2. **Labels** should be read carefully. Products containing milk, milk products, milk solids, whey, curd, casein, lactose, galactose, skim milk powder, skim milk solids, or milk sugar contain lactose. Foods that may contain "hidden" lactose include "nondairy" creamers, powdered sweeteners, breads and cakes, creamed soups, pancakes and waffles, puddings and custards, and candies. Many patients can tolerate small doses of lactose and need not be so cautious about restricting their intake of prepared foods containing small amounts of lactose. Often, however, the amount of lactose is not stated on the label. Practical information can be obtained from many internet sites, listed on the No Milk page (*www.panix.com/~nomilk*) along with sites for milk allergy and casein intolerance.
3. **Commercially available fermented milk products** (buttermilk, yogurt) are sometimes sweetened by adding cream or milk and are not necessarily low in lactose. The lactose content of homemade yogurt will be lower, but some lactose will remain. Nearly complete fermentation produces an inedible product. Yogurt is better tolerated by lactose-intolerant persons because the fermentation of lactose continues in the intestinal lumen (101). However, tolerance must be individualized. Frozen yogurt does not contain active bacterial cultures and is less well tolerated than fresh yogurt.
4. The average lactose-intolerant patient becomes symptomatic after ingesting 12 g of lactose, the approximate content of an 8-oz glass of milk. More lactose may be tolerated when it is ingested with other foods that delay gastric emptying. Some patients become symptomatic after ingesting as little as 3 g of lactose (102). These people must take great care to avoid foods that contain even small amounts of lactose. Patients with both lactase deficiency and irritable bowel syndrome are often extremely sensitive to small amounts of lactose.
5. **Prepared foods** that contain lactose. Not all samples of the foods listed below contain lactose, but the labels of such food groups should be read with care.

   Foods with large amounts of lactose: cakes and sweet rolls, caramels, fudge, coated candies, cheese spreads, infant formulas, party dips, powdered soft drinks, puddings, sour cream, white sauces.

   Foods with small amounts of lactose (<1 g/100 g): canned or frozen fruits and vegetables, cookies and cookie sandwich fillings, cordials and liqueurs, dietetic and

diabetic preparations, dried soups, French fries, corn cereals, instant coffee, instant potatoes, meat products prepared with fillings (e.g., frankfurters), pie crusts and fillings, salad dressings, liquid antibiotics, vitamin and mineral mixtures.

Lactose-free foods: plain meat, fish, poultry, peanut butter, broth-based soups, cereals, fruits, vegetables (plain), tofu and tofu products, breads and desserts made without any milk products.

6. **Hospital diets** provide lactose-containing foods with most meals. Lactose-intolerant patients may become symptomatic in the hospital, especially if they are given a modified-consistency diet with many milk products but little selection. Many commercially available protein and calorie supplements are now lactose-free (see Chapter 10).
7. **Enzyme replacement.** Lactose-depleted milk can be prepared by hydrolyzing the lactose with a yeast enzyme preparation (e.g., LactAid, Dairy Ease, Lactrase). Mixing five drops of LactAid liquid enzyme, which contains lactase from the yeast *Kluyveromyces lactis,* with 1 qt of milk or 12 oz of "liquid diet" or "instant breakfast" formulas at 4°C results in 70% hydrolysis of lactose in 1 day and 90% hydrolysis in 2 or 3 days. Patients with limited tolerance to lactose can use this milk, which is sweeter than regular milk but well accepted in cooking or on cereal. Dairy products other than milk cannot be treated in this way. Table 12-18 lists many of the sources of lactase, along with milk substitutes. Lactase in tablets is not always from the same source. For example, Lactrase, derived from *Aspergillus oryzae,* is stable at both acid and alkaline pH, and this stability may be advantageous in some cases. One to three capsules are ingested with milk or food, depending on the amount of lactose ingested and on individual sensitivity. Alternatively, the capsule can be opened and

TABLE 12-17. Lactose Content of Selected Milk Products

Product	Lactose content (g/unit)
Whole milk (1 cup)	11
2% Milk (1 cup)	9–13
Skim milk (1 cup)	11–14
Chocolate milk (1 cup)	10–12
Sweetened condensed milk (1 cup)	35
Reconstituted dry whole milk (1 cup)	48
Buttermilk (1 cup)	9–11
Light cream (1 tbs)	0.6
Half and half (1 tbs)	0.6
Whipped cream topping (1 tbs)	0.4
Low-fat yogurt (1 cup)	11–15
Cheeses	
Hard (Parmesan, blue, Gouda) (1 oz)	0.6–0.8
Semihard (American, Cheddar) (1 oz)	0.4–0.6
Soft (Camembert, Limburger) (1 oz)	0.1–0.2
Spread (added cream) (1 oz)	0.8–1.7
Cottage	
Regular (1 cup)	5–6
Low-fat (1 cup)	7–8
Ice creams	
Regular (1 cup)	9
Sherbet (1 cup)	4
Ice milk (1 cup)	10
Sorbets, ices (1 cup)	0
Butter (1 tbs)	0.15
Oleomargarine	0

Adapted from Welsh JD. Diet therapy in adult lactose malabsorption: present practices. *Am J Clin Nutr.* 1978;31:592.

TABLE 12-18. Selected Lactase Replacement Products and Milk Substitutes

Lactase products	Nondairy creamers	Milk substitutes
Lactaid (+ drops), 250 mg	Cremora	"a.m." (lactose-free)
Lactrase, 250 mg	Coffee-mate	Bordens Plus (lactose-free)
Say Yes to Dairy, 250 mg	Coffee Rich	Dairy Ease (70% ↓)
Prevail dairy enzyme, 125 mg	Vitamite	Lactaid (70% ↓)
Milk Digest-Aid, 125 mg	Creme Supreme	NutriMil (lactose-free)
Super Lactase, 125 mg	Cool Whip	Lacta-Care (99% ↓)
Swanson softgels, 150 mg	Rich Whip	
Dairy Ease (+ drops), 200 mg		

From: Steve Carper's Lactose Intolerance Clearing House/The Product Clearinghouse (*http://ourworld.compuserve.com/homepages/stevecarper*).

sprinkled on the food or liquid containing lactose. Lactaid tablets come in three sizes—regular, extra, and ultra—containing 3,000, 4,500, and 9,000 lactase units per tablet. The corresponding recommended doses with food are three, two, and one tablet, respectively.

8. **Milk substitutes.** Chemically defined products are now available that simulate milk; corn solids are used as the carbohydrate source (Table 12-18). These products can be used as milk substitutes if the taste is acceptable, but the sugar content is 12 g per 8-oz glass and the vegetable fat content is 5%, as in whole milk. Some of these products are cholesterol-free, and some contain micronutrient supplements.
9. **Ice cream substitutes.** A wide variety of lactose-free frozen desserts are now available that provide 300 to 440 kcal per cup and contain little or no calcium. In most of the desserts, tofu is used as the base. Although they are cholesterol-free, they are high in polyunsaturated fat (10 to 26 g of fat per cup). Some widely marketed varieties are Tofree, Tofutti, and Tofulite. Frozen desserts that are both lactose-free and fat-free include fruit sorbets and ices. Low-lactose desserts can be tolerated by some patients. LactAid brand ice cream contains about 2 g of lactose per cup, compared with 9 g for regular ice cream. Frozen yogurt contains 5 g per cup but may not be tolerated because the action of the bacteria in yogurt is diminished by freezing.
10. **Lactose-free supplements** include Ensure drink and powder, Boost pudding, Slimfast powder with soy protein, and Slimfast fruit juice powder or cans with soy protein. Care must be taken to read labels, as products with similar trade names do contain lactose. These include Ensure bars (2 to 3 g per bar), Ensure pudding (5 g per 4 oz serving), Carnation Instant Breakfast (8 g per poweder packet or 9 to 13 g per can), Slimfast powder (15 to 16 g per scoop with milk) or Slimfast cans (10 to 12 g per can).

Websites

National Library of Medicine/NIH http://www.nlm.nih.gov/medlineplus/lactoseintolerance.html

National Digestive Diseases Information Clearinghouse http://www.niddk.nih.gov/digest/pubs/lactose/lactose.htm

The Lactose Intolerance Nutrition Guide (American Dietetic Association) www.eatright.com/catalog/cat.php?CatNum=307x

Side Effects

A negative calcium balance may result if meat, nuts, and vegetables do not provide 0.8 to 1.0 g of calcium daily. Symptoms similar to those of lactose intolerance may develop when milk substitutes are used, which are also high in available carbohydrates.

Supplement Required

Calcium supplements (0.8 to 1.2 g of elemental calcium) should be given (see Chapter 7) if other sources are not ingested.

Low-Fat Diet

Principles

Different Types of Fat. Fatty acids derived from triglycerides supply energy and essential fatty acids and help absorb lipid-soluble compounds, such as fat-soluble vitamins. Saturated fats are found in high-fat dairy products, fatty fresh and processed meats, skin and fat of poultry, and lard, palm, and coconut oils. They tend to raise serum cholesterol levels. Levels of *trans* fatty acids, which also tend to raise serum cholesterol, are high in partially hydrogenated vegetable oils (margarines, shortenings) and in some commercially fried foods and bakery goods. *Trans* fatty acids are not essential and have no known benefit to humans. Like saturated fatty acids there is a linear trend with intake and LDLs, so that it is recommended that intake be kept as low as possible. Dietary sources include dairy products, meats, and commercially prepared products (31). Unsaturated fats, which tend to keep blood cholesterol levels low, are found in vegetable oils, nuts, olives, avocados, and fatty fish. Conjugated linoleic acid occurs in foods derived from ruminants. There is a suggestion that one of its isomers may reduce body fat and enhance lean body mass (103). Nuts provide a dense source of polyunsaturated fatty acids (Table 12-19).

The three types of fat (saturated, *trans*, and polyunsaturated) are equivalent calorically, all produce symptoms of malabsorption, and all must be decreased in a low-fat diet designed to reduce gastrointestinal symptoms. Dietary cholesterol, found in liver and other organ meats, egg yolks, and dairy fats, is not of concern in this diet. Diets designed to lower serum cholesterol are based on an altered ratio of intake of these fats (see Chapter 13).

Essential fatty acids (linolenic, linoleic) are found in high levels in vegetable oils (especially flaxseed, canola, and soy oils) and human milk, and dietary deficiency is rare in persons ingesting a balanced diet. Lack of linoleic acid leads to rough, scaly skin, and an increased plasma ratio of eicosatrienoic acid:arachidonic acid (triene:tetraene). The AI is 17 g per day for young men and 12 g per day for young women. α-Linolenic acid, the other essential dietary fat, has an AI of 1.6 g per day and 1.1 g per day for men and women, respectively (31). NHANES III mean data show that intake of total fat and saturated fat in the United States is 34% and 15% of total calories, respectively (104). Carnitine is a nonessential nutrient (synthesized from lysine and methionine) required for the entry of long-chain fatty acids into mitochondria. It is abundant in the diet, but some infant and

TABLE 12-19. Lipid Content of Nut-Derived Oils

Nut	PUFA (%)	Fatty acids unsat/sat (ratio)	Vitamin E		Phytosterol and sitosterol
			α-tocopherol (μg/100 g oil)	γ-tocopherol (μg/100 g oil)	
Almonds	85	10.8	440	13	2071
Hazelnuts	87	9.9	310	61	991
Macademia	58	5.6	122	trace	1507
Peanuts	45	5.45	88	60	1363
Walnuts	45	9.5	200	300	1130

From Maguire LS, O'Sullivan SM, Galvin K, et al. Fatty acid profile, tocopherol, squalene, and phytosterol content of walnuts, almonds, peanuts, hazelnuts, and the macademia nut. *Int J Food Sci Nutr.* 2004;55:171.

other non–milk-based formulas are supplemented with carnitine. Sphingolipids occur widely in food (consumption ~0.3 to 0.4 g per day in the United States) and have some role in colon cancer prevention and lowering cholesterol in animals (105). Their role in human nutrition is not yet known.

"Global" Malabsorption versus Predominantly Fat Malabsorption. Steatorrhea of any cause is relieved when the triglyceride intake is decreased. Fat malabsorption typically predominates in disorders in which the secretion or absorption of bile acids is limited; bile acids are needed for micelle formation and the absorption of fat, but not protein or carbohydrate. Both fat malabsorption and protein malabsorption occur in pancreatic insufficiency or diffuse small-bowel mucosal disorders. When protein malabsorption accompanies fat malabsorption, it produces few symptoms except perhaps that the putrid smell of feces is increased. Severe carbohydrate malabsorption causes some of the symptoms often associated with fat malabsorption (diarrhea, bloating, gas). The demonstration of steatorrhea or carbohydrate malabsorption by itself does not always determine which factor is most important in causing symptoms in an individual patient. Response to a trial of either a low-fat or a low-carbohydrate diet is often needed to resolve this issue in patients with "global" malabsorption.

Pathophysiology. As used in this diet, the term *fat* refers to triglycerides in food, not to other lipid components, such as cholesterol. Diarrhea is relieved by a low-fat diet because the diarrhea associated with steatorrhea is partly caused by the formation of hydroxyl fatty acids that act as secretagogues in the colon (106). If fewer fatty acids reach the colon, the diarrhea is diminished and the colonic absorption of other nutrients (especially short-chain fatty acids) improves. The low-fat diet is relatively rich in other sources of calories, especially carbohydrate, and is difficult to use when carbohydrate restriction is also desired. Low-fat diets are used to control symptoms of diarrhea, bloating, and gas—not to reverse abnormal physiology. Therefore, no single level of restriction is appropriate for all patients. A low-fat diet is also relatively low in protein because most sources of protein in a Western-type diet contain triglycerides. When malabsorption is severe and strict fat restriction is required, protein supplements must sometimes be given.

Indications

Patients with Malabsorption. Many disorders of digestion or absorption are characterized by steatorrhea. In general, patients with disorders in which steatorrhea is significant require a low-fat diet. These include diseases in which bile acids are poorly absorbed in the entire small bowel (e.g., sprue) or terminal ileum (e.g., Crohn disease with or without resection, short-bowel syndrome) or in which triglyceride absorption is limited (e.g., pancreatic insufficiency). When the coefficient of fat absorption is 85% to 95% (normal, $\geqslant$95%), fat restriction need not be stringent to achieve good results. For example, in a patient with a daily intake of 80 g of triglyceride and 90% efficient absorption (mildly abnormal), the fecal output would be only 8 g per day. However, if absorption is only 60% efficient, restriction must be more severe; with an intake of 50 g, 20 g of fat would still be excreted per day.

Patients with Nonspecific Intestinal Symptoms. Many patients complain that fatty foods cause a variety of intestinal symptoms. For such patients, it is usually enough to avoid fried foods and very fatty meats (bacon, sausage). Because the ingestion of fat is usually not specifically related to the symptoms of cholecystitis, ulcer, irritable bowel syndrome, and similar disorders, a low-fat diet is usually not indicated. Because protein is also a potent stimulus of intestinal and gastric motility, a selective restriction of fat intake serves no purpose.

Prevention of Disease. The reduced-fat diets advocated to prevent chronic diseases stipulate a reduction in fat intake of no more than 30% (107) (see Chapter 2). These diets are not the same as the low-fat diet being discussed here, and the labeling terms "light" and "lite," which mean fewer calories (see below), must be understood. However, many of the practical points relevant to a low-fat diet are also useful in a moderately

reduced-fat diet. To achieve the recommended fat intake, the U.S. Department of Agriculture recommends the following upper limit of fat intake at different levels of calorie consumption:

Total kcal/day	Saturated fat (g/day)	Total fat (g/day)
1,600	≤18	53
2,200	≤24	73
2,800	≤31	93

No randomized studies of long-term use of low saturated fat intake have been peformed. Reduced total fat and cholesterol diets have shown no cardiovascular benefit after 6 months (108). One can remove particular foods easily from the diet, but not all sources of saturated fat.

Practical Aspects

General Instructions. *Patient information on this topic is available in Appendix D.*

1. Broil, bake, or boil meats and fish.
2. Use chicken and turkey without skin as major sources of meat. The flat fish fillets usually served with sauces (flounder, sole) contain less fat than steaklike fish (salmon, halibut, tuna, trout, mackerel). Red meat trimmed of all fat or U.S. Department of Agriculture select-grade meat (8% fat content) also can be used in smaller amounts.
3. Use skim milk.
4. Avoid most desserts (cakes, cookies, pies, pastry, candy).
5. Avoid cream sauces and gravies.
6. **Label information for fat content.** As of May 1994, all manufacturers of processed foods are required by the Food and Drug Administration to use uniform definitions of claims such as "light" or "low-fat." *Light* means only that the product has one-third fewer calories or one-half the fat of its original version. Under the new law, the "% fat-free" claim appears only on low-fat products. The total grams of fat is the most important item and it is found in the middle of the label, where it may not be seen at first glance. Also, the "% daily value for calories" refers to a 2,000-calorie diet needed by "the average person." This estimate may be excessive for many people (see Appendix C for further discussion of the new food labels).

   Beef, pork, and lamb products also may appear with labels indicating approval by the Nutritional Effects Foundation (NEF), a new nonprofit organization. Most producers must apply for approval and comply with limits on fat content. "NEF-1" meat contains 3.5% fat or less by weight, and "NEF-2" contains 6% fat or less. This compares with the 15% to 20% fat content in the usual meat choices.

   Nearly all hard cheeses are high in fat. Part-skim cheeses are lower in fat, but most (>50%) of the calories are still derived from fat.

Specific Recommendations. To suggest a given intake of fat, the content of table foods must be known. A list of some foods with their fat content appears in Table 12-20. Based on the values for fat in this table, a general scheme of low-fat intake can be offered.

1. **When the fat intake must be 40 g per day,** foods allowed each day include most vegetables and fruits, breads, cereals with skim milk, two servings of lean meat (3 oz each), one egg, and 1 tsp of margarine.
2. **When fat intake must be 60 g per day,** in addition to the preceding foods, one can add 2 cups of 2% milk or one more ounces of meat or one egg with each serving or four more teaspoons of margarine or oil.
3. **When fat intake is 75 g per day,** in addition to foods allowed on the 60-g diet, the patient can ingest whole milk instead of 2% milk *or* two slices of bacon *or* 4 oz of ice cream *or* two larger servings of lean meat (6 oz each).

TABLE 12-20. Fat Content of Selected Table Foods

Food	Fat (g/unit)
Milk products	
Milk	
Whole (1 cup)	8.6
2% (1 cup)	4.9
1% (1 cup)	2.5
Skim (1 cup)	0.2
Buttermilk (1 cup)	2.4
Ice cream	
Regular (1 cup)	14.1
Rich grade (1 cup)	23.8
Ice milk (1 cup)	6.7
Yogurt	8.3
Cheese and butter	
Butter	
Regular (tbs)	11.5
Whipped (tbs)	7.6
Margarine (tbs)	11.5
Cheese	
Blue (1 oz)	8.6
Cheddar (1 oz)	9.1
Cottage (1 oz)	1.2
Cream (1 oz)	10.7
Parmesan (1 oz)	8.7
Swiss (1 oz)	7.9
American (1 oz)	8.5
Vegetables	
Eggplant (1/2 cup)	0.6
Peas, green (1/2 cup)	0.3
Spinach, cooked (1/.2 cup)	0.3
Sweet potato (1/2 cup)	2.8
Beans, dry (1/2 cup)	2.0
Avocado (1)	37
All others (1/2 cup)	<0.3
Grains and cereals	
Bread (1 slice)	0.8
Cereal, dry (3/4 cup)	0.3
Rice, cooked (1/2 cup)	0.1
Roll (1)	0.6
Spaghetti, cooked (1/2 cup)	0.4
With tomato sauce and meatballs (1/2 cup)	5.8
Noodles (8 oz)	0.4
Meats (yield from 3 oz cooked)	
Beef	
Chuck with fat	13.5
Chuck, lean	5.6
Chuck steak	10.9
Trimmed	3.4
Flank steak	4.1
Porterhouse steak with bone	23.9
Trimmed	3.4
T-bone with bone	23.9
Trimmed	3.2
Club steak with bone	21.2
Trimmed	3.9
Sirloin with bone	18.6
Trimmed	3
Rib roast with bone	22.6
Trimmed	4.9
Rump roast with bone	14.5
Trimmed	3.8
Ground beef	12.4
Lean	7.1
Corned beef	25.9
Chicken	
White, no skin	2.9
Dark, no skin	5.4
Chicken, fried	
White, no skin	5.2
Dark, no skin	7.9
Turkey	
Roasted with skin	14
White, no skin	3.3
Dark, no skin	7.1
Lamb	
Leg	9.4
Chops with bone	15.8
Shoulder	13.7
Liver, fried	9.8
Pork	
Chop with bone	13.2
Bacon (2 slices)	7–12
Sausages	
Liverwurst (1 slice)	2.7
Boiled ham (1 slice)	4.8
Pork sausage (1 link)	5.7
Salami (1 slice)	1.9
Frankfurters (1)	15.2
Bologna (1 slice)	1.0
Fruit	
Apple (1)	0.6
Pear (1)	0.3
Watermelon (1 cup)	0.4
All others (1)	0.3
Fats and oils	
Lard (1 tbs)	13
Oils, corn, olive, peanut, soy, sesame (1 tbs)	13.6
Salad dressing (1 tbs)	6.2–9
Desserts	
Cake	
Chocolate (1 slice)	6.7
Devil's food (1 slice)	12.3
Pound (1 slice)	8.9
Sponge (1 slice)	1.9
White (1 slice)	9.7
Yellow (1 slice)	9.5

(*continued*)

TABLE 12-20. Fat Content of Selected Table Foods (*Continued*)

Food	Fat (g/unit)	Food	Fat (g/unit)
Candy		Lobster, boiled	1.3
Chocolate, milk (1 oz)	9.2	Oysters, raw	0.5
Fudge (1 piece)	5.3	Sardines, canned (1 fish)	1.3
Cookies		**Nuts**	
Brownie (1 piece)	5	Almonds, roasted (1 cup)	97
Chocolate chip (1)	3	Peanuts, roasted (10 nuts)	4.5
Ginger snap (1)	0.6	Pecans (10 nuts)	10
Oatmeal (1)	2	Sesame seeds (1 tbs)	4.3
Sugar (1)	1.3	Peanut butter (1 tbs)	8.1
Pies (1/8 of pie)	7–23		
Fish (yield from 3 oz cooked)		**Miscellaneous and snack foods**	
Flatfish fillets (sole, flounder)	4.8	Egg	
Steaklike fish (swordfish, salmon)	6.5	Boiled (1)	5–6
Salmon, canned	11.9	Fried (1)	7–9
Tuna, canned		Popcorn (1 cup)	2
Canned in oil	17.5	Potatoes	
Solids only	7	French fried (3 oz)	11.3
Canned in water	0.7	Chips (1 oz)	11.3
Shrimp		Salad (1 cup)	7
Boiled	0.9	Olives (10)	8.3
Fried	9.2		

4. **Low-fat substitutes** are available for many foods, including whole milk (skim milk), cream (evaporated skim milk), butter/oils (apple or prune sauce, no-stick sprays), eggs (egg substitute), cheese, salad dressings, coffee cream, and ice cream (ice milk, sorbet).

Side Effects

The low-fat diet is a high-carbohydrate, high-osmolarity diet, and carbohydrate-induced diarrhea may occur. In such a case, the restriction of fat must be titrated to individual needs. When meats and fish must be severely restricted to control fat intake, low-fat dietary supplements may be needed to deliver adequate protein and calories (see Chapter 10). A low-fat diet is often quite bland because fat supplies much of the flavor in foods. Care must be taken to season foods so that adequate caloric intake is maintained.

Fat Supplements

When steatorrhea is present, fat-soluble vitamins often must be replaced. Bile acids are necessary for the absorption of fat-soluble vitamins; thus, the requirements are greatest in patients who have disorders associated with bile acid depletion (e.g., most cases of short-bowel syndrome). The large doses of vitamins needed to treat malabsorption are often available only as the individual vitamin, not as part of a multivitamin preparation. A discussion of vitamins A, D, E, and K is included in Chapter 6. If pancreatic insufficiency is the cause of steatorrhea, enzyme replacement is needed. When fat restriction is severe, medium-chain triglycerides or fat substitutes can be added to the diet.

Medium-Chain Triglycerides (MCTs)

MCTs are composed of fatty acids with 6 to 12 carbon residues and are found in high concentration in kernel oils (e.g., palm oil) and coconut oil. The commercially available MCT oil is made from coconut oil; it contains mostly fatty acids with 8 to 10 carbon atoms (vs. 16 to 18 for dietary fats) and very rapidly undergoes β-oxidation. MCT oil provides 8.3 kcal per g; 1 tbs weighs 14 g and provides 116 kcal. MCTs are relatively water-soluble

and can be hydrolyzed in the absence of bile salts and with minimal concentrations of pancreatic enzymes, so that they are ideal for use as a caloric supplement in fat malabsorption (109). Much interest has been shown in using MCTs as an aid to weight loss (110) and as a rapid source of energy, especially during prolonged endurance exercising, because they are metabolized more rapidly than other fats. However, little convincing evidence has been found that MCTs are useful in these roles. Human studies show that the addition of MCTs (10 g) to a mixed meal increases postprandial thermogenesis by 5% (111), but the role of MCTs in treatment of obesity is not clear.

Precautions. The rapid oxidation of MCTs leads to ketone formation. Thus, they are contraindicated in patients prone to ketosis. In cirrhosis, reduced hepatic clearance leads to increased serum MCT levels and hyperventilation, lactic acidemia, and symptoms compatible with hepatic encephalopathy. Side effects of MCT oil include nausea, vomiting, diarrhea, and abdominal cramps when the dose is excessive, either at one feeding or daily. Symptoms may be a consequence of the hyperosmolarity that develops during rapid hydrolysis of MCTs.

Practical Aspects

1. Give divided doses of 1/2 tbs up to six times a day.
2. For palatability, even though the oil is tasteless, add MCT oil (1 tbs/8 oz) to fruit juice or flavored beverages.
3. Use MCT oil in cooking or baking if the temperature does not exceed 300° to 325°F.
4. Use MCT oil as a salad or vegetable dressing.
5. Write to Mead Johnson Nutritionals, Evansville, Indiana 47721-0001 for a copy of *Recipes Using MCT Oil and Portagen.*

Fat Substitutes

The two available substitutes have been marketed as aids in weight reduction for obese patients, but they may prove useful to patients on low-fat diets. No data are currently available to evaluate this role for the compounds.

Simplesse is made from egg white and milk protein processed in such a way as to produce a creamy liquid with the texture of fat. It is marketed in an ice cream product (Simple Pleasures), and approval is being sought from the Food and Drug Administration to use it in other products, such as mayonnaise, salad dressings, dips, sour cream, yogurt, and cheese spreads. It cannot be used in cooking because the creamy texture is lost.

Olestra, a compound in which up to eight fatty acids from vegetable oil are linked to a sucrose core, is resistant to the action of pancreatic lipase. It can be used in cooking and has been approved for deep-fried snacks such as potato and corn chips. In a short-term (6-week) randomized, controlled trial of snack foods containing olestra or triglycerides, no clinically meaningful gastrointestinal symptoms were caused by the ingestion of snacks that contained olestra (112). Because olestra is a nonabsorbed lipid, it can cause a false-positive reaction in measurements of stool fat (113). Public concern continues about the effects of long-term or unregulated use because unlike products made from egg and milk proteins, olestra is an entirely new compound in the food supply. Thus, the FDA considers that olestra must be approved as a new food additive and that studies must be performed to ensure that it is safe for each approved use. Minor changes have been reported in serum fat-soluble vitamin concentrations, but the significance of these changes is not clear (114).

Conditionally Essential Lipids

Carnitine

Carnitine is essential for neonates (115). It functions to transfer long-chain fatty acids into mitochondria, improves glucose disposal, and may reduce insulin resistance (116). Carnitine is made in the liver and kidney, and is available in the diet in milk and meat products. Various disease states can alter carnitine status (117). Increasing loss from the body is a common cause, including renal tubular dysfunction, chronic renal failure, and dialysis. Inborn errors of fatty acid oxidation or branched-chain amino acid metabolism or liver cirrhosis can decrease synthesis, and certain drugs (e.g., valproic acid, zidovudine) can

cause deficiency. Decreased intake from malnutrition, malabsorption, or TPN can lower carnitine levels, and increased requirements for carnitine can occur following trauma, sepsis, or burns. Mitochondrial function (e.g., in HIV infection) may also cause conditional deficiency. Levocarnitine (Carnitor) is approved for such deficiencies, but data for improved clinical outcomes are not available for all the conditions listed above. Levocarnitine produces modest effects when given at 2 g per day to patients with anemia of renal failure (118). Its most promising use is in dialysis patients with resistance to human recombinant erythropoietin (119). The Medicare criteria for levocarnitine use is in patients who have been on hemodialysis for at least 3 months, and who have documented carnitine deficiency (plasma-free carnitine level <40 μmol per L) along with signs and symptoms of resistance to erythropoietin.

L-carnitine and propionyl-L-carnitine have been used in a variety of disorders, including cardiac and muscle ischemia (120). Theoretically, L-carnitine prevents loss of high energy phosphate stores by increasing fatty acid transport into mitochondria, and in deficient states might improve heart recovery. The use of 9 g per day after coronary artery bypass surgery for 5 days, and 6 g per day orally for 12 months attenuated left ventricular dilatation. Propionyl-L-carnitine has higher affinity for muscle carnitine transferase, creating potentially better efficiency of the Krebs cycle during hypoxis by providing propionate. Long-term treatment has been shown to improve exercise duration and oxygen consumption when taken at 1.5 g per day for 1 to 6 months (120).

Acetyl-L-carnitine (Alcar) has been used to improve symptoms in early Alzheimer disease (121). In this meta-analysis doses of 1.5 to 3.0 g per day taken for 3 to 12 months showed improvement in Clinical Global Impression, but another meta-analysis using mostly the same studies found no difference (122). Acetyl-L-carnitine has also been found to be deficient in diabetes, and analysis of two randomized, placebo-controlled trials suggests that 1 g tid improves pain and vibratory sensation in patients with chronic diabetic neuropathy (123).

Choline

Choline is a precursor for acetylcholine, phospholipids, and the methyl donor betaine. Choline can be synthesized in sufficient amounts to support normal metabolism of normal animals and humans, so in the past has not been considered an essential nutrient. 5-Adenosylmethionine (AdoMet) is the major methyl donor in mammals. The methyl group in AdoMet is derived from the diet (methionine, choline, and betaine) and from *de novo* synthesis with the methyl group supplied by 5′-methyltetrahydrofolate (124). The major consumer of these methyl groups had been thought to be creatine, but is more likely to be phosphatidylcholine synthesis via phosphatidylethanolamine methyltransferase (PEMT). Also, it had been thought that when intake of the labile methyl group (from choline and betaine) was decreased, methylneogenesis was enhanced by decreasing creatine synthesis.

However, in some pathological conditions and even in normal neonates this nutrient is considered essential (115,125). A choline deficiency syndrome has never been described in humans, but the Food and Drug Nutrition Board of the Institute of Medicine now classifies choline as an essential nutrient (125), based on a study that showed lower plasma choline and phosphatidylcholine levels in subjects on a choline-free diet for 3 weeks (126). In addition, some data in patients on total parenteral nutrition suggest a partial reversal in hepatic abnormalities following choline supplementation (127). A population-based case-control study of birth defects in which subsequent dietary histories were taken found evidence for decreased risk of cleft lip with or without cleft palate in mothers ingesting the highest quartile of choline, methionine, and total protein (128).

Choline is absorbed from the intestine, but it is not clear if this process is related to the high affinity choline transporter (CHT1) that mediates endocytosis in neural tissue. Foods with high choline content include liver, eggs, peanut butter, and milk, but lower amounts occur in all raw foods. Human intake is estimated at ~0.6 to 1.0 g per day. Gut flora degrades choline in part to betaine and methylamines. The AI for infants was set at 17 to 18 mg per kg, and for adults at 440 mg per day for men and 425 mg per day for women. A 20% lipid emulsion for TPN provides 11.6 to 13.2 mmol per L of phosphatidylcholine.

The UL for choline is 3.5 g per day, the limiting factors being hypotension and a fishy body odor from a metabolite, trimethylamine.

Omega-3 essential fatty acids (EFA)

Linolenic acid is found primarily in canola and soy oils, and the metabolic products, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are abundant in fish and fish oils. A proposed intake of 0.65 g per day has been suggested for EPA and DHA. One gram of fish oil contains about 300 g of these substances, and commercially available sources (e.g., EPA, Max EPA, Promega, SuperEPA, Sea-Omega, Marine Lipid Concentrate) contain from 300 to 800 mg of n-3 fatty acids per capsule. However, the commercial products are not the same mixture as fish oil, and the optimal dose has not been established. Doses of 10 to 20 g per day may be needed to produce a biochemical effect on LDL and HDL cholesterol. It is still uncertain whether these nutrients should be added to commercial supplements, such as infant formulas. Food enrichment with n-3 fatty acids has not been successful thus far because it causes a fishy taste, and oxidation occurs during processing. These fatty acids are not required for patients on a low-fat diet who are ingesting vegetable oils or fish. It has been proposed that n-3 fatty acids play a role in preventing or treating many diseases, including coronary artery disease, Crohn disease, autoimmune disorders, and various cancers, but it is premature to recommend their routine use (108). The best data on prevention of sudden death from myocardial infarction are those from the large Italian trial (129), but other studies have not been so positive (130).

The main source of omega-3 (n-3) polyunsaturated fatty acids is fatty fish, e.g., salmon, tuna, although small amounts are present in nuts, seeds, and plant oils. Omacor (Reliant) is the only fish oil supplement approved by the FDA, and is available by prescription for treatment of hypertriglyceridemia >500 g per dL (*Med Lett* 2006;129:59). Other brands of fish oil are available over the counter, some of them now validated for content by the US Pharmacopeia (www.usp.org). Prices are less than for Omacor, but the doses are about one-third and so three times as many capsules must be taken for equivalent dosing.

The American Heart Association recommends that all patients with coronary artery disease should eat at least 1 g per day of fat containing EFAs. Despite this recommendation there is not uniformity on what the evidence shows. Four different meta-analyses have selected randomized controlled trials that differ by over 40%, and it is not surprising that these analyses have reached diverse conclusions (131–134). Most studies have looked at the ability of ingested EFA supplements to lower mortality. But the type of pathology in the trials has varied, and the populations have varied in terms of baseline EFA blood levels. There is also a question as to whether results only apply to fish oils that are rich in EPAs or apply also to plant-derived α-lipoic acid, and the extent to which this is converted to EPA. There are enough positive randomized controlled trials that there is some merit in recommending EFA supplementation to patients with cardiovascular disease. The questions still to be answered are which patient populations, which cardiovascular diseases, and what dose of EFA. Until these issues are resolved, it will be difficult to make general recommendations for these supplements.

Low-Protein Diet

Principles

Pathophysiology. In chronic hepatic disease with cirrhosis and portal–systemic shunting, exogenous protein bypasses the liver, and the products of protein degradation induce hepatic encephalopathy. Protein restriction is most effective when liver disease is stable and the episodes of encephalopathy are related to exogenous sources. When encephalopathy is caused by active hepatic disease and an inability to utilize endogenous amino acids, the diet is less effective. The cause of encephalopathy is uncertain. The "false-neurotransmitter" theory suggests that biogenic amines derived from tyrosine and phenylalanine may be involved in the development of hepatic encephalopathy. In cirrhosis, the ratio of branched-chain amino acids (BCAAs) (leucine, valine, and isoleucine) to tyrosine and phenylalanine is decreased from between 3 and 3.5 to less than 1.0. Because BCAAs

TABLE 12-21. Nutritional Support Guidelines for Management of Protein Intake in Patients with Alcoholic Liver Disease

Disease/ complications	Aim of support	Calories (g/kg)	Protein (g/kg)	CHO	Lipid	Other
Fatty liver	EtOH abstinence	Decreased	nr	nr	nr	nr
Alcoholic hepatitis	Prevent PEM	40	1.5–2.0	4–5	1.2	Vitamins
Cirrhosis, no malnutrition	Prevent PEM	35	1.3–1.5	4–5	1–1.5	
Cirrhosis + malnutrition	Prevent PEM	35–40	1.5–2.0	3–4	2–2.5	Vitamins
Protein intolerance	Prevent encephalopathy	~25 BCAA	0.3–0.5	2.5–3.5	1–1.5	Fluid restrict
Ascites, edema		Recompensate				Fluid 1–1.5 L/day Na restrict

EtOH, ethanol; nr, no recommendation; PEM, protein-energy malnutrition; BCAA, branched-chain amino acids; Na, sodium.
Adapted from Stickel F, Hoehn B, Schuppan D, Seitz HK. Review article: nutritional therapy in alcoholic liver disease. *Alimen Pharmacol Ther.* 2003;18:357.

compete with aromatic and sulfur amino acids for transport into the brain, it is rational to use either a low intake of protein or a relative increase in BCAAs in the diet to prevent this effect (135).

However, it is not known whether BCAA mixtures are superior to standard amino acid mixtures. Protein-sparing nutritional support produces some improvement in liver function, but it is not clear that such support alters mortality or morbidity (136). Guidelines for nutritional management of alcoholic liver disease have been developed by the American College of Gastroenterology and by the European Society for Parenteral and Enteral Nutrition (137) (Table 12-21). BCAAs are recommended only for protein intolerance. A systematic review of 11 randomized studies comparing BCAA to isonitrogenous regimes showed that for a median intake of 28 g per day (range 11 to 57) and mean duration of 7 days (range 4 to 90 days), BCAA increased the percent of patients improving from encephalopathy (59% versus 41%), but without evidence of improved survival or adverse events (138,139). Some studies show a high frequency of noncompliance and side effects when BCAAs are used, factors that limit the practicality of using this form of supplement (140).

Chronic Renal Failure. In chronic renal failure, a low-protein diet is used to decrease the production of nitrogenous waste products that must be excreted (e.g., urea, uric acid). This diet stresses the essential amino acids because they tend to be used preferentially for protein synthesis and are not deaminated with subsequent production of urea. Restriction of dietary protein to about 0.6 g per kg of body weight reduces the relative risk for renal failure by about 33% (141). The details of this special use of the low-protein diet are discussed in Chapter 13.

Hospitalized Patients. Many elderly hospitalized patients meet less than 50% of their recommended protein and energy requirements, so that the risk for a poor outcome is increased (142). This unintended low-protein diet is a consequence of many factors, including a decreased appetite and the administration of medications. Supplementing the hospital diet with 20 g of milk protein per day (up to about 1.0 g of total protein per kilogram per day) slowed the rate of bone loss, increased levels of insulin-like growth factor 1, and shortened hospital stay in patients after hip fracture (143). Whether supplementation with

specific growth factors is needed or whether protein replacement alone is enough is still a matter of considerable debate (144).

Indications

In patients with **chronic liver disease** and hepatic encephalopathy, a low-protein diet can be useful. However, the diet must still supply protein at the required rate of 0.5 to 0.8 g per kg per day. For this reason, restricted diets that provide less than 40 g per day for an adult or 1.0 to 2.5 g of protein per kg daily for a growing child may be associated with a negative nitrogen balance.

In **hyperammonemia** of any cause, such as certain *inborn errors of metabolism* (e.g., isovaleric acidemia), this diet decreases available substrate.

Renal failure, whether acute or chronic, must be treated with a low-protein diet (see Chapter 13).

Practical Aspects

General Instructions

1. The caloric intake as carbohydrate should be sufficient to prevent the use of protein in muscle for energy (25 to 40 kcal per g of protein). For patients too ill to eat, parenteral administration is appropriate.
2. For patients with renal disease, 80% of the daily protein allotment should be protein of high biologic value—eggs, meat, fish, poultry, milk.
3. For patients with hepatic encephalopathy, the intestinal absorption of protein by-products should be reduced by concomitant treatment with lactulose (30 mL three or four times daily to produce loose stools) or neomycin (1 g two to four times daily).
4. An intake of 40 g of protein barely maintains nitrogen balance. Lesser amounts of protein can be used acutely but should not be prescribed on a long-term basis. Vegetable protein may be better tolerated than animal protein because it contains less tryptophan and sulfur amino acids, which are thought to contribute to hepatic encephalopathy.
5. The use of BCAA supplements is still not established, and no convincing data are available to indicate that such supplements are more effective in relieving acute or chronic encephalopathy than are standard amino acid mixtures (136). The guidelines for patient selection and the endpoint of therapy are unclear, as is the demonstration of clear long-term benefit to the patient. Recommended doses of the oral products (e.g., Hepatic-Aid) are 15 to 60 g per day; for IV use (e.g., HepatAmine), they are 80 to 120 g per day (see Chapters 10 and 11 for the composition of these products). HepatAmine contains three amino acids (methionine, phenylalanine, and tryptophan) thought to contribute to hepatic encephalopathy. The doses mentioned above are recommended by the manufacturer and may be too high. Because efficacy is not proven, these products should be used with caution, especially at the recommended high doses.
6. For patients with renal disease, sodium and potassium must also be restricted.

Specific Instructions. Each ounce of meat, fish, poultry, or cheese contains about 7 g of protein, an egg contains 6 g, and 1 cup of milk contains 8 g. One-half cup of cereal, bread, pasta, or a vegetable contains 2 g of protein, whereas the same amount of dried beans, peas, or nuts contains 5 g or more. Table 12-22 lists the protein content of various foods. The National Kidney Foundation (116 East 27th Street, New York, New York 10016) provides further information useful for patients. See Chapter 13 for details of the use of protein restriction in renal disease.

Side Effects

When protein restriction is too severe, catabolized muscle mass provides the amino acids needed for daily use (see Chapter 5). It is not wise to restrict protein to less than 0.4 g per kg of body weight (~30 g of protein for the average 70-kg patient). If the symptoms of hepatic encephalopathy or uremia do not respond to this degree of restriction, it is unlikely

TABLE 12-22. Protein Content of Selected Foods

Food	Protein (g/unit)	Food	Protein (g/unit)
Egg, 1 large (100)[a]	**6.5**	**Breads and cereals (65)**	
Milk products (93)		Bread (1 slice)	2.2
Milk		Cereal, dry (3/4 cup)	1.1–2.1
Whole (1 cup)	8.5	Rice, cooked (1/2 cup)	2.0
Skim (1 cup)	8.8	Roll (1)	2.6
Buttermilk (1 cup)	8.1	Spaghetti, cooked (12 cup)	3.4
Ice cream (1 cup)	9.6	**Vegetables (72)**	
Cheese (1 oz)	6.6–7.5	Asparagus, cooked (2/3 cup)	2.2
Yogurt, low-fat, fruit (1 cup)	9.8	Broccoli, cooked (2/3 cup)	1.7
Meat, fish, poultry (75)		Cabbage, raw (1/2 cup)	1.3
Hamburger (3 oz)	21.9	Cauliflower, cooked (2/3 cup)	2.3
Sirloin steak (3 oz)	22.2	Cucumber, raw (1/2 cup)	0.3
Lamb chop (3 oz)	19.2	Eggplant, cooked (1/2 cup)	2.0
Lamb leg (3 oz)	23.4	Lettuce (4 leaves)	1.7
Pork chop (3 oz)	22.2	Green pepper, raw (1)	1.2
Liver, beef (3 oz)	23.7	Spinach, cooked (1/2 cup)	3.0
Chicken, white meat (3 oz)	21.6	Green beans (1/2 cup)	0.8
Chicken, dark meat (3 oz)	18.6	Tomato (1)	1.1
Frankfurter (3 oz)	18.6	Green peas, cooked (12 cup)	4.3
Fish		Legumes, dried (1 oz)	6.7
Cod (3 oz)	25.5	**Fruits**	
Halibut (3 oz)	22.8	Apple (1)	0.2
Salmon, canned (3 oz)	17.7	Apricots (1)	0.5
Tuna, canned (3 oz)	26.1	Bananas (1)	1.2
Shellfish		Cantaloupe (quarter)	1.0
Crabmeat (3 oz)	12.9	Orange (1)	1.0
Lobster (3 oz)	12.6	Orange juice (1/2 cup)	0.7
Shrimp (3 oz)	14.4	Pear, peach (1)	0.6
Bacon (2 slices)	6.0	Watermelon (1 cup)	0.9
Nuts (55)			
Peanuts (6 nuts)	2.6		
Peanut butter (1 tbs)	4.2		

[a] Biologic value is based on the ability of the protein to produce positive nitrogen balance. The numbers in parentheses correspond to an average value for that food group versus 100% for egg.

that more stringent restriction will help. When the intake of meat and milk is restricted, it is possible that calcium, iron, and B vitamins (thiamine, riboflavin, niacin) will be needed.

Supplements Required

In renal failure, calcium is often needed to compensate for hypocalcemia and a decreased calcium intake. Iron deficiency resulting from bleeding gastrointestinal lesions often complicates renal failure, but iron is sometimes needed even in the absence of overt gastrointestinal bleeding.

High-Protein Diet and Protein Supplements

High-Protein Diet

The traditional diet for reducing the risk of obesity, heart disease, and cancer has been a high-carbohydrate, low-fat diet (~15%, 15%, and 70% of calories as protein, fat, and carbohydrate, respectively), but results have been disappointing. The average diet in the United States contains ~14%, 34%, and 48% of calories as protein, fat, and carbohydrate,

respectively (145). The success of the low-carbohydrate, high-protein (~30%, 30%, and 40% of calories as protein, fat, and carbohydrate, respectively) diet in causing initial weight loss (145, and Chapter 14) has led to a number of new observations on the relative effects of these two diets. Obesity is currently viewed as a problem equally as important as lowering lipoprotein levels, and the high-protein diet has become popular. There is little evidence that the high-protein diet can maintain weight loss for an extended period of time (87), nor that such diets can prevent heart disease (146). The DRI Committee of the Institute of Medicine has allowed a higher amount of protein in the DRI than previously allowed, suggesting 10% to 35% of calories as an acceptable protein proportion (31). Although high protein intake can increase urinary calcium and nitrogenous waste products, the DRI Committee found no evidence that a high protein intake increases the risk of renal stones, cancer, osteoporosis, or cardiovascular disease. However, the effect of consumption of large amounts of protein (30% to 35% of calories) on kidneys and bones is not known. Moreover, high-protein diets restrict other healthful foods, and are not recommended for weight loss by the American Heart Association (145).

Protein Supplements

Undernutrition is seen with many chronic medical disorders, and represents either a marker for disease severity, or the result of a primary effect on food intake, or both. Thus, oral protein and energy supplements have been prescribed for many patients at risk for undernutrition. A meta-analysis of 55 such randomized trials in older people found that such supplements might reduce mortality and complications of undernourished elderly patients in the hospital (147). However, these supplements did not seem to have an effect when given to patients in a home setting. Many trials reported gastrointestinal problems, e.g., nausea, vomiting, and diarrhea, associated with the use of the supplements.

Energy-protein supplements have been advocated as a means to improve wound healing. A meta-analysis of five randomized controlled studies showed that supplementation (250 to 500 kcal per day) reduced the incidence of pressure ulcers by ~25% (148). The amino acid arginine potentially has a role in wound healing as an immunomodulator, but there are no convincing data for its efficacy when supplements are provided.

Glutamine

Glutamine, along with aspartate, is an important energy source for the small intestine, but it has not been classified as an essential amino acid (31). A special role for glutamine has been suggested for critically ill patients, as it is the most abundant extracellular amino acid, is utilized at high rates by intestine, CNS, and immune cells, and its serum levels fall during critical illness. However, the data do not clearly support such a claim (149–151). Clinical efficacy of supplemental glutamine (either p.o. or parenteral in doses from 10 to 60 g per day) leads in some studies to some improvement in immunologic measures, reduction in costs, in rates of infectious complications (150), and in treatment of mucositis from chemo- or radiotherapy (152), although not all reports confirm these conclusions. One study with surgical ICU patients shows an increase in mortality (6.2% in controls to 17.7% in those supplemented with glutamine 0.25 to 0.5 g/kg/day) (153). The problems with assessing the considerable literature on glutamine are many, and include the greatly different patient populations, the variety of endpoints tested, the relatively short follow-up, the lack of adequately powered studies, and the lack of reproducible improvement of significant endpoints (151). Further studies are needed before glutamine supplementation can be recommended for use in critically ill patients.

The other use for glutamine that has been recommended is to stimulate small intestinal growth in patients with short bowel syndrome. All of the studies have combined oral glutamine (Gln) with parenteral recombinant human growth hormone (GH), providing both substrate and hormonal stimulation to enterocyte growth, although neither stimulus is specific for the intestine. Most of the early studies were open label and not controlled. One randomized double-blind controlled trial of 41 patients has shown some efficacy for the combination (154). Patients receiving GH + Gln + diet had a larger reduction in

parenteral nutrition volume per week than either Gln + diet or diet alone. There was no effect of glutamine alone, nor was there any added effect of glutamine to GH when compared to GH alone. GH alone may be indicated in patients with <150 cm of small bowel remaining or with 60 to 90 cm of small bowel with a portion of functioning colon, if a specialized diet is included, one rich in protein (~20% of calories), low-moderate fat content (~30%), and high in complex carbohydrates (~50%). However, it is not clear how many patients are able to be weaned from parenteral nutrition completely. Current data do not support the addition of glutamine to this program.

Arginine

Arginine is not considered an essential amino acid according to the current Institute of Medicine recommendations (31). However, as in the case of glutamine, it is suggested that critical illness, in this case sepsis, produces a state of conditional deficiency (155). Arginine is a precursor for nitric oxide, and its potential benefits are related to replacing NO in severe illness (156). It can be provided safely at doses of 12 to 14 g per L parenterally (2 L per day) or 30 g orally per day, and can improve certain laboratory endpoints in some studies, but evidence for clinical efficacy is still uncertain (157). Most studies providing arginine do so when combined with n-3 fatty acids, branched chain amino acids, and nucleotides in commercial products that are marketed to modulate immunity. The benefits reported include reductions in infectious complications, increased immune function, and length of hospital stay, similar to the range of benefits suggested for glutamine supplementation. The same problems with study design that are found with glutamine recur in studies with arginine supplementation. Reviews of the data either do (158–160) or do not support the recommendation of providing arginine or other immunomodulatory substances to critically ill patients (161–163). If there is a role for such intervention it is not clear at what degree of severity the benefit would begin, or which component(s) of the commercial immunonutrition products are important. Currently it is not possible to make a recommendation for routine addition of arginine or the commercial immunonutrition products that contain it. Further studies are needed to see if there is indeed an effect on infectious complications, the situation in which the data are the most suggestive of a benefit.

Taurine

Taurine is a semiessential amino acid that is not incorporated into proteins. It is the most abundant free amino acid in the heart, retina, skeletal muscle, and leukocytes, reaching 20 to 50 mM in the latter tissue (164). The intracellular concentration is largely controlled by the synthetic enzymes cysteine dioxygenase (CDO) and cysteine sulfinate decarboxylase (CSD), and the taurine transporter, TauT (165). Taurine scavanges perchlorate (HOCl) formed by myeloperoxidase activity, to form the less toxic Tau-Cl. It is this action that is thought to contribute to its anti-inflammatory action in animal models. Taurine is an essential amino acid for preterm neonates to prevent retinal damage, and is provided in breast milk. Individuals at risk for deficiency who may benefit from supplementation include premature and newborn infants on parenteral nutrition, and those with chronic hepatic, heart, or renal failure (166).

The diet is the usual source of taurine, although it can be synthesized from methionine and cysteine in the presence of vitamin B_6. Taurine is included in commercially produced mixtures of amino acids. Trophamine was designed for term and premature infants up to age 3 months, and replicates the serum amino acid concentrations of a breast-fed infant. A 1.6% solution contains 4 mM taurine. Taurolidine (Geistlich Pharma, AG, Wolhusen, Switzerland) is a derivative of taurine that is used in Europe, the United Kingdom, and the United States as adjunctive treatment for infections. It is composed of two taurolidine rings derived from taurine and three molecules of formaldehyde to form a two-ringed structure. It has a short half-life, and its activity may be due to more than just the taurine components. When impregnated into cathetes, taurolidine has been effective in preventing bloodstream infections in a few studies (167). However, it does not appear to be antibacterial enough to be useful in a serious infection, such as peritonitis (168). Further studies will be needed to determine the benefits of replenishing taurine pools or adding taurine routinely to parenteral nutrition regimens.

Gluten-Restricted Diet

Principles

Toxic Grain Products. Nontropical sprue (celiac sprue, gluten-sensitive enteropathy) is a disorder characterized by sensitivity to certain glutens. Glutens are a family of proteins found in many grains, including corn and rice, which are safe for patients with celiac disease. The glutens that produce symptoms in this disorder are those in wheat, rye, and barley (169). Foods containing gluten include bread, pasta, cereals, gravies, sauces, pastries, cakes, cookies, crackers, soups, and any food with bread or grain additives from the list in Table 12-23. The data implicating oats have been shown to be misleading, because there is a high risk of gluten contamination in their preparation. Oats have been well tolerated in patients with dermatitis herpetiformis, a related disorder (170). No clinical or biopsy differences were seen in adults with celiac disease ingesting oats over a 5-year period (171).

Substitutions. Glutens from corn and rice, in addition to those from wheat starch, potato flour, soybean flour, and tapioca, may be used as substitutes for the omitted cereal grains. Other "grains" that do not contain disease-causing gluten include amaranth, millet, quinoa, sorghum, teff, wild rice, and buckwheat. The latter is not a true cereal grain, and when toasted is known as kasha. Its flour is used to produce the unique flavor of crepes from the region of Normandy in France.

Wheat products are used as fillers in many processed foods. It is helpful for the patient with sprue to develop an extensive list of acceptable products.

Duration of Diet. Although a gluten-free diet was formerly thought to be needed only until remission occurred in some patients, it is now clear that use of the diet should be lifelong (172). No convincing evidence indicates that the diet is useful for the nonspecific therapy of other diarrheal illness. However, acute intestinal damage resulting from conditions other than sprue may cause temporary gluten intolerance, especially in children. The long-term use of this diet should be limited to patients with gluten-induced enteropathy.

Relationship to Traditional Allergy. The abnormal response to wheat and other glutens in sprue differs from other food allergies in that the process is not mediated by immunoglobulin E. However, abnormalities of the intestinal immune system are involved in some way. In some cases, treatment with glucocorticosteroids can supplement dietary management of the disease (106).

TABLE 12-23. Classification of Grains According to Gluten Content

Gluten containing	Gluten-free
Barley	Amaranth
Bran	Buckwheat/kasha, whole or cracked grain
Bulgur	Corn, whole grain and flour
Couscous	Millet, whole grain
Durum wheat	Oats (some products may be contaminated with wheat)
Farro	Popcorn
Farina	Potato flour
Graham flour	Quinoa, whole grain
Kamut	Rice, brown/white/wild
Orzo	Sorghum, whole grain
Rye	Soybeans
Spelt	Teff, whole grain
Wheat, any type	Tapioca

Modified from See J, Murray JA. Gluten-free diet: the medical and nutrition management of celiac disease. *Nutr Clin Pract*. 2006;21:1.

Indications

A gluten-restricted diet is necessary for patients with biopsy-proven *nontropical sprue* or the related disorder *dermatitis herpetiformis*.

Practical Aspects

General Instructions

1. Eliminate foods containing wheat, rye, barley, and probably oats (Table 12-23 and Table 12-24). These glutens are the components that give form to dough. The flours allowed on a gluten-restricted diet produce flat or crumbly baked products. Any commercial product with a crown contains forbidden gluten. To meet the codex standard to be labeled "gluten-free" the product must contain <20 ppm of gluten, i.e., if the total nitrogen content of the product gluten does not exceed 0.05 g per 100 g based on dry matter (World Health Organization standard).
2. Read labels carefully. Avoid products that contain wheat, rye, barley, oats, unspecified flour or starch, emulsifiers, stabilizers, hydrolyzed plant/vegetable protein, vegetable monoacylglycerols or diacylglycerols, and natural flavorings. Some of these products may in fact be gluten-free, but the absence of gluten should be verified with an up-to-date gluten-free product list, or the company should be contacted.
3. The foods most likely to contain glutens include cereal beverages (beer, Ovaltine), some commercial ice creams, commercial cakes and cookies, salad dressings, canned or processed meats, soups, candy bars, catsups, mustards, frozen foods with sauces, processed cheeses, chocolate milk, cream soups, most soy sauces, and breaded, creamed, or scalloped vegetables.
4. Products made from cornmeal, cornstarch, corn flour, rice, rice flour, tapioca, soybean, potato starch, or arrowroot may be used. For baking, 1 cup of wheat flour may be replaced by 1 cup of corn flour, 1 cup of fine cornmeal, 3/4 cup of coarse cornmeal, 10 tbs of potato flour, or 14 tbs of rice flour. For thickening, 1 tbs of wheat flour can be substituted with 1/2 tbs of cornstarch, potato flour, rice, or arrowroot starch or 2 tbs of quick-cooking tapioca.
5. Fresh meats, milk, fish, eggs, fresh vegetables, and fruits are all acceptable.

A low-lactose diet may be needed in the early stages of treatment if lactose intolerance is present.

Over-the-counter and prescription medications and vitamin/mineral supplements may contain gluten (starch, dextrins, etc.) as an inert component in the capsule or coating, or mixed with the medication itself. Products made with generic ingredients should be avoided unless the manufacturer can confirm the source of the product components.

Patient information on this topic is available in Appendix D.

Specific Recommendations

Patient support groups. Each of these groups can provide recipes, lists of gluten-free commercial products, and information on gluten content in medications.

CSA/USA (Celiac Sprue Association)
PO Box 31700, Omaha, NE 68131-0700
Tel: 402-558-0600, url: *www.csaceliacs.org*.

The website contains useful information on grains and flours, gluten-free diets, and lactose intolerance.

Gluten Intolerance Group of North America
15110 10th Ave SW, Suite A, Seattle, WA 98166
Tel: 206-246-6652, url: *www.gluten.net*.

Celiac Disease Foundation
13251 Ventura Blvd, Suite 1, Studio City, CA 91604-1838
Tel: 818-990-2354, url: *www.celiac.org*

TABLE 12-24. Sources of Gluten[a]

Food groups	Foods that contain gluten	Foods that may contain gluten	Foods that do *not* contain gluten
Beverage	Cereal beverages (e.g., Postum), malt Ovaltine, beer, and ale	Commercial chocolate milk; cocoa mixes; other beverage mixes; dietary supplements; commercial rice and corn cereals[b]	Coffee; tea; decaffeinated coffee, carbonated beverages; chocolate drinks made with pure cocoa powder; wine; distilled liquor
Meat and meat substitutes		Meat loaf and patties; cold cuts and prepared meats; sausage; stuffing; breaded meats; cheese foods and spreads; commercial soufflés, omelets, and fondues; soy protein meat substitutes	Pure meat, fish, fowl, egg, cottage cheese, cheeses, and peanut butter
Fat and oil		Commercial salad dressing and mayonnaise, gravy, white and cream sauces, nondairy creamer	Butter, margarine, vegetable oil
Milk	Milk beverages that contain malt	Commercial chocolate milk	Whole, low-fat, and skim milk; buttermilk
Grains and grain products	Bread, crackers, cereal, and pasta that contain wheat; oats; rye; malt and, malt flavoring; graham flour, durum flour, pastry flour; bran or wheat germ; barley; millet; pretzels; communion wafers	Commercial seasoned rice and potato mixes, commercial corn, rice, and potato snacks	Specially prepared breads made with wheat starch,[c] rice, potato, or soybean flour, or cornmeal; pure corn or rice cereals; hominy grits; white, brown, and wild rice; popcorn; low-protein pasta made from wheat starch
Vegetable		Commercial seasoned vegetable mixes; commercial vegetables with cream or cheese sauce; canned baked beans	All fresh vegetables; plain commercially frozen or canned vegetables
Fruit		Commercial pie fillings	All plain or sweetened fruits; fruit thickened with tapioca or cornstarch

Soup	Soup that contains wheat pasta; soup thickened with wheat flour or other gluten-containing grains	Commercial soup, broth, and soup mixes	Soup thickened with cornstarch, wheat starch, or potato, rice, or soybean flour; pure broth
Desserts	Commercial cakes, cookies, and pastries; commercial dessert mixes	Commercial ice cream and sherbet	Gelatin; custard; fruit ice; specially prepared cakes, cookies, and pastries made with gluten-free flour or starch; pudding and fruit filling thickened with tapioca, cornstarch, or arrowroot flour; some commercial ice creams
Sweets		Commercial candies, especially chocolates	
Miscellaneous		Catsup; prepared mustard; soy sauce; commercially prepared meat sauces and pickles; vinegar; flavoring syrups (syrups for pancakes or ice cream)	Monosodium glutamate; salt; pepper; pure spices and herbs; yeast; pure baking chocolate or cocoa powder; flavoring extracts; artificial flavoring

[a] The terms *commercially prepared* and *commercial* are used to refer to partially prepared foods purchased from a grocery or food market and to prepared foods purchased from a restaurant.
[b] Check up-to-date lists of gluten-free commercial products.
[c] Wheat starch may contain trace amounts of gluten. Avoid if not tolerated.
Modified from *Mayo Clinic Diet Manual,* 6th ed. Toronto: BC Decker, 1988.

Coeliac Society of the United Kingdom (*www.coeliac.co.uk*)

Canadian Celiac Association
5170 Dixie Road, Suite 204, Mississauga, ON L4W1E3, Canada
Tel: 905-507-6208, url: *www.celiac.ca*

Gluten-free cookbooks. These are available in many of the large retail bookstores. Useful books that may not be available in such stores include:

Shelley Case. The gluten-free diet: a comprehensive resource guide (expanded edition), Centax Books, 2006

Donna Washburn & Heather Butt. The best gluten-free family cookbook. Robert Rose, Inc, 2005.

Safe commercial products. The new Food Allergen and Consumer Protection Act of January 1, 2006 should be helpful to consumers. If any product contains one of the top eight allergens (milk, egg, soybean, tree nuts, peanuts, shell fish, fish, or wheat), the ingredient must be clearly identified on the label. However, the new law does not require foods with barley or rye to be identified. Among the many foods that often contain offending glutens, it is possible to select products that are safe. Therefore, another brand name should not be substituted for one known to be gluten-free unless it, too, is known to be gluten-free. The Celiac UPC database (*www.brandbeach.com/celiac/upc/index.html*) has been created to help patients with celiac disease determine whether a product is gluten-free according to the product's UPC code. The database can be used on line or on a hand-held personal computer. For a "complete" list of products, one of the patient support groups can also be contacted. The chain health food store, Wild Oats, maintains a gluten-free product guide (www.wildoats.com). An approach to providing effective education and resources for patients emphasizes the overlooked sources of gluten, and provides many book titles, magazines and newsletters, cookbooks, travel and dining resources, and other helpful items (173). Useful websites for obtaining grain substitutes include www.arrowheadmills.com, www.thebirkettmills.com, www.bobsredmill.com, www.quinoa.com, and www.wholegrainscouncil.org.

Gluten in drug products. Gluten is often added as an "inert" filler in tablets, capsules, and suspensions. Most major manufacturers do not use gluten. The CSA/USA has a listing of relevant pharmaceuticals.

Gluten when eating out. The physician/dietitian should be able to assist patients in eating out in restaurants. The factors to keep in mind are the gluten content of the foods, how they have been prepared, and whether they might have come into contact with any source of gluten. The patient should announce that they have an allergy to wheat, and then ask whether the food has been marinated in soy sauce, teriyaki sauce, or Worcestershire sauce, whether it has been dusted with flour before pan-frying, whether it was cooked in oil or a utensil that was also used to cook breaded products, whether there are croutons in the salad, and whether artificial products that might contain gluten are used, such as mashed potato mix, seitan (meat substitute), imitation crabmeat, or artificial bacon. Menu terms that include flour include au gratin, béchamel, a la meuniere, encrusted, dusted, fricassee, fritter, gnocchi, gravy, roux, scallopini, tempura, and veloute. Terms that include soy sauce (unlikely to be gluten-free) include marinade and teriyaki sauce.

Side Effects

The gluten-restricted diet can be well balanced for all nutrients and so no side effects are associated.

Supplements Required

No supplements are needed unless the malabsorption has caused specific deficiencies or unless the lactose intolerance is permanent and calcium supplements are required. Celiac disease is an important cause of osteoporosis, and adequate calcium (1,200 mg per day) and vitamin D (400 IU) must be provided to restore bone density in patients whose axial bone density is decreased.

Low-Oxalate Diet

Principles

Hyperoxaluria resulting from an increased absorption of dietary oxalate occurs in disorders in which bile acids are poorly absorbed, enter the colon, and increase its permeability (106). The degree of oxaluria in such cases is inversely correlated with the degree of fat absorption. The excessive free fatty acids in the lumen of the small bowel that result from fat malabsorption bind calcium, which is then not available to form the insoluble calcium oxalate salt. Consequently, the more soluble sodium oxalate forms and is absorbed in the colon. However, only about 10% of the body oxalate is normally derived from the diet. Therefore, a low-oxalate diet is not always effective in reducing hyperoxaluria.

Indications

This diet is used in cases of *hyperoxaluria* (>40 mg per day). Hyperoxaluria develops in a subset of patients with renal stones (idiopathic hyperoxaluria) and in patients with *steatorrhea* resulting from *bile acid malabsorption* (e.g., short bowel syndrome, SBS). The diet can begin before calcium oxalate stones have formed. After the diet has been started, urinary excretion should be remeasured to ascertain that the diet is effective.

Calcium supplements often must be added in cases of SBS because poor calcium absorption and a negative calcium balance can lead to osteopenia. When luminal calcium is increased, the calcium oxalate salt may re-form and the hyperoxaluria decrease without use of the diet. In some instances, both treatments are given together.

Practical Aspects

The low-oxalate diet is often part of the regimen of patients requiring a *low-fat diet*. In evaluating the progress of a patient on a restrictive diet, one should determine the patient's compliance. General guidelines for reducing the risk of developing renal stones have been provided by the American Dietetic Association's *Nutrition Care Manual* (174). The oxalate content of foods varies according to soil conditions, ripeness of the food, and processing. There are differences in analytic methods as well that make it difficult to provide precise values for food. With these caveats, a full listing of oxalate content of selected foods is available from the General Clinical Research Center, University of California, San Diego Medical Center (Brzezinski E, Durning AM. Oxalate content of selected foods with recipes and menu suggestions. 2002). To order call 800/520-7323.

Foods High in Oxalate. Certain snack foods are high in oxalates, such as cola beverages, nuts, potatoes, tea, and foods containing chocolate. Meats and dairy products are generally low in oxalate. Only recently has the oxalate content of flours been published, and it is clear that whole grain wheat, especially durum wheat, has a high oxalate content (175). Foods with a very high content (>10 mg per serving) should be avoided completely. A detailed listing of the oxalate content of foods can be found in standard diet manuals and nutrition textbooks (1,2,176). The following paragraphs indicate the oxalate content of selected foods.

Patient information on this topic is available in Appendix D.

Foods very high in oxalate (>10 mg per serving): spinach, rhubarb, cocoa, chocolate, tea, Ovaltine, beer, peanut butter, green beans, beets, Swiss chard, collards, kale, eggplant, sweet potatoes, blueberries, Concord grapes, strawberries, raspberries, fruit cocktail, wheat germ, wheat bran, whole grain wheat bread or other whole wheat grain products, pepper (>1 tsp per day), turmeric, tomato soup, nuts (especially peanuts, pecans, walnuts, almonds). Indian or Chinese teas made from *Camellia sinensis* are rich in oxalate; herbal teas, which are not true teas but derived from other plant sources, contain much less oxalate (176).

Foods moderately high in oxalate (2 to 20 mg per serving): parsley, turnip greens, brussels sprouts, tomatoes, lima beans, lettuce, corn, broccoli, figs, oranges, cola beverages, juices (orange, tomato, grape), apple, pear, pineapple, sardines.

Side Effects
None.

Supplements Required
None.

Elimination Diets for Allergy or Intolerance to Foods

Principles

Food Allergy and Intolerance. The Committee on Adverse Reactions to Foods of the American Academy of Immunology defines *food allergy* as a reaction to a specific food that is mediated by classic immune mechanisms (177,178). In the absence of evidence of classic immune mechanisms, it is better to refer to such a reaction as *food intolerance* (Table 12-25). Even in the latter case, the food should provoke a clear reaction that recurs each time the food is eaten. This sequence is lacking in many cases of so-called food intolerance.

True Allergic Reactions to Food. Allergic reactions to food, which occur infrequently in adults, are most often caused by fruit juices, nuts, chocolate, milk, and shellfish (179). The organs usually affected are the skin (~45%), respiratory tract (~25%), and gastrointestinal tract (~20%). In the oral allergy syndrome, the most common form, early symptoms develop within minutes of ingestion and include swelling of the lips, tingling in the throat, and rhinorrhea. Later symptoms (developing within 2 hours of ingestion) may include asthma, urticaria, eczema, vomiting, diarrhea, abdominal pain, headache, and general malaise. Allergens can be inhaled as well as ingested (e.g., flour, spices, egg white, steam produced when legumes or crustaceans are cooked), and inhalation leads to respiratory symptoms.

Diagnostic Tests. The best diagnostic test for suspected food allergy is the controlled double blind food challenge (180). Tests that identify immunoglobulin G antibodies (e.g., radioallergosorbent test, enzyme-linked immunosorbent assay) do not prove the presence of an immunoglobulin E immune complex. Allergies are more common in children because their immunoglobulin E levels are much higher than those of adults. For this reason most of the diagnostic procedures have been validated and used most extensively in children. Most reactions to fruits/juices disappear by age 3. Allergy to pollen-related food is the most common food allergy in adults in countries where tree pollen allergy is common. Primary pulmonary sensitization to pollen from trees, grasses, or herbs can give rise to food allergies when epitopes are shared. These cross reactions lead most often to symptoms of the

TABLE 12-25. Classification of Food-induced Reactions

IgE-mediated	Not IgE-mediated	Food intolerance	Food aversion
Urticaria/ angioedema	Dermatitis herpetiformis	Lactose/sucrose	Chronic fatigue
Atopic dermatitis	Contact dermatitis	Fructose/sorbitol	Irritable bowel
Rhinoconjunctivitis	Celiac disease	Histamine (scombroid)	Depression
Oral allergy syndrome	Eosinophilic enteritis		Phobias
Anaphylaxis	Heiner syndrome[a]	Bacterial enterotoxins Plant/phytotoxins	ADHD
Food protein enteropathies	Migraine headaches	Food additives	IBD, flatus

ADHD, attention-deficit hyperactivity disorder; IBD, inflammatory bowel disease.
[a] Heiner syndrome is milk-induced alveolitis and hemorrhagic gastroenteritis in infants.

oral allergy syndrome and occur most often in patients with hay fever. Birch pollen proteins cross react with proteins in apple, carrot, cherry, apricot, plum, and celery; ragweed pollen cross reacts with melons; and grass pollen cross reacts with peach, potato, tomato, and cherry (181). Because these proteins are labile, cooked fruits and vegetables do not produce symptoms. For example, natural latex dermatitis can be associated with food allergies to banana or avocado, and birch pollen allergy can be associated with hazelnut or kiwi food allergy (177). The value of an elimination diet is that an offending food is identified by adding a single food at a time. This maneuver is necessary when the history does not provide the clue, and it can be used to identify allergies to both food additives and natural food components. The history remains the best means of identifying symptom complexes caused by true allergies.

Diagnosis

Foods. Foods most commonly implicated include milk, eggs, nuts, and shellfish. Less commonly involved are wheat, chocolate, cheese, soft fruits, and meat. Artificial coloring agents in addition to virtually all foods have been implicated in nonimmunologic adverse food reactions. One should remember the rules for food labeling when trying to determine the presence of a food additive. The Codex General Standard on Labeling states that "all ingredients shall be listed in descending order of ingoing weight at the time of the manufacture of the food." When a compound ingredient constitutes less than 25% of a food, ingredients other than food additives need not be declared (177). In other words, a substance that is present as only a minor ingredient of a food must be declared, but a substance that is more abundant but part of a compound ingredient may not be listed. In addition, food additives with no technologic function in the finished product (e.g., egg whites or milk used as clarifying agents in juices or wine) may not be declared on the label. New labeling laws may change these rules, but currently one must realize that not all substances that might cause a food allergy must be listed on the label.

Tests. If anaphylaxis occurs, no challenge should be given. If the response is mild, skin tests and food challenge may be used. If the response is sporadic, a food diary may help. Double-blinded challenge may be needed because many patients are placebo reactors, and food intolerance is demonstrated in only a few of the adults in whom it is suspected (182). Both skin tests and radioallergosorbent tests give many false-positive results, and cross-reactions between allergens occur. The use of native food allergens seems to give better results than commercial extracts. Using native allergens, a large wheal diameter (e.g., 7 mm for egg, 8 mm for cow's milk) appears to be fairly specific (183). In most patients with irritable bowel syndrome presenting with possible food allergy, symptom over-reporting related to psychiatric disease may be a major cause of symptoms (184). Other tests have been suggested for diagnosis (179). These include radioallergosorbent tests for total serum immunoglobulin E and allergen-specific immunoglobulin E. Microdot arrays on chips can reliably identify antibodies against food allergens for those patients who have IgE mediated allergy (185). Food allergen-specific IgE serum concentrations have been correlated with the outcome of food challenge tests to develop diagnostic decision-making cutoff values for a few allergens (e.g., peanut, egg, milk, and fish), but these values vary among authors and populations (186). Atopy patch tests (APT) involve the application of intact protein allergens in a patch directly onto the skin. The test is quite reliable for some allergens, less so for others. The European Task Force on Atopic Dermatitis has developed a standardized APT technique (187), but the test is still not as well validated as the other tests. If the results of oral testing (elimination and provocation) are positive, the results of IgE or APT testing should match the clinical history. The problem with oral testing is that it is time consuming, so prospective IgE tests can be useful when used selectively.

Double-Blinded Oral Control Challenge. This is the "gold standard" but is difficult to carry out in clinical practice and can be dangerous if anaphylaxis is suspected. It is usually more convenient to use an open or single-blinded food challenge. Both negative and positive results are highly predictive of the correct answer. When a positive allergic history is present or a food allergy is strongly suspected, an *elimination diet* can be tried. This diet is usually reserved for patients having daily or almost daily symptoms.

Practical Aspects

True Food Allergies (Adults). The strictest diet, which is rarely needed, consists of lamb, rice, dry puffed rice, salt, and water for 5 to 7 days. One new food is then added each day, with relatively nonallergenic foods usually added first. Allergenic foods such as milk, eggs, wheat, and corn are finally added. No fat can be added to any prepared food. Salt or baking soda must be used to brush the teeth (77).

A less strict initial diet (modified from Golbert TM. In: Patterson R, ed. *Allergic Diseases*. Philadelphia: JB Lippincott Co, 1972:362) allows the following foods and beverages (all fruits and vegetables *must be cooked*): lamb, poi, rice, rice cereals, water, pineapple, apricot, cherries, blueberries, lettuce, artichokes, beets, spinach, celery, sweet potatoes, salt, sugar, and tapioca. Any vegetable oil is allowed except oleomargarine and soy oil. Mazola margarine contains no milk and is acceptable. Specific foods to be avoided include pork, beef, fish and seafood, eggs, milk and milk products, and baked goods made with wheat, oats, corn, or rye flour. Also to be avoided are butter, margarine, tea, coffee, cola, soft drinks, chewing gum, alcohol, and chocolate. This diet may be more useful for outpatient use. Egg is often hidden in such foods as pastries, ice creams, marshmallows, sausages, salad dressings, instant coffee, and root beer.

Addition of other foods. The patient is instructed to continue the basic diet for 5 to 7 days. On each successive day, a single cooked food is added. The patient keeps a diet diary and records the time foods are ingested, with any untold reactions. For those unable to begin with such a strict diet, the same basic diet can be used, with the following foods added: chicken, turkey, beef, boiled ham, bacon, potatoes, potato chips, carrots, soybeans, asparagus, maple syrup, ginger ale, plums, prunes, lentils, navy beans, and kidney beans. These are poorly allergenic foods that can be added in the early stages of an elimination diet. When foods must be added in double-blinded fashion, dried foods can be placed into gelatin capsules. A dose of 8 g of each food is commonly used.

Foods should be cooked in the strictest diets because heating can denature proteins and render them less allergenic.

Patients with a history of severe (anaphylactic) reactions to eggs or chicken should be tested with intradermal extracts before receiving egg-derived vaccines.

Milk Allergy (Infants). In infants with suspected milk allergy, formulas containing casein hydrolysates (e.g., Pregestimil, Nutramigen, Alimentum) work well. Because 20% of milk-allergic patients react to soy protein, soy-based formulas are not suggested.

Elimination Diet for Intolerance to Foods. A low-lactose diet for lactose intolerance is discussed separately in this chapter. The other intolerance most commonly encountered is to gas-producing foods (primarily flatus). Although it is not clear that gas production or the perception of gas production is related to the intake of specific foods, some foods undoubtedly contain oligosaccharides (e.g., stachyose, raffinose) or components of dietary fiber that escape digestion in the small bowel and are fermented in part in the colon. For the occasional patient with intolerance to gas-producing foods, an elimination diet can be suggested (188).

Foods to be avoided in a diet for gassy food intolerance (elimination on a trial basis):

Class	Examples
High-lactose foods	Dairy products
Vegetables	Legumes (beans, peas, lentils)
	Cruciferous vegetables (broccoli, cauliflower, brussels sprouts)
	Root vegetables (radishes, onion, rutabaga), cabbage, kohlrabi, cucumber, sweet peppers
Fruits	Prunes, apples, raisins, bananas
Grains	Whole wheat bread, bran cereals
Fatty foods	Fried foods, cream sauces, gravies
Artificial sweeteners	Fructose (soft drinks), sorbitol

The enzyme **α-galactosidase (Beano)**, derived from a mold, is marketed with the claim that it prevents gas from occurring with a high fiber intake. The manufacturer recommends that three to eight drops of Beano be added to a food after it has cooled below 130°F. Some evidence indicates that the treatment may be effective (189).

Adverse Reactions to Food Additives. The same range of symptoms seen in food allergy can be caused by food additives. However, food allergies are much less common, and it may not be necessary to eliminate foods with troublesome additives from the diet completely. The mechanisms for many of the reactions are unknown but may be pharmacologic, toxic, or truly allergic. These reactions are most often to salicylates, tyramine, sulfites, and monosodium glutamate.

- **Pharmacologic reactions:** caffeine (see earlier section in this chapter), monosodium glutamate (headache, asthma), tyramine, phenylethylamine in chocolate (headache), nitrite and nitrates (headache), histamine-releasing foods such as egg white, strawberry, shellfish (anaphylactoid reaction), histamine poisoning from tuna, mackerel, Swiss cheese (anaphylactoid reaction), sodium metabisulfite (asthma), salicylates in candies
- **Toxic reactions:** ethanol, acid juices (heartburn), toxins from infectious agents
- **Allergic reactions to common food chemicals:** tartrazine, menthol in breakfast cereals, candy, gum (urticaria), EDTA in mayonnaise and salad dressings (dermatitis), erythrosine in maraschino cherries and fruit cocktail, breakfast cereals (photosensitivity), sodium benzoate in catsup (purpura), quinine in tonic water, bitter lemon (purpura), sulfites

Side Effects

Care must be taken to provide a well-balanced diet, including foods from all basic groups.

Supplements Required

None.

Restricted Diets for Allergy or Intolerance to Food Additives

Salicylates/Tartrazine

The most common drug allergy for which an altered diet is important is salicylate hypersensitivity. Salicylates and tartrazine, a salicylate-related compound, can produce chronic urticaria in the sensitive patient. Most patients sensitive to aspirin also react to tartrazine.

Food Sources. Food souces of salicylates include many colas, Dr. Pepper, root beer, most carbonated soft drinks, many cereals and baked goods mixes, many fruits (apples, oranges, peaches, plums, cherries, grapefruit, berries), prepared meats, nondairy creamers, yogurt, ice cream, sherbet, most commercial dessert mixes, prepared pies and cakes, frostings, puddings, rolls, and candies. Methyl salicylate is commonly used as a flavoring agent under the name *wintergreen*. Candies containing wintergreen include gums, mints, and jelly beans. Cereals containing salicylate include breakfast squares and fruit turnover pastries. Tartrazine is included in many yellow and green candies, fruit crushes, and many antibiotic capsules and vitamin preparations.

Salicylate or Tartrazine-Free Foods. Included in this category are milk and milk products, most vegetables (except cucumbers, peppers, broccoli, asparagus, okra, spinach, squash, sweet potato, zucchini, and tomatoes), all fish, red meat, cheese, eggs, poultry, pasta, rice, white potatoes, most breads, all fats, sugar, syrup, and molasses. A more complete list of foods allowed has been published (190).

Supplements Required

A salicylate-free diet is adequate for all nutrients except vitamin C. Supplements (60 mg per day) can be provided for such patients.

Tyramine

Population at Risk. Patients taking monoamine oxidase inhibitors are at risk for the development of headache, palpitations, nausea, vomiting, and in some cases hypertensive crises if they ingest sympathomimetic drugs (methyl dopa, L-dopa, dopamine, epinephrine, ephedrine) or foods with a high concentration of tyramine. Tyramine is a biogenic amine derived from tyrosine metabolism. Inhibition of tyramine metabolism can cause hypertensive crises, which begin 30 to 60 minutes after the offending food is ingested, with headache, palpitations, nausea, and vomiting. At high doses (60 mg per kg of body weight), tyramine can cause cardiac arrhythmias, with a loss of P waves, atrial ectopies, ventricular and atrial premature beats, junctional rhythm, bigeminy, and Wenckebach phenomenon (191). It is not known whether the intake of tyramine-rich foods should be decreased in patients with arrhythmias.

Drugs That Inhibit Monoamine Oxidase. Included in this widely distributed complex enzyme system are furazolidone (Furoxone), isocarboxazid (Marplan), phenelzine sulfate (Nardil), procarbazine (Matulane), selegiline HCl (Eldepryl), transdermal selegiline (Emsam), and tranylcypromine (Parnate). Patients taking these drugs should also refrain from taking medications containing sympathomimetic drugs, especially nose drops and cold capsules, and most antidepressant medications.

Restricted-Tyramine Diet. A restricted-tyramine diet should be followed by patients taking these drugs, as they may be intolerant of ingested tyramine. The details of this diet, which provides less than 2 mg of tyramine per day, are listed in Table 12-26. Usually, more than 6 mg of tyramine must be ingested to cause symptoms when it cannot be metabolized. Cheeses with the highest content of tyramine (>200 mg per g in some cheeses) are cheddar, Camembert, and Stilton.

Sulfites

Uses and Abundance. Six sulfiting agents have been declared safe by the FDA. These chemicals are listed on labels as sulfur dioxide, sodium sulfite, sodium and potassium bisulfite, and sodium and potassium metabisulfite. Sulfites are widely used in the processing of wine and beer and in restaurants to maintain the crispness and freshness of salads, fruits, and potatoes. They are also used for bleaching food starches and in producing cellophane for food packaging. The FDA prohibits the use of sulfites in foods that are important sources of thiamine because they destroy the vitamin. In 1986, the FDA also banned the use of sulfites in fruits and vegetables meant to be eaten raw. Sulfite sensitivity can develop even in persons without an allergic history, and it is not certain that all reactions are mediated by allergy. Symptoms include wheezing, hives, nausea, and diarrhea. Rarely, anaphylaxis may occur. With increased awareness and restricted use, adverse reactions to sulfites are now relatively uncommon. Updated information can be obtained from the FDA website (*http://vm.cfsan.fda.gov/~dms*).

Foods containing sulfites are so common that the average person ingests 2 to 3 mg per day, and when beer or wine is included in the diet, this figure can reach 5 to 10 mg per day. Foods frequently preserved with sulfites include instant tea, beer, wine, wine coolers and spirits, dried citrus fruit beverage mixes, condiments and relishes, confections and frostings, canned soups, dried mixes, seafood (especially shrimp), baked goods, processed and dried fruits, gelatin, puddings and fillings, jams and jellies, corn and maple syrup, molasses, breading, batters, noodle mixes, and processed vegetables (vegetable juices; canned, pickled, dried vegetables; potato chips).

Treatment is complicated by the widespread presence of the chemical, which makes the problem difficult to diagnose before the episode is complete. Moreover, several treatments for acute allergic response may contain potassium metabisulfite as a preservative, especially epinephrine and some IV solutions and medications. Terbutaline can be used safely in such a situation.

Monosodium Glutamate (MSG)

Use in Foods. MSG is the sodium salt of glutamic acid. It is made by fermenting starch, sugar beets, sugar cane, or molasses and is used to enhance flavor, perhaps by stimulating

TABLE 12-26. Restricted-Tyramine Diet

Food group	Unrestricted foods (<5 μg/g)	Foods allowed in moderation (5–20 μg/g)	Foods to avoid (>20 μg/g)
Cheese	Cottage cheese, ricotta, cream cheese	Processed American cheese, Gouda	Aged cheeses—brick, blue, cheddar, Camembert, Swiss, Romano, Roquefort, Stilton, mozzarella, Parmesan, provolone, Emmentaler, boursin, sour cream, Brie
Beverages	Milk	Coffee, hot chocolate, cola drinks (1–3 cups per day)	Ale, beer, sherry, red and white wines,[a] yogurt, bouillon
Meats	Fresh or fresh frozen meat, poultry		Canned meats, chicken liver, beef liver, fermented (hard) sausage or salami, pepperoni, summer sausage, bologna, Genoa salami
Fish	Fresh or fresh frozen fish or shellfish		Salt herring, dried fish, caviar, pickled herring
Vegetables	Most		Italian flat beans, Chinese pea pods, broad (fava) beans, mixed Chinese vegetables, eggplant
Fruit	Most		Figs, avocados
Miscellaneous			Chocolate, soy sauce, protein extracts, yeast concentrates or products made with them

[a]Fermentation of wine and beer does not ordinarily involve processes that result in the production of tyramine. Despite this, levels in beer are variable. The production of appreciable amounts of tyramine in red wines results from contamination with other than the usual fermenting organisms and from the inclusion of grape pulp and seeds in the process. These potential sources of amino acids are not used in making white wines. Because of the unpredictable variability in tyramine levels, all the beverages listed are generally excluded (*Med Lett Drugs Ther.* 1976;18:32).

glutamate receptors on the tongue. Foods labeled "no MSG" may in fact contain hydrolyzed protein, a source of free glutamate. Some products containing protein hydrolysates with substantial amounts of glutamate are labeled "contains glutamate."

Safety. MSG has been classified as GRAS (generally recognized as safe), but because of its presumed role in "MSG syndrome" and asthma attacks, its use is subject to repeated review by the FDA, American Medical Association, European Communities, and World Health Organization. All have found the additive to be safe. The most recent FDA/Federation of Associated Societies of Experimental Biology (FASEB) review (1995) concluded that a symptom complex may develop in an unknown percentage of people after the ingestion of 3 g or more of MSG without other food (*http://vm.cfspan.fda.gov/~lrd*). Most food servings contain no more than 0.5 g of MSG. The syndrome includes burning and numbness in the neck and arms, chest pain, facial pressure, headache, nausea, tachycardia, weakness, and bronchospasm in patients with asthma. However, no evidence for causation of other medical illnesses has been documented.

Benzoate-Cinnamon-Free Diet

Patients with orofacial granulomatosis (OFG) present with swelling of the lips primarily, but also of the gingivae, buccal mucosa, floor of the mouth, and other parts of the oral cavity. Unlike the usual orofacial presentation of food allergy, this condition also has chronic inflammatory changes in those sites. Common allergens on patch testing in this condition include cinnamon and benzoate. Benzoate is a common preservative, and occurs naturally in many foods, especially fruits. Cinnamic aldehyde, a constituent of cinnamon, is one of the compounds lending the typical odor and flavor to the spice, and is used as flavoring in mixed spices, soft drinks, chewing gum, ice cream, cakes, toothpaste, and mouthwashes. A diet free of these compounds improved oral inflammation after 8 weeks in patients with OFG, but did not eliminate all symptoms (192). The benzoate–cinnamon-free diet includes avoidance of dishes using products including benzoate or cinnamon, e.g., dishes with a spicy sauce, many ready-to-eat meals, fruits (many of which are naturally high in benzoate), bleached-flour pasta, fats with hydrolyzed lecithin (requiring preservative), tea, some carbonated beverages, tartar-control toothpaste, some mouthwashes, mixed spice, allspice, curry powder, cinnamon, and chocolate. The mouth and oral cavity are exposed to many antigens aside from the diet, including those in drugs, cosmetics, toothpastes, microorganisms, and dental filling materials. It would not be surprising if other allergens are identified that contribute to symptoms in this condition.

Low-Sodium Diet

Principles

Disorders in which sodium retention or hypertension is a prominent feature are treated with a low-sodium diet. The usual intake of sodium in a Western-style diet is greatly in excess of daily needs. Moreover, many processed foods contain sodium (see Chapter 7). Therefore, the diet seems quite restrictive. When sodium is retained, the ability to excrete excess ingested sodium is limited. The less sodium ingested, the easier the task of removing excess sodium from the body. Potassium salts are often used to replace sodium. A high-sodium diet alone will not cause hypertension in an otherwise normotensive person. Thus, the diet is probably not needed to prevent hypertension.

Indications

A low-sodium diet is used in the management of *acute and chronic congestive heart failure, chronic hepatic failure with ascites, acute and chronic renal failure,* and *hypertension.* Less often, it may be indicated when the administration of exogenous corticosteroids causes salt retention in women with premenstrual edema. A low-sodium diet is often used together with diuretic agents. In certain cases, only one or the other of these therapies is necessary. In disorders associated with sodium retention and low levels of urinary sodium, the diet may be very important. In many cases of hypertension, drug therapy, perhaps in conjunction with mild sodium restriction, may be more useful, with better patient compliance.

The American Heart Association has developed guidelines for diet-related lifestyle modifications that are useful in lowering blood pressure (193). These include weight loss to achieve a normal BMI, reduced salt intake, DASH-type dietary patterns, increased potassium intake, and moderation of alcohol intake. Salt (sodium chloride) intake is to be lowered as much as possible, ideally to ~65 mmol per d of sodium (1.5 g per day of sodium or 3.8 g per day of sodium chloride). The DASH diet (dietary approaches to stop hypertension) includes a rich supply of fruits and vegetables (8 to 10 servings per day) and low-fat dairy products (2 to 3 servings per day), while it is reduced in fat and cholesterol. Potassium intake should be increased to 120 mmol per day (4.7 g per day), the level provided in DASH-like diets. Alcohol intake is suggested at no more than two drinks per day for men, and one for women.

It is not a single dietary component that has the most influence on blood pressure, but the overall dietary pattern, as in the DASH diet. The DASH diet reduces systolic pressure by ~8 to14 mm Hg, compared with a reduction of ~5 to 20 mm Hg for weight loss, and ~2 to 8 mm Hg for reduced sodium intake alone (194). The DASH diet shows the most efficacy in African-Americans. Sympathetic tone increases with stimulation of the renninangiotensin-aldosterone system (RAAS), and is under the influence of salt intake. When the amount of urinary salt is accounted for (as a reflection of salt intake), polymorphisms of components of the RAAS show correlations with autonomic regulation of the cardiovascular system (195). These correlations are not yet far enough advanced to make genetic testing a practical addition to hypertension management, but that is the goal of the European Project on Genes in Hypertension (185).

Practical Aspects

General Instructions. *Patient information on this topic is available in Appendix D.*

1. The degree of sodium restriction required differs greatly among patients; a no-added-salt diet may suffice, or one that strictly limits salt-containing foods may be necessary.
2. Sodium is present in table salt, drinking water (depending on the source), medicines, and baked goods in which regular baking powder or soda is used. It is also present in foods seasoned with monosodium glutamate; preserved with brine, sodium benzoate, or sodium sulfite; or processed with sodium hydroxide, sodium alginate, or sodium propionate.
3. Many products used in food preparation contain sodium. Products that should not be used in food preparation unless their sodium content is known include baking powder, baking soda, barbecue sauce, beverages (fruit-flavored mixes, many carbonated sodas), bouillon cubes, canned broth, catsup, celery salt, celery flakes, celery seed, chili sauce, consommé, garlic salt, horseradish (prepared), instant cocoa mixes, olives, onion salt, commercial gelatin (Jell-O), monosodium glutamate, mustard (prepared), meat extract and sauces, meat tenderizers, molasses, parsley flakes, pickles, relishes, soy sauce, salad dressing, sodium saccharine, Worcestershire sauce, rennet tablets, some salt substitutes, mayonnaise, bacon bits, maraschino cherries, and salted nuts.
4. The **sodium content** given for foods is approximate but much larger than usually appreciated. It is helpful to consider which foods are equivalent to a given amount of sodium. For example:

   50 mg of sodium: 1 tsp salted butter or margarine, 1/2 cup raw carrots, 1 1/2 tsp mayonnaise, one small egg, 1/2 cup ice cream or sherbet

   250 mg of sodium: 1 oz canned tuna, 2/3 cup buttermilk, 1/2 cup canned vegetables, five salted crackers, 1 1/2 tbs salad dressing, one large strip of bacon, 1/2 cup cold cereal, 1/4 cup cottage cheese, one-eighth of a 9-in pie, two slices of bacon

   500 mg of sodium: 1/4 scant tsp salt, 3/4 tsp monosodium glutamate, one-half bouillon cube, 2/3 cup canned tomato juice, one average-sized frankfurter, seven or eight green olives (small), 2 tsp regular soy sauce

   800 to 1,000 mg of sodium: one dill pickle, 1 cup canned vegetable soup (preparations vary)

5. **Sodium labeling.** The daily value for sodium is 2,400 mg in the United States.

Sodium-free: <5 mg per serving
Very low in sodium: ≤35 mg per serving
Low in sodium: ≤140 mg per serving
Light in sodium/lightly salted: ≤50% reduction in sodium per serving versus reference food
Reduced in sodium or less sodium: ≤25% reduction in sodium per serving versus reference food

6. Cooking "from scratch" is usually the best way to prepare foods. Salt should not be added in cooking unless the patient can tolerate the added sodium. Patients should cook with oil or with unsalted butter or margarine.
7. Lemon juice, onion, red pepper, Tabasco sauce, and garlic are excellent substitute seasonings for meats and fish. See Table 7-10 for a list of other natural seasonings that can be substituted for salt to flavor foods.
8. Low-sodium baking powder is available in many stores that sell dietetic foods. If it is not available, the pharmacist can make it up with the following formula:

Potassium bicarbonate	39.8 g
Cornstarch	28.0 g
Tartaric acid	7.5 g
Potassium bitartrate	56.1 g

If the patient is on a diet that limits potassium, excessive amounts of potassium-containing baking powder should not be ingested.

9. A large number of **cookbooks for low-sodium diets** are available in most retail bookstores. One suggested title is Franey P. *Low-Calorie Gourmet* (New York: Times Books, 1984). The recipes use small amounts of salt that can be replaced with a salt substitute. Many spices are included in the recipes, so that the replacement is relatively easy.

Specific Recommendations

1. Diets are ordered as salt (sodium chloride) or as sodium, which is about 40% of the weight of salt. Ordering *dietary prescriptions* by sodium content is more sensible because the "salt" content cannot actually be measured. The usual restrictions ordered are listed in Table 12-27.
2. Decrease the use of table salt and seasonings high in sodium (e.g., soy sauce, garlic salt, onion salt), and substitute herbs and other spices. If salt substitutes are used, make certain that the patient is not on medication that causes hyperkalemia (e.g., triamterene).
3. Limit intake of foods known to be high in sodium.
4. Avoid less obvious sources of sodium, including foods that contain MSG, sodium saccharine, sodium nitrate (curing agent), and sodium benzoate (preservative). Some over-the-counter medications, such as antacids, laxatives, and sleeping pills, contain large quantities of sodium. For example, Alka-Seltzer effervescent antacid tablets contain 276 mg of sodium per tablet. Labels of over-the-counter products should be read carefully.
5. Modify recipes to include low-sodium ingredients—either prepared products labeled as such or fresh fruits, vegetables, meats, and fish. Particularly avoid canned products. Low-sodium cheese and peanut butter are available, as are unsalted crackers, low-sodium canned soups, and unsalted chips and popcorn.
6. When dining out, choose foods without sauces or gravies, use oil/vinegar dressing for salads, choose fresh fruit for dessert, and ask that no salt be added to individually prepared dishes (e.g., steak or fish). Avoid fast foods.

Side Effects

The low-sodium diet is not easy for some patients to follow because the intake of sodium in most Western diets is large. Care must be taken to maintain good protein intake.

TABLE 12-27. Salt-restricted Diets

Daily intake (g)		Restrictions					
Sodium	Salt	Added salt	Visibly salted items[a]	Processed foods[b]	Milk, bread[c]	Meat, eggs	Practicality
5–6	12.5–15	Yes	Yes	Yes	Yes	Yes	Average U.S. diet
4	10	No	Yes	Yes	Yes	Yes	Home use
3	7.5	No	No	Many	Yes	Yes	Home use
2	5.0	No	No	Few	Yes	Yes	Home use; needs cooperation
1	2.5	No	No	No	Salt-free bread	Yes	Needs great cooperation for home use
0.5	1.25	No	No	No	1 pt milk	4 oz meat, 1 egg	Hospital use

[a] Includes potato chips, pretzels, crackers or snacks, pickles, olives, and bacon.
[b] Includes most canned foods, dry cereals, prepared meats, ham, cheese, and prepared desserts.
[c] One hundred twenty milligrams of sodium per 8 oz of milk or 1 slice of bread.

Because large amounts of fruits and vegetables are allowed, the intake of most vitamins and minerals is adequate. When a patient on a low-sodium diet also takes a diuretic, *hypokalemia* often develops. Potassium can be replaced by table foods or by medication (see Chapter 7).

Sodium depletion can develop in a patient on a low-sodium diet when urinary sodium losses are continuously high, as in chronic renal disease. Patients with obligatory sodium losses from ileostomies are also at risk for the development of sodium depletion if dietary sodium is restricted.

Supplements Required

Potassium may be needed if diuretics are used, but no other supplements are required.

Restriction of Serotonin-Rich Foods

When a urinary collection for 5-hydroxyindoleacetic acid (5-HIAA) is ordered, the patient should not consume foods rich in serotonin or medications that react with the reagents used in the test. Foods to be avoided include avocado, bananas, butternut squash, eggplant, kiwi fruit, pecans, plantains, pineapple, plums, tomatoes, walnuts, and alcohol (196). Alcohol presumably stimulates the production of serotonin. Medications to be avoided are glyceryl guaiacolate, acetaminophen, and phenacetin; they interfere with the urinary and serum determinations.

Diet for Occult Blood Screening (Low-Peroxidase Diet)

Screening for occult blood in stool is of proven efficacy. When standard low-sensitivity, peroxidase-based tests (e.g., Hemoccult) are used, the ingestion of red meat and uncooked peroxidase-rich plants (radish, turnip, broccoli) can produce false-positive results, although the effect is small. The low-meat diet and six mail-in stool sample cards are generally used, especially if the level of meat intake is high. The specificity of the available tests for routine fecal blood testing is affected by peroxidase-containing foods. The use of rehydrated Hemoccult or similar guaiac-impregnated cards increases the false-positive rate, and a low-peroxidase diet has been shown to reduce the false-positive rate from above 6% to 0.6% (106). Many clinicians have abandoned rehydrated guaiac techniques and ignore diet in their screening programs (197). However, a small increase in specificity can have a major impact on clinical decisions, so that when outpatient screening for occult blood is performed, it seems prudent at the present time to recommend a meat-free, low-peroxidase diet (198).

A low-peroxidase diet is indicated when guaiac-containing cards are used to screen for colorectal neoplasms.

Practical Aspects

General Instructions. The low-peroxidase diet avoids red meat, raw or cooked. Although the peroxidase activity of most fruits and vegetables is destroyed completely by cooking at 100°C for 20 minutes, well-cooked red meat retains some activity. Because of the high level of peroxidase activity in red meat and uncertainty regarding how thoroughly cooked meat may be, all red meat is proscribed. Peroxidase-rich fruits and vegetables (categories 1 through 5, Table 12-28) are also eliminated.

Specific Recommendations. Foods in categories 1 to 5 (Table 12-28) are eliminated for 1 to 2 days before stool sampling begins and for 3 days consecutively, during which time one sample is collected per day. Aspirin-containing medications are not permitted, but it is not clear whether aspirin in modest doses increases fecal blood loss.

Patient information on this topic is available in Appendix D.

Vitamin K–Enriched Diet

Principle

Foods with a high content of vitamin K may interfere with the smooth control of anticoagulation. The dietary intake of vitamin K is only one of many factors influencing blood

TABLE 12-28. Peroxidase Levels in Foods

Category	Peroxidase activity[a] (mL of blood equivalent)	Food items
1	>20	Broccoli, turnip[b]
2	10–20	Rare red meat, cantaloupe, cauliflower, red radish, parsnips
3	5–10	Bean sprouts, cucumber, green beans, mushrooms, parsley, zucchini, lemon rind
4	2–5	Grapefruit, carrot, cabbage, potato, pumpkin, fig
5	1–2	Peach, celery, lettuce, spinach, pickles
6	0.2–1.0	Blackberries, pineapple, watermelon, walnuts, sweet peppers
7	0.1–0.2	Banana, black grapes, pear, plum
8	<0.1	Well-cooked meat, apples, apricot, olives, raspberries
9	Peroxidase undetectable	Roast chicken, turkey, cooked fish, organ meats, pork, ham and bacon, white grapes, lemon, nectarine, orange, strawberries, tomato, raisins

[a] The peroxidase activity in 100 g of food is reported as the equivalent of "x" milliliters of blood.
[b] The data refer to uncooked vegetables. Adequate cooking destroys peroxidase activity.
Adapted from Caligore P, et al. *Am J Clin Nutr.* 1982;35:1487.

clotting in patients on long-term warfarin therapy. It is not clear whether the dietary intake of vitamin K is a significant factor because fecal flora produce the vitamin, and it can be absorbed in the colon.

Indication

This diet is used for patients receiving anticoagulant therapy when the regulation of anticoagulation is difficult or the patient is more resistant to warfarin therapy than expected.

Practical Aspects

All foods are allowed except those containing more than 100 mg of vitamin K per 100 g. These include broccoli, brussels sprouts, green or white cabbage, cauliflower, kale, lettuce, soybeans, spinach, turnip greens, beef liver or kidney, and pork liver.

Copper-Restricted Diet

Principle

Wilson disease is characterized by an increase in total body and hepatic copper. Treatment consists of a low copper intake plus chelating therapy. Other cholestatic liver diseases (e.g., primary biliary cirrhosis) are characterized by elevated levels of hepatic copper, but it is not clear that removal of copper alters the clinical course.

Indication

For patients with Wilson disease.

Practical Aspects

Milk, coffee, lemonade, carbonated beverages, and vanilla ice cream may be consumed freely. Regular table salt should be avoided. Analytic reagent-grade salt, available

through the pharmacist, may be used as desired. Almost no foods are copper-free, so the more caloric and protein needs that can be met by low-copper foods, the better. A list of foods low in copper has been published (199). As Wilson disease is diagnosed earlier and effective drug therapy is used to create a negative copper balance, the strict use of low-copper diets becomes unnecessary. Obviously, the less copper ingested, the less drug theoretically needed to produce a negative copper balance, although this effect has not been quantified.

Specific Diets for Gastrointestinal Disorders

Inflammatory Bowel Disease

Enteral diets are useful in producing and maintaining remission in children with Crohn disease (200). The evidence is less compelling for adults or for patients of any age with ulcerative colitis. The rationale for the efficacy of elemental diets is not clear, but is presumed to improve the permeability of the bowel, providing decreased access of luminal antigens to the mucosa. Relapses of ulcerative colitis (UC) have been associated with intake of red meat, alcohol, and high sulphur/sulphate (201). A diet consisting of mixed components (fish oil, antioxidants, soluble fiber) in a randomized trial produced a faster rate of decrease in prednisone dosing (202). Use of diets in adults with IBD who do not have short bowel syndrome is still empiric, and no standardized recommendations can be made at this time.

Acute Pancreatitis

The standard therapy for acute pancreatitis in the past was cessation of eating, to avoid the pain that was produced by food. However, because such patients are catabolic, starvation could worsen the course of the disease, and nutritional supplementation has been used extensively, at first by the parenteral route, but in recent years, by the enteral route. Meta-analyses of randomized trials show that enteral nutrition leads to shorter hospital stays and lower infection rates than parenteral nutrition (203,204). Although these results seem clear, there are not enough data to determine whether enteral nutrition (EN) improves overall outcome over standard therapy without artificial supplementation (204). There has been some suggestion of benefit from individual studies in which immune modulators (e.g., glutamine, arginine, and omega-3 polyunsaturated fatty acids, were added to EN alone, but there are insufficient data to make specific recommendations. The mode (continuous or bolus) or site of delivery (gastric or jejunal) of the EN probably makes no difference in the clinical outcome. One randomized trial shows that mortality was nearly twice as high in the nasojejunal group, but the difference was not statistically significant (205).

Irritable Bowel Syndrome

The response of IBS patients to food is due to many factors. These include food intolerances (e.g., lactose) (206), food allergies (e.g., nuts), and possibly an alteration in bacterial flora with consequent changes in intestinal function (207). The one randomized trial of elimination diets in IBS patients suggested that these might be useful (208), but the diets of the two groups were not comparable, in that only the treated group had diets restricted in yeast, milk, egg, and wheat, foods often associated with food intolerances in IBS studies. The difficulty in determining the response to changes in diet or to food supplements resides in the over-reporting of many IBS patients, related to somatization responses or multiple chemical sensitivity (209). None of these factors likely occurs in all patients with IBS, so it is difficult to predict whether dietary manipulation will improve symptoms in a consistent fashion. It is best to document as carefully as possible any food intolerance or allergy, but to expect only partial improvement to a dietary program that eliminates the offending agents. The traditional use of fiber to alleviate symptoms of IBS is not supported by most studies (210).

Gastroparesis

The symptoms that can be attributed to delayed gastric emptying are not specific, but include bloating, nausea, and vomiting. When patients have chronic nausea and vomiting,

initial therapy should ensure correction of fluid and micronutrient deficiencies. Dietary modifications have been developed to mitigate symptoms, and they benefit patients with mild or moderate symptoms who still have some degree of intact gastric emptying. These modifications include minimizing food components that delay gastric emptying (e.g., hyperosmotic foods, high protein, high fat), and employing tactics that may provide a mechanical basis for more rapid gastric emptying (e.g., eating small frequent meals, eating in the upright position, walking for 1 to 2 hours after meals, chewing food well, avoiding high fiber-containing foods). Patients with delayed gastric emptying are at risk for developing phytobezoars, and should follow a diet that avoids high-risk foods (see Indications for Modified Fiber Diets earlier in this chapter). For more information on a diet for gastroparesis (and other GI diets) go to the University of Virginia Health System Digestive Health Center website at www.healthsystem.virginia.edu/internet/digestive-health/nutrition/patientdu.cfm.

Probiotics

Probiotics have been defined by Schrenzenmeir and deVrese as "a preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects in this host" (211). Major differences in diet type (e.g., Westgern, Japanese, Indian, etc.) can affect intestinal microflora, so it is possible that probiotics might reflect a downstream result of dietary alterations (212). A review of 185 studies using probiotics in humans included positive studies in 239 disorders (more than one condition was reported per study) and negative results in 49 (213). Disorders studied include infectious gastroenteritis, antibiotic–associated diarrhea/pseudomembranous colitis, necrotizing enterocolitis, IBD, IBS, pancreatitis, colorectal cancer, *Helicobacter pylori*, radiation-induced diarrhea, lactose intolerance, infant atopic eczema, atopic diseases, and allergy/immune function. Studies have included single organisms (mostly strains of lactobacillus or bifidobacterium) or multiple organisms in a variety of doses, very few of which have been documented to alter the native microflora. The properties of the different species used do vary, and the doses have not been standardized. In general, efficacy has been greater in infant populations, perhaps because these patients have not yet established a completely stable microflora. However, caution must be used when giving probiotics to neonates and to patients with innate or acquired immune deficiency, because of the potential hazard associated with providing living organisms (214).

Mindful of these caveats, one can examine preliminary reviews of the efficacy of probiotics in some conditions where studies have been numerous enough. The clearest positive data come from 23 studies (adult and pediatric) in which probiotics decrease the duration of infectious diarrhea by ~30 hours (215). Chronic pouchitis following construction of a neorectum appears to respond to probiotics, but the role of probiotics in management of idiopathic inflammatory bowel disease is not yet well supported (216). Six of eight trials in IBS showed some benefit, but the number of total subjects is small (217), although one trial of 77 individuals provides promising results (207). The most intriguing possibility was highlighted by studies in which Lactobacillus GG alleviated allergic symptoms in IgE-sensitized infants with atopic dermatitis (218). Probiotics can affect T-helper cell balance and responsiveness (219). Thus, gut organisms may be able to modify disease risk by modulating cytokine production (220), although only about 10% of all species tested have strong immunomodulatory effects (221). Many randomized studies have been reported showing an effect of probiotics on improvement of symptoms or inflammatory biomarkers in allergic disease or on immune function in healthy individuals (222). If indeed probiotics are able to modulate overall inflammatory response of the body, there may be great potential for the use of such agents. On the other hand, without more specificity of organism or dose, or without more sensitivity of a general effect in the face of local tissue inflammatory responses, there are no current recommendations that can be made for the use of these supplements.

"Functional" Foods and Supplements

The definition of food in the Food, Drug, and Cosmetic act of 1938 is very general, and includes anything that is eaten or drunk by humans (foods, beverages, chewing gum). "Functional" foods were defined in this Act as "articles intended for the diagnosis, cure, mitigation, treatment, or prevention of disease." More recently, they have been defined as "any food or food ingredient that may provide a health benefit beyond that conferred by the nutrients the food contains" (223). The European definition is by consensus the following: "A food can be regarded as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way which is relevant to either the state of well-being and health or the reduction of the risk of a disease" (224). "Functional food" is used to describe physiologically active foods and is often used synonymously with the terms *neutriceutical, designer food,* and *medical food*. The older term for these foods was "foods for special dietary use." The orphan drugs amendment to the Food, Drug, and Cosmetic Act (1988) defines *medical food* as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Examples of medical foods include oral rehydration solutions and enteral formulas. However, medical foods are not subject to regulation by the FDA, and in 1990, the National Labeling Education Act exempted medical foods from its labeling requirements (225).

Infant formulas are another category of food, and the Infant Formula Act (1980) gives the FDA authority to create standards for these foods. Dietary supplements are defined by the Dietary Supplement Health and Education Act (DSHEA) as products other than tobacco that contain one or more dietary ingredients, including "a vitamin, mineral, herb or other botanical, or amino acid," and is provided to increase dietary intake. It can be provided as "a concentrate, metabolite, constituent, extract, or combination of any of the aforementioned ingredients." Products are marketed as supplements, functional foods, "dietetic" foods, neutriceuticals, and phytochemicals. Their purpose is to improve function not only in healthy people but also in patients with restricted diets. Such use has been spurred by the passage of the Dietary Supplement Health and Education Act of 1994, which formally defined dietary supplements. Because these supplements were regulated as foods and not as drugs, manufacturers did not have to prove efficacy. As of March 1999, all vitamin, mineral, herbal, and supplement products must include "nutrition facts" in their label. Nutrients are listed as percentage of daily value, although the dose is called a "serving." Nutrients labeled "high potency" must supply at least 100% of the daily value, and multivitamins must supply 100% of the daily value of two-thirds of the contents. "Antioxidants" must prevent chemical damage *in vitro*. However, neither label means that the product is effective. For any health claims, the label must carry the following disclaimer: "This statement has not been evaluated by the Food and Drug Administration." The National Institutes of Health Office of Dietary Supplements views a supplement as any substance consumed in addition to the regular diet—that is, in addition to meals, snacks, and beverages (223). The American Dietetic Association has published a useful guide to many of these supplements (226).

Table 12-29 lists many of the supplements that are specific nutrients. Those that are micronutrients (vitamins and minerals) are discussed in Chapters 6 and 7. Some of the others are discussed in Chapter 8, "Alternative Nutritional Therapy." The National Institutes of Health Office of Dietary Supplements and the Consumer Healthcare Products Association have initiated a bibliography to highlight scientifically sound research on dietary supplements and their role in health maintenance. Copies of the document are posted on the Internet (*http://ods.od.nih.gov/publications/publications.html*) and are available from the Office of Dietary Supplements at *ods@nih.gov* or by ordering from 301-435-2920.

Currently, the FDA has approved health claims for some foods in the prevention of chronic disease, and other claims are pending (Table 12-30). These claims include

TABLE 12-29. Selected Dietary Supplements

Supplement	Marketing claims	Efficacy	Adverse effects
Alanine	Spares muscle	Not proven	None
	Stabilizes blood sugar	Equivocal	
Arginine	Helps CV disease, immune Fx	Possibly Equivocal	None
	Builds muscle mass	Not proven	
Boron	Prevents osteoporosis	Not proven	Toxic >50 mg/d
	Improves memory, libido		
BCAA	↑ Muscle mass, exercising	Not proven	↑ NH_3 if >20 g/d
Calcium	Prevents osteoporosis	Proven	U.L. 2,500 mg/day
	↓ Blood pressure	Possibly	↑ Absorption of Fe, other drugs
	↓ Colon cancer risk	Equivocal	
L-Carnitine	Helps heart, immune function	Not proven	Diarrhea >6 g/day
β-Carotene	↓ Cancer prevalence	Probably not	May ↑ lung cancer in male smokers
	↑ Immunity, helps CV disease	No	
Chromium	Helps control diabetes	Possibly	Safe daily intake 50–200 μg
	Lowers cholesterol	Equivocal	
	↓ Body fat	No	
Creatine	↑ Muscle strength, ↑ muscle mass	Equivocal Not proven	Water retention
Folate	Prevents birth defects	Yes	Masks B_{12} deficiency at >400 μg/d, impairs Anticonvulsants >5 mg/d
	Prevents colon cancer	Not proven	
	Prevents depression	Not proven	
Fructo-oligosaccharides	Supports GI tract health	Equivocal	Bloating, cramps, diarrhea at >50 g/day
	Controls blood sugar, cholesterol	Not proven	
Glucosamine	Relieves arthritis pain	Possibly	None
Glutamine	Enhances immune system	Equivocal	None
Lecithin	Helps Alzheimer's, memory	No	Diarrhea >20 g/day
Lysine	↓ Herpesvirus effect	Equivocal	↓ Arginine absorption
	↓ Angina	Not proven	
Magnesium	↓ CV disease, BP	Equivocal	U.L. 350 mg/day
	↓ Migraine, PMS	Equivocal	
Pantothenate	Blocks stress, ↓ cholesterol	Not proven	None
Phosphatidylserine (source, bovine brain extract)	Improves memory in elderly, raises IQ	Equivocal Not proven	? Contains B_{12}
Potassium	↓ Blood pressure	Possibly	GI ulcer, bleeding >6 g/day ↑ [K], inhibits ACE
Pyruvate	↓ Cholesterol, weight	Not proven	Flatus, diarrhea
Selenium	↓ Cancer risk	Possibly	Toxic >750 μg/day
	Helps heart, immune function	Not proven	
Vitamin A	Improves immunity	Possibly	Toxic >50,000 IU/day
	Improves skin disease	Yes	Teratogenic >3,000 IU/day
	Reverses skin aging	Not proven	

(*continued*)

TABLE 12-29. Selected Dietary Supplements (*Continued*)

Supplement	Marketing claims	Efficacy	Adverse effects
Vitamin B_1	↑ Energy	No	None
B_2	↑ Energy, helps migraine	No	None
B_3	↓ Cholesterol	Yes	Flushing, diarrhea
B_6	Improves PMS, autism	Equivocal	Nerve damage >500 mg/day
	Improves heart Fx	Possibly	
B_{12}	Improves dementia, energy	No	None
	↑ Function in elderly deficient	Yes	
Vitamin C	Improve cold Sx, ↓ heart disease	Equivocal	Diarrhea >3 g/day
	Protects vs. cancer, cataracts	Possibly	↑ Fe absorption in hemochromatosis ↑ Oxalate excretion
Vitamin D	↑ Ca^{++} absorption, bone health	Yes	U.L. 1,000 IU (50 μg)
	↓ Cancer risk	Equivocal	↑ Bleeding if on
Vitamin E	Improve diabetes, immunity	Possibly	Anticoagulants
	↓ Heart attack, cataracts	Possibly	
	Improve lung Fx, psychiatric illness	Possibly	
Zinc	Improve cold Sx, taste	Not proven	↓ Cu absorption >100 mg/day
	↑ immunity, fertility, skin	No	↑ Cholesterol, nausea at high dose

Explanation of efficacy: Yes, several controlled trials in humans; possibly, preliminary data from controlled trials; equivocal, conflicting controlled data in humans; not proven, not enough data in humans or data are poor; no, human data not supportive. A detailed listing of many supplements is available in the *PDR for Nutritional Supplements*, 1st ed., Medical Economics, Montvale, NJ, 2001.
U.L., upper limit recommended by Food and Nutrition Board, National Academy of Science; PMS, premenstrual syndrome; ACE, angiotensin-converting enzyme; BCAA, branched-chain amino acid.

fiber-containing products for cancer and cardiovascular disease, fruits and vegetables for cancer, and calcium for osteoporosis (227). It also recognizes the relationship between saturated fat and cholesterol and the risk for cardiovascular disease, dietary fat and cancer, sodium and hypertension, and sugar alcohols and dental caries (223,225). The Dietary Supplement Health and Education Act of 1994, which exempts dietary supplements from regulation as drugs and food additives, also allows structure/function claims to be made and literature about functional foods to be distributed. Claims can be made that functional foods are modifiers of oxidative damage, anticarcinogens, enhancers of gastrointestinal function (including probiotics and prebiotics), and agents of immunomodulation, neuroregulation, cholesterol metabolism, blood pressure control, and allergic responses. Prebiotics and probiotics are considered "functional" foods by some because they contain or produce components similar to those in some functional foods (228). Table 12-31 lists some of the compounds included in functional foods and the claims that may be made for them (226).

TABLE 12-30. FDA-Approved and Qualified Health Claims

Dietary substance	Approved claim	Permitted qualified claim
Calcium	Osteoporosis	Bone fractures, cancer, menstrual disorders, hypertension, renal stones
Chromium picolinate		Insulin resistance, diabetes
Dietary lipids (fat)	Cancer	
Dietary saturated fat and cholesterol	Coronary heart disease	
Omega-3 fatty acids (supplements/food)		Coronary heart disease
Monounsaturated fatty acids (olive oil)		Coronary heart disease
Dietary noncariogenic sweeteners	Dental caries	
Fiber-containing grain products, fruits, and vegetables	Cancer	
Fruits and vegetables	Cancer	
Soluble fiber from certain foods	Coronary heart disease	
Whole grain foods	Heart disease and certain cancers	
Soy protein	Coronary heart disease	
Plant sterol/stanol esters	Coronary heart disease	
Folic acid	Neural tube defects	
0.8 mg folic acid (supplement)		Neural tube defects
Sodium	Hypertension	
Selenium (dietary supplement)		Cancer
Vitamin C or E (supplement)		Cancer
Green tea		Cancer
Tomatoes, lycopene containing tomato-based products		Cancer
Nuts (almonds, hazelnuts, peanuts, pistachio nuts, walnuts)		Heart disease
Vitamin B_6, B_{12} and/or folic acid		Vascular disease
Phosphatidylserine (supplement)		Cognitive dysfunction, dementia

Source: U.S. FDA. Health claims that meet significant scientific agreement are approved by the FDA Center for Food Safety & Applied Nutrition, website available at: www.cfsan.fda.gov/~dms/lab-ssa.html. In 2002 the FDA began allowing qualified health claims that did not meet the standard of "significant scientific agreement" and that would be misleading without such qualification. These are available on the qualified health claims website at: www.cfsan.fda.gov/~dms/qhc-sum.html. Details of the criteria for each of these claims are reviewed by Turner et al. (227).

TABLE 12-31. Physiologically Active Compounds in Functional Foods

Compound	Food source	Potential health benefit
Isothiocyanates	Cruciferous vegetables	Chemoprevention of cancer by altering drug-metabolizing enzymes
Epigallocatechin	Green tea	↓ Cancer/heart disease by antioxidation
Carotenoids	Tomatoes, carrots, citrus fruits, yams	↓ Cancer/heart disease by antioxidation
Lactoferrin	Milk	Stimulate immune system, antimicrobial
Conjugated linoleic acid	Dairy products	Prevention of cancer/ atherosclerosis
Genestein and other isoflavones	Soybeans, soy foods	↓ Menopausal symptoms, osteoporosis, cancer, heart disease
Diallyl disulfide	Garlic, onions	Prevention of cancer, ↑ immune function, ↓ serum cholesterol, triglyceride
Limonene	Citrus fruits	Prevention of cancer
Nondigestible oligosaccharides	Garlic, asparagus, chicory	↑ Immune function, ↓ serum cholesterol
Omega-3 fatty acids	Algae, fish	↓ Serum cholesterol/heart disease, suppress immune function
Coumarins	Vegetables, citrus fruits	↓ Blood clotting, anticarcinogenic

References

1. American Dietetic Association, Dietitians of Canada. *Manual of Clinical Dietetics*, 6th edition looseleaf, American Dietetic Association, Chicago, IL, 2002.
2. Nelson JK, Moxness KE, Gastineau CF, Jenson MD. Mayo Clinic diet manual: A handbook of nutritional practice, Mayo Medical Center, Rochester, MN. 1994.
3. Guo LQ, Yamazoe Y. Inhibition of cytochrome P450 by furanocoumarins in grapefruit juice and herbal medicines. *Acta Pharmacol Sin*. 2004;25:129.
4. *Beverages in Nutrition and Health,* Wilson T, Temple NJ, eds. Humana Press, Totowa, NJ, 2004.
5. Rainey C, Affleck M, Bretschger K, et al. The California avocado. *Nutrition Today.* 1994;29:23.
6. United States Department of Agriculture. MyPyramid. *http://mypyramid.gov.*
7. Eastwood M, Kritchevsky D. Dietary Fiber: How did we get where we are? *Annu Rev Nutr.* 2005; 25:1–8.
8. Caulfield LE, de Onis M, Blossner M, Black RE. Undernutrition as an underlying cause of child deaths associated with diarrhea, pneumonia, malaria, and measles. *Am J Clin Nutr.* 2004;80:193.
9. Nandy S, Irving M, Gordon D, et al. Poverty, child undernutrition and morbidity: new evidence from India. *Bull World Health Organ*. 2005;83:210.
10. Position of the American Dietetic Association and Dietitians of Canada: vegetarian diets. *J Am Diet Assoc*. 2003;103:748.
11. Sabate J. The contribution of vegetarian diets to health and disease: a paradigm shift? *Am J Clin Nutr.* 2003;78(suppl):502S.
12. Singer AJ, Werther K, Nestle M. The nutritional value of university-hospital diets. *N Engl J Med*. 1996; 335:1466.
13. Wotecki CE, Thomas PR. *Eat for Life*. Washington, DC: National Academies Press, 1992.
14. Lichtenstein AH, Appel LJ, Brands M, et al. Diet and lifestyle recommendations revision 2006. A scientific statement from the American Heart Association Nutrition Committee. *Circulation*. 2006;114:82.
15. Scott K. Taste recognition: food for thought. *Neuron*. 2005;48:455.
16. Murphy C, Schubert CR, Cruickshanks KJ, et al. Prevalence of olfactory impairment in older adults. *JAMA*. 2002;288:2307.
17. Hancock S, Cresci G, Martindale R. The clear liquid diet: When is it appropriate? *Curr Gastroenterol Reports*. 2002;4:324.

18. Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. *BMJ*. 2001;323:1.
19. Diks J, van Hoorn DEC, Nijveldt RJ, et al. Preoperative fasting: an outdated concept? *JPEN*. 2004;29:298.
20. Popkin MB, Armstrong LE, Bray GM, et al. A new proposed guidance system for beverage consumption in the United States. *Am J Clin Nutr*. 2006;83:529.
21. Higdon JV, Frei B. Coffee and health: a review of recent human research. *Crit Rev Food Sci Nutr.* 2006; 46:101.
22. Emerson JL, Chappel CI. Health effects of coffee, tea, mate, cocoa, and their major methylxanthine components. In: Van der Heijden K, Younes M, Fishbein L, et al., eds. *International Food Safety Handbook*. New York: Marcel Dekker, 1999:141.
23. Paulson GW. Restless legs syndrome. How to provide symptom relief with drug and nondrug therapies. *Geriatrics*. 2000;55:35.
24. Cnattingius S, Signorello LB, Anneren G, et al. Caffeine intake and the risk of first-trimester spontaneous abortion. *N Engl J Med*. 2000;343:1839.
25. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. *JAMA*. 2005;294:97.
26. Michaels KB, Willett WC, Fuchs CS, Giovannucci E. Coffee, tea, and caffeine consumption and incidence of colon and rectal cancer. *J Natl Cancer Inst*. 2005;97:282.
27. Peters U, Poole C, Arab L. Does tea affect cardiovascular disease? A meta-analysis. *Am J Epidemiol*. 2001;154:495.
28. Saluja SS, Kaur N, Shrivastava UK. Enteral nutrition in surgical patients. *Surgery Today*. 2002;32:672.
29. Pehl C, Waizenhoefer A, Wendl B, et al. Effect of low and high fat meals on lower esophageal sphincter motility and gastroesophageal reflux in healthy subjects. *Am J Gastroenterol*. 1999;94:1192.
30. The Definition of Dietary Fiber: Report of the Dietary Fiber Definition Committee to the Board of Directors of the American Association of Cereal Chemists, January 10, 2001. *Cereal Foods World*. 2001; 46:112.
31. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients)*. Washington DC: National Academies Press, 2005.
32. Food and Agriculture Organization (FAO)/World Health Organization (WHO) Codex Alimentarius Commission. Proposals for a Definition and Methods of Analysis for Dietary Fibre Content. 26th Session, Codex Committee on Nutrition and Foods for Special Dietary Uses: November 21, 2004, Bonn, Germany.
33. Jones JR, Lineback DM, Levine MJ. Dietary Reference Intakes: Implications for fiber labeling and consumption: A summary of the International Life Sciences Institute North America Fiber Workshop, June 1–2, 2004, Washington, DC. *Nutr Rev.* 2006;64:31.
34. Canadian Food Inspection Agency. Dietary Fibre and Novel Fibre. Canadian Food Directorate Guideline No. 9, Guidelines Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them. Ottawa, ON: Canadian Food Inspection Agency, 2000.
35. Englyst KN, Englyst HN. Carbohydrate availability. *Br J Nutr*. 2005;94:1.
36. Manach C, Scalbert A, Morand C, et al. Polyphenols: food sources and bioavailability. *Am J Clin Nutr*. 2004;79:727.
37. Trevisanato SI, Kim Y-I. Tea and health. *Nutr Rev.* 2000;58:1.
38. Decker EA. Phenolics: prooxidants or antioxidants. *Nutr Rev.* 1997;55:396.
39. Roberfroid MB. Fructo-oligosaccharide malabsorption: benefit for gastrointestinal functions. *Curr Opin Gastroenterol*. 2000;16:173.
40. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr.* 1995;125:1401.
41. Jenkins DJA, Kendall CWC. Resistant starches. *Curr Opin Gastroenterol*. 2000;16:178.
42. Van Soest PJ, McQueen RW. The chemistry and estimation of fibre. *Proc Nutr Soc*. 1973;32:123.
43. Englyst HN, Quigley ME, Hudson GJ. Determination of dietary fibre as non-starch polysaccharides with gas-liquid chromatographic, high-performance liquid chromatographic or spectrophotometric measurement of constituent sugars. *Analyst*. 1994;119:1497.
44. Anderson JW, Bridges SR. Dietary fiber content of selected foods. *Am J Clin Nutr.* 1988;47:440.
45. Southgate DAT, Waldron K, Johnson LT, Fenwick GR. *Dietary Fiber: Chemical and Biological Aspects*. Boca Raton, FL: CRC Press, 1991.
46. Cummings JH. Cellulose and the human gut. *Gut*. 1984:25:805.
47. Cummings JH, Englyst HN. Fermentation in the human large intestine and the available substrates. *Am J Clin Nutr.* 1987;45:1243.
48. *National Health and Nutrition Examination Survey III, 1988–94*. NCHS CD-ROM series 11, No. 2A. ASCII version. Hyattsville, MD: National Center for Health Statistics, April 1998.
49. Kritchevsky D, et al., eds. *Dietary Fiber.* New York: Plenum Publishing, 1990.
50. Slavin JL. Dietary fiber and body weight. *Nutrition*. 2005;21:411.
51. Howarth NC, Saltzman E, Roberts SB. Dietary fiber and weight regulation. *Nutr Rev.* 2001;59:129.
52. Saper RB, Eisenberg DM, Phillips RS. Common dietary supplements for weight loss. *Am Fam Phys*. 2004; 70:1731.
53. Wolk A, Manson JE, Stampfer MJ, et al. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *JAMA*. 1999;281:1998.

54. Erkilla AT, Lichtenstein AH. Fiber and cardiovascular disease risk: how strong is the evidence? *J Cardiovasc Nurs*. 2006;21:3.
55. Chandalia M, Garg A, Jutjohann D, et al. Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med*. 2000;342:1392.
56. Brennan CS. Dietary fibre, glycaemic response, and diabetes. *Mol Nutr Food Res*. 2005;49:560.
57. Aldoori WH, Giovannucci EL, Rimm EB, et al. A prospective study of diet and the risk of symptomatic diverticular disease in men. *Am J Clin Nutr*. 1994;60:757.
58. AGA Clinical Practice and Practice Economics Committee. AGA technical review: impact of dietary fiber on colon cancer occurrence. *Gastroenterology*. 2000;118:1235.
59. Hill MJ. Cereals, cereal fibre and colorectal cancer risk: a review of the epidemiological literature. *Eur J Cancer Prev*. 1998;7[Suppl 2]:S5.
60. Fuchs CS, Giovannucci, Colditz GA, et al. Dietary fiber and the risk of colorectal cancer and adenoma in women. *N Engl J Med*. 1999;340:169.
61. Bingham SA, Day NE, Luben R, et al. Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. *Lancet*. 2003;361:1496.
62. Peters U, Sinha R, Chatterjee N, et al. Dietary fibre and colorectal adenoma in a colorectal cancer early detection programme. *Lancet*. 2003;361:1491.
63. Jacobs ET, Lanz E, Alberts DS, et al. Fiber, sex, and colorectal adenoma: results of a pooled analysis. *Am J Clin Nutr*. 2006;83:343.
64. Michels KB, Giovannucci E, Chan AT, et al. Fruit and vegetable consumption and colorectal adenomas in the Nurses' Health Study. *Cancer Res*. 2006;66:3942.
65. Park Y, Hunter DJ, Spiegelman D, et al. Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *JAMA*. 2005;294:2849.
66. Brown L, Rosner B, Willett WW, et al. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr*. 1999;69:30.
67. Levin EG, Miller VT, Muesing RA, et al. Comparison of psyllium hydrophilic mucilloid and cellulose as adjuncts to a prudent diet in the treatment of mild to moderate hypercholesterolemia. *Arch Intern Med*. 1990;150:1822.
68. Jenkins DJA, Kendall CWC, Vuksan V. Viscous fibers, health claims, and strategies to reduce cardiovascular risk. *Am J Clin Nutr*. 2000;71:401.
69. Kim YI. Short-chain fatty acids in ulcerative colitis. *Nutr Rev*. 1998;56:27.
70. Alaimo K, McDowell MA, Briefel RR, et al. Dietary intake of vitamins, minerals, and fiber of persons ages 2 months and over in the United States: Third National Health and Nutrition Examination Survey, Phase 1, 1988–91. *Adv Data*. 1994;14:1.
71. Lin HC, Zhao XT, Chu AW, et al. Fiber-supplemented enteral formula slows intestinal transit by intensifying inhibitory feedback from the distal gut. *Am J Clin Nutr*. 1997;65:1840.
72. Mennen LI, Walker R, Bennetau-Pelissero C, Scalbert A. Risks and safety of polyphenol consumption. *Am J Clin Nutr*. 2005;81(suppl):326S.
73. Geller SE, Studee L. Botanical and dietary supplements for menopausal symptoms: what works, what does not. *J Womens Health*. 2005;14:634.
74. Lapointe A, Couillard C, Lemieux S. Effects of dietary factors on oxidation of low-density lipoprotein particles. *J Nutr Biochem*. 2006 [Epub ahead of print].
75. Schenker S. The nutritional and physiological properties of chocolate. *Nutr Bull*. (Br Nutr Fdn) 2000;25:303.
76. Mathur S, Devaraj S, Grundy SM, Jialal. Cocoa products decrease low density lipoprotein oxidative susceptibility but do not affect biomarkers of inflammation in humans. *J Nutr*. 2002;132:3663.
77. Fraga CG. Cocoa, diabetes, and hypertension: should we eat more chocolate? *Am J Clin Nutr*. 2005;81:541.
78. Brouns F, Senden J, Beckers EJ, Saris WH. Osmolarity does not affect the gastric emptying rate of oral rehydration solutions. *JPEN*. 1995;19:403.
79. Foster-Powell K, Holt SHA, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr*. 2002;76:5.
80. Neuhouser ML, Tinker LF, Thomson C, et al. Development of a glycemic index database for food frequency questionnaires used in epidemiologic studies. *J Nutr*. 2006;136:1604.
81. Frost G, Leeds A, Dore C, et al. Glycaemic index as a determinant of serum HDL-cholesterol concentration. *Lancet*. 1999;353:1045.
82. Kelly S, Frost G, Whittaker V, Summerbell C. Low glycaemic index diets for coronary heart disease. *Cochrane Database Syst Rev*. 2004;18:CD004467.
83. Ukleja A. Dumping syndrome: pathophysiology and treatment. *Nutr Clin Pract*. 2005;20:517.
84. Lin HC, Zhao T, Wang L. Intestinal transit is more potently inhibited by fat in the distal (ileal brake) than in the proximal (jejunal brake) gut. *Dig Dis Sci*. 1997;42:19.
85. Matarese LE, O'Keefe SJ, Kandil HM, et al. Short bowel syndrome: clinical guidelines for nutrition management. *Nutr Clin Pract*. 2005;20:493.
86. Parrish CR. The clinician's guide to short bowel syndrome. *Pract Gastroenterol*. 2005;Sept:67.
87. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med*. 2003;248:2082.

88. Astrup A, Meinert Larsen T, Harper A. Atkins and other low-carbohydrate diets: hoax or an effective tool for weight loss? *Lancet*. 2004;364:897.
89. O'Donnell K. Bariatric surgery: nutritional concerns on the weigh down. *Pract Gastroenterol*. 2004;18:33.
90. Riby JE, Fujisawa T, Kretchmer N. Fructose absorption. *Am J Clin Nutr.* 1993;58[Suppl 5]:748S.
91. Nobigrot T, Chasalow FI, Lifshitz F. Carbohydrate absorption from one serving of fruit juice in young children: age and carbohydrate composition effects. *J Am Coll Nutr.* 1997;16:152.
92. Elliott SS, Keim NL, Stern JS, et al. Fructose, weight gain, and the insulin resistance syndrome. *Am J Clin Nutr.* 2002;76:911.
93. American Dietetic Association. Position of the American Dietetic Association: use of nutritive and nonnutritive sweeteners. *J Am Diet Assoc*. 2004;104:255.
94. Kulczycki A. Aspartame-induced urticaria. *Ann Intern Med.* 1986;104:207.
95. Ludwig DS. The glycemic index: physiological mechanism relating to obesity, diabetes, and cardiovascular disease. *JAMA*. 2002;287:2414.
96. Savaiano DA, Bouchey CJ, McCabe GP. Lactose intolerance symptoms assessed by meta-analysis: a grain of truth that leads to exaggeration. *J Nutr*. 2006;136:1107.
97. Byers KG, Savaiano DA. The myth of increased lactose intolerance in African-Americans. *J Am Coll Nutr.* 2005;24:569S.
98. Shaw AD, Davies GJ. Lactose intolerance: problems in diagnosis and treatment. *J Clin Gastroenterol.* 1999;28:208.
99. Di Stefano M, Missanelli A, Miceli E, et al. Hydrogen breath test in the diagnosis of lactose malabsorption: accuracy of new versus conventional criteria. *J Lab Clin Med.* 2004;144:313.
100. Heyman MB, Committee on Nutrition, American Academy of Pediatrics. Lactose intolerance in infants, children, and adolescents. *Pediatrics*. 2006;118:1279.
101. Kolars JC, Levitt MD, Aouji M, et al. Yogurt—an autodigesting source of lactose. *N Engl J Med.* 1984;310:1.
102. Martini MC, Savaiano DA. Reduced intolerance symptoms from lactose consumed during a meal. *Am J Clin Nutr.* 1988;47:57.
103. Riserus U, Berglund L, Vessby B. Conjugated linoleic acid (CLA) reduced abdominal adipose tissue in obese middle-aged men with signs of the metabolic syndrome: a randomized controlled trial. *Int J Obes Relat Metab Disord*. 2001;25:1129.
104. German JB, Dillard CJ. Saturated fats: what dietary intake? *Am J Clin Nutr*. 2004;80:550.
105. Vesper H, Schmelz E-M, Nikolova-Karakashian MN, et al. Sphingolipids in food and the emerging importance of sphingolipids to nutrition. *J Nutr.* 1999;129:1239.
106. Powell D. Approach to the patient with diarrhea, in *Textbook of Gastroenterology,* 4th ed., Yamada T, Alpers DH, Kaplowitz N, et al., eds. Philadelphia: Lippincott–Raven Publishers, 2003:844.
107. American Dietetic Association. *Nutrition Trends Survey 1997*. Chicago: The American Dietetic Association, 1997.
108. Metaanalysis of reduced fat diets. *BMJ*. 2001;322:757.
109. Bach A, Babayan VK. Medium-chain triglycerides—an update. *Am J Clin Nutr.* 1982;36:950.
110. Bach AC, Ingenbleek Y, Frey A. The usefulness of dietary medium-chain triglycerides in body weight control: fact or fancy? *J Lipid Res.* 1996;37:708.
111. Papamandjaris AA, MacDougall DE, Jones PJH. Medium chain fatty acid metabolism and energy expenditure: obesity treatment implications. *Life Sci.* 1998;62:1203.
112. Sandler RS, Zorich NL, Filloon TG, et al. Gastrointestinal symptoms in 3,181 volunteers ingesting snack food containing olestra or triglycerides. *Ann Intern Med*. 1999;130:253.
113. Balasekaran R, Porter JL, Santa Ana CA, et al. Positive results on tests for steatorrhea in persons consuming olestra potato chips. *Ann Intern Med*. 2000;132:279.
114. Neuhouser ML, Rock CL, Kristal AB, et al. Olestra is associated with slight reductions in serum carotenoids but does not markedly influence serum fat-soluble vitamin concentrations. *Am J Clin Nutr.* 2006;83:624.
115. Carnitine. The science behind a conditionally essential nutrient. Proceedings of a conference. March 25–26, 2004. *Ann NY Acad Sci*. 2004;1033:1
116. Anonymous. L-carnitine. *Med Lett.* 2004;46:95.
117. Famularo G. Carnitine and its congeners: a metabolic pathway to the regulation of immune response and inflammation. *Ann NY Acad Sci.* 2004;1033:132.
118. Golper TA, Goral S, Becker BN, Langman CB. L-carnitine treatment of anemia. *Am J Kidney Dis*. 2003;41 (Suppl 4):S27.
119. Schreiber B. Levocarnitine and dialysis: a review. *Nutr Clin Pract.* 2005;20:218.
120. Ferrari R, Cicchitelli MG, Dele D, et al. Therapeutic uses of L-carnitine and propionyl-L-carnitine on cardiovascular diseases: a review. *Ann NY Acad Sci.* 2004;1033:79.
121. Montgomery SA, Thal LJ, Amrein R. Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol.* 2003;18:61.
122. Hudson S, Tabet N. Acetyl-L-carnitine for dementia. *Cochrane Database Syst Rev.* 2003;CD003158.
123. Sima AAF, Calvani M, Merhra M, Amato A. Acetyl-L-carnitine improves pain, nerve regeneration, and vibratory perception in patients with chronic diabetic neuropathy: an analysis of two randomized placebo-controlled trials. *Diabetes Care*. 2005;28:89.

124. Stead LM, Brosnan JT, Brosnan ME, et al. Is it time to reevaluate methyl balance in humans? *Am J Clin Nutr.* 2006;83:5.
125. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. Washington, DC: National Academies Presss, 2000.
126. Zeisel SH, daCosta KA, Franklin PD, et al. Choline, an essential nutrient for humans. *FASEB J*. 1991;5:2093.
127. Buchman AL, Ament ME, Sobel M, et al. Choline deficiency causes reversible hepatic abnormalities in patients receiving parenteral nutrition: proof of a human choline requirement: a plabebo-controlled trial. *JPEN*. 2001;25:260.
128. Shaw GM, Carmichael SL, Laurent C, Rasmussen SA. Maternal nutrient intakes and risk of orofacial clefts. *Epidemiology*. 2006;17:285.
129. Marchioli R, Barzi F, Bomba E, et al. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell-Infarto Miocardico (GISSI)-Prevenzione. *Circulation*. 2002;105:1897.
130. McCowen KC, Bistrian BR. Essential fatty acids and their derivatives. *Curr Opin Gastroenterol.* 2005; 21:207.
131. Hooper L, Thompson RL, Harrison RA, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *BMJ*. 2006;332:752.
132. Harper CR, Jacobson TA. Usefulness of omega-3 fatty acids and the prevention of coronary heart disease. *Am J Cardiol*. 2005;96:1521.
133. Scientific Advisory Committee on Nutrition (SACN) and the Committee on Toxicity. Advice on fish consumption: benefits and risks. The Stationery Office, London, 2004.
134. Wang C, Chung M, Lichtenstein A, et al. Effects of omega-3 fatty acids on cardiovascular disease. Evidence report/technology assessment number 94, AHRQ publication number 04-E009-1, Rockville, MD: Agency for Healthcare Research and Quality, 2004.
135. Brosnan JT, Brosnan ME. Branched-chain amino acids: enzyme and substrate regulation. *J Nutr*. 2006; 136:207S
136. Klein S, Kinney J, Jeejeebhoy K, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. *JPEN J Parenter Enteral Nutr.* 1997;21:133.
137. Stickel F, Hoehn B, Schuppan D, Seitz HK. Review article: nutritional therapy in alcoholic liver disease. *Alimen Pharmacol Ther.* 2003;18:357.
138. Als-Nielsen B, Koretz RL, Kjaergard LL, et al. Branched-chain amino acids for hepatic encephalopathy (Cochrane review). The Cochrane Library 2004(2):CD???
139. Charlton M. Branched-chain amino acid enriched supplements as therapy for liver disease. *J Nutr.* 2006;136:295S.
140. Marchesini G, Bianchi G, Merli M, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. *Gastroenterology.* 2003;124:1792.
141. Pedrini MT, Levey AS, Lau J, et al. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a meta-analysis. *Ann Intern Med*. 1996;124:627.
142. Sullivan DH, Sun S, Walls RC. Protein-energy undernutrition among elderly hospitalized patients: a prospective study. *JAMA*. 1999;281:2013.
143. Schurch M-E, Rizzoli R, Slosman D, et al. Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1998;128:801.
144. Ziegler TR, Mulligan K, eds. ASPEN research workshop: anabolic hormones in nutrition support. *JPEN J Parenter Enteral Nutr.* 1999;23[Suppl 6]:S173.
145. St Jeor ST, Howard BV, Prewitt E, et al. Dietary protein and weight reduction: a statement for healthcare professionals from the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. *Circulation*. 2001;104:1869.
146. Katan MB. Alternatives to low-fat diets. *Am J Clin Nutr*. 2006;83:989.
147. Milne AC, Avenell A, Potter J. Meta-analysis: protein and energy supplementation in older people. *Ann Intern Med*. 2006;144:37.
148. Stratton RJ, Ek AC, Engfer M, et al. Enteral nutritional support in prevention and treatment of pressure ulcers: a systematic review and meta-analysis. *Ageing Res Rev.* 2005;4:422.
149. Buchman AL. Glutamine: commercially essential or conditionally essential? A critical appraisal of the human data. *Am J Clin Nutr.* 2001;74:25.
150. Novak F, Heyland DK, Avenell A, et al. Glutamine supplementation in serious illness: a systematic review of the evidence. *Crit Care Med*. 2002;30:2022.
151. Alpers DH. Glutamine: Do the data support the cause for glutamine supplementation in humans? *Gastroenterology*. 2006;130:S106.
152. Savarese DMF, Savy G, Vahdat L, et al. Prevention of chemotherapy and radiation toxicity with glutamine. *Cancer Treat Rev.* 2003;29:501.
153. Schulman AS, Willcutts KF, Claridge JA, et al. Does the addition of glutamine to enteral feeds affect patient mortality? *Crit Care Med.* 2005;33:2501.
154. Byrne TA, Wilmore DW, Iyer K, et al. Growth hormone, glutamine, and an optimal diet reduces parenteral nutrition in patients with short bowel syndrome. *Ann Surg.* 2005;242:655.

155. Luiking YC, Poeze M, Dejong CH, et al. Sepsis: an arginine deficiency state? *Crit Care Med*. 2004;32:2135.
156. Appleton J. Arginine: clinical potential of a semi-essential amino acid. *Altern Med Rev*. 2002;7:512.
157. Morris SM, Loscalzo J, Bier D, Souba WW. Arginine metabolism: enzymology, nutrition, and clinical significance. *J Nutr*. 2004;134 [Suppl 10S]:2741S
158. Kudsk KA. Immunonutrition in surgery and critical care. *Annu Rev Nutr*. 2006;May8 [Epub ahead of print]
159. O'Callaghan G, Beale RJ. The role of immune-enhancing diets in the management of perioperative patients. *Crit Care Resusc*. 2003;5:277.
160. Grimble RF. Immunonutrition. *Curr Opin Gastroenterol*. 2005;21:216.
161. Heyland DK, Dhaliwal R, Drover JW, et al. Canadian clinical practice guidelines for nutritional support in mechanically ventilated, critically ill patients. *JPEN*. 2003;27:355.
162. Bistrian BR, McCowen KC. Nutritional and metabolic support in the adult intensive care unit: key controversies. *Crit Care Med*. 2006;34:1525.
163. Duggan C, Gannon J, Walker WA. Protective nutrients and functional foods for the gastrointestinal tract. *Am J Clin Nutr*. 2002;75:789.
164. Schuller-Levis GB, Park E. Taurine: new implications for an old amino acid. *FEMS Microbiol Lett*. 2003; 226:195.
165. Tappaz ML. Taurine biosynthetic enzymes and taurine transporter: molecular identification and regulations. *Neurochem Res*. 2004;29:83.
166. Lourenco R, Camilo ME. Taurine: a conditionally essential amino acid in humans? An overview in health and disease. *Nutr Hosp*. 2002;17:262.
167. Koldehoff M, Zakrzewski JL. Taurolidine is effective in the treatment of central venous catheter-related bloodstream infections in cancer patients. *Int J Antimicrob Agents*. 2004;24:491.
168. Schneider A, Sack U, Rothe K, Bennek J. Peritoneal taurolidine lavage in children with localised peritonitis due to appendicitis. *Pediatr Surg Int*. 2005;21:445.
169. See J, Murray JA. Gluten-free diet: the medical and nutrition management of celiac disease. *Nutr Clin Pract*. 2006;21:1.
170. Hardman CM, Garioch JJ, Leonard JN, et al. Absence of toxicity of oats in patients with dermatitis herpetiformis. *N Engl J Med*. 1997;337:1884.
171. Janatuinen EK, Kemppainen TA, Julkunen RJ, et al. No harm from 5 year ingestion of oats in celiac disease. *Gut*. 2002;50:332.
172. National Institutes of Health Consensus Development Conference Statement on Celiac Disease, June 28–30, 2004. *Gastroenterology*. 2005;128:S1.
173. Case S. The gluten free diet: how to provide effective education and resources. *Gastroenterology*. 2005;128:S128.
174. Marcason W. Where can I find information on the oxalate content of foods? *J Am Diet Assoc*. 2006; 106:627.
175. Siener R, Honow R, Voss S, et al. Oxalate content of cereals and cereal products. *J Agric Food Chem*. 2006;54:3008.
176. Bloch AS, Shils ME. Appendix. In: Shils ME, Olson JA, Shike M, et al., eds. *Modern Nutrition in Health and Disease,* 9th ed. Baltimore: Williams & Wilkins, 1999:A198.
177. Madsen C, Wuthrich B. Food sensitivities, allergic reactions, and food intolerances. In: van der Heijden K, Younes M, Fishbein L, et al., eds. *International Food Safety Handbook*. New York: Marcel Dekker, 1999:447.
178. Frieri M, Kettelhut BV. *Food Hypersensitivity and Adverse Reactions: a Practical Guide for Diagnosis and Management*. New York: Marcel Dekker, 1999.
179. Sampson HA. Food allergy. *JAMA*. 1997;278:1888.
180. Beyer K, Teuber SS. Food allergy diagnostics: scientific and unproven procedures. *Curr Opin Allergy Clin Immunol*. 2005;5:261.
181. Sicherer SH. Allergic disorders, in *Handbook of Nutrition and Food,* Berdanier CD, ed. Boca Raton, FL: CRC Press, 2002:833.
182. Sampson HA, Sicherer SH, Birnbaum AH. AGA technical review on the evaluation of food allergy in gastrointestinal disorders. *Gastroenterology*. 2001;120:1026.
183. Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. *Pediatr Allergy Immunol*. 2004;15:435.
184. Monsbakken KW, Vandvik PO, Farup PG. Perceived food intolerance in subjects with irritable bowel syndrome—etiology, prevalence, and consequences. *Eur J Clin Nutr*. 2006;60:667.
185. Hamilton RG, Franlin Adkinson N Jr. In vitro assays for the diagnosis of IgE-mediated disorders. *J Allergy Clin Immunol*. 2004;114:213.
186. Niggemann B, Rolinck-Werningaus C, Mehl A, et al. Controlled oral food challenges in children—when indicated, when superfluous? *Allergy*. 2005;60:865.
187. Kerschenlohr K, Darsow U, Burgdorf WH, et al. Lessons from atopy patch testing in atopic dermatitis. *Curr Allergy Asthma Rep*. 2004;4:285.
188. Levitt MD, Bond JH. Flatulence. *Annu Rev Med*. 1980;31:127.
189. Alpha-galactosidase to prevent gas. *Med Lett Drugs Ther*. 1993;35:29.
190. Swain AR, Dutton P, Truswell AS. Salicylates in foods. *J Am Diet Assoc*. 1985;85:950.
191. Tiller JW, Dowling JT, Tung LH, et al. Tyramine-induced cardiac arrhythmias. *N Engl J Med*. 1985;313: 266.

192. White A, Nunes C, Escudier M, et al. Improvement in orofacial granulomatosis on a cinnamon- and benzoate-free diet. *Inflamm Bowel Dis*. 2006;12:508.
193. Appel LJ, Brands MW, Daniels SR, et al. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension*. 2006;47:296.
194. Reusser ME, McCarron DA. Reducing hypertensive cardiovascular disease risk of African Americans with diet: Focus on the facts. *J Nutr*. 2006;136:1099.
195. Kuznetsova T, Staessen JA, Brand E, et al. Sodium excretion as a modulator of genetic associations with cardiovascular phenotypes in the European Project on Genes in Hypertension. *J Hypertension*. 2006;24:235.
196. Feldman JM, Lee EM, Castleberry CA. Catecholamine and serotonin content of foods: effect on urinary excretion of homovanillic and 5-hydroxyindoleactetic acid. *J Am Diet Assoc*. 1987;87:1031.
197. Simon JB. Occult blood screening for colorectal carcinoma: a critical review. *Gastroenterology*. 1985; 88:820.
198. Markowitz AJ, Winawer SJ. Screening and surveillance for colorectal cancer. *Semin Oncol*. 1999;26:485.
199. Pennington TH, Calloway DH. Copper content of foods. Factors affecting reported values. *J Am Diet Assoc*. 1993;63:143.
200. Griffiths AM. Enteral feeding in inflammatory bowel disease, *Curr Opin Nutr Metab Care*. 2006;9:314.
201. Jowett SL, Seal CJ, Pearce MS, et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. *Gut*. 2005;53:1479.
202. Seidner DL, Lashner BA, Brzezinski A, et al. An oral supplement enriched with fish oil, soluble fiber, and antioxidants for corticosteroid sparing in ulcerative colitis: a randomized, controlled trial. *Clin Gastroenterol Hepatol*. 2005;3:358.
203. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. *BMJ*. 2004;238:1407.
204. McClave SA, Chang WK, Dhaliwal R, Heyland DK. Nutrition support in acute pancreatitis: a systematic review of the literature. *JPEN*. 2006;30:143.
205. Eatock FC, Chong P, Menezes N, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. *Am J Gastroenterol*. 2005;100:432.
206. Lea R, Whorwell PJ. The role of food intolerance in irritable bowel syndrome. *Gastroenterol Clin North Am*. 2005;34:247.
207. O'Mahoney L, McCarthy J, Kelly P, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*. 2005;128:541.
208. Atkinson W. Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomized controlled trial. *Gut*. 2004;53:1459.
209. Alpers DH. Diet and irritable bowel syndrome. *Curr Opin Gastroenterol*. 2006;22:136.
210. Quartero AO, Meineche-Schmidt V, Muris J, et al. Bulking agents, antispasmodics and antidepressant medication for the treatment of irritable bowel syndrome (review). The Cochrane Database of systematic reviews 2005;CD003460.
211. Kappelman M, Bousvaros A. Probiotic therapies: the crossroads of traditional and alternative medicine. *Pract Gastroenterol*. 2005;April:20.
213. Montrose DC, Floch MH. Probiotics used in human studies. *J Clin Gastroenterol*. 2005;39:469.
214. Boyle RJ, Robins-Browne RM, Tang MLK. Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr*. 2006;83:1256.
215. Allen SJ, Okoko B, Martinez E, et al. Probiotics for treating infectious diarrhea. *Cochrane Database Syst Rev*. 2004:CD003048.
216. Jones JL, Foxx-Orenstein AE. Probiotics in inflammatory bowel disease. *Pract Gastroenterol*. 2006; March:44.
217. Floch MH. Use of diet and probiotic therapy in the irritable bowel syndrome: analysis of the literature. *J Clin Gastroenterol*. 2005;30(Suppl 3):S243.
218. Viljannen M, Savilahti E, Haahtela T, et al. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double blind placebo-controlled trial. *Allery*. 2005;60:494.
219. Kalliomaki MA, Isolauri E. Probiotics and down-regulation of the allergic response. *Immunol Allergy Clin North Am*. 2004;24:739.
220. Salminen SJ, Guiemonde M, Isolauri E. Probiotics that modify disease risk. *J Nutr*. 2005;13:1294.
221. Bengmark S, Martindale R. Prebiotics and synbiotics in clinical medicine. *Nutr Clin Pract*. 2005;20:244.
222. Arbor Clinical Nutrition Updates. Probiotics, immunity and allergy. 2006; 246:1.
223. Marriott BM. Functional foods: an ecologic perspective. *Am J Clin Nutr*. 2000;71[Suppl]:1728S.
224. Bidlack WR, Wang W. Designing functional foods. In: Shils ME, Olson JA, Shike M, et al., eds. *Modern Nutrition in Health and Disease*, 9th ed. Baltimore: Williams & Wilkins, 1999:1823.
225. Ross S. Functional foods: the Food and Drug Administration perspective. *Am J Clin Nutr*. 2000;71[Suppl]:1735S.
226. DHHS/FDA. Food labeling: general requirements for health claims for food. *Fed Reg*. 1993;58:2478.
227. Turner RE, Degnan FH, Archer DL. Label claims for foods and supplements: a review of the regulations. *Nutr Clin Pract*. 2005;20:21.
228. Diplock AT, Aggott PJ, Ashwell M, et al. Scientific concepts of functional foods in Europe: consensus document. *Br J Nutr*. 1999;8[Suppl]:S1.

Nutritional Management of Specific Diseases

IV

DIETARY MANAGEMENT OF DIABETES, RENAL DISEASE, AND HYPERLIPIDEMIA

13

DIABETES

Introduction

In 2005, nearly 21 million Americans had diabetes, representing 7% of the adult population (1). Of these, 6.2 million cases were undiagnosed. The National Diabetes Surveillance System has shown a disturbing temporal trend in diabetes prevalence. In 1980 there were about 5.6 million Americans with diagnosed diabetes. In 2005, this number had increased to 15.8 million (2,3). Currently, another 54 million people are estimated to have "pre-diabetes" on the basis of an impaired fasting value or an abnormal postprandial plasma glucose level following oral glucose challenge. About 176,000 diabetics are less than 20 years old, representing 0.22% of the childhood and adolescent population (1). The incidence of diabetes in American youth is estimated at 24.3 per 100,000 person years (4). Approximately one in every 400 to 600 children and adolescents has type 1, insulin-dependent diabetes and almost all the diabetes identified below the age of 10 years is type 1 diabetes. The incidence of type 1 diabetes remains relatively infrequent in American adolescents, averaging about 11.8 to 13.5 per 100,000 across racial and ethnic groups. Although non-Hispanic White adolescents have a type 2 diabetes incidence of only about 6 per 100,000, American Indian children have an incidence of almost 50 per 100,000, and African-American, Hispanic, and Asian/Pacific Islander adolescents have a type 2 diabetes incidence in the range of about 20 per 100,000 (4). Another two million adolescents (or about one in six overweight adolescents) are estimated to have pre-diabetes. Since the prevalence of obesity is increasing in children and adolescents, it is highly likely that both the incidence and prevalence of type 2 diabetes in youth will continue to rise (4).

Diabetes is the sixth leading cause of death in the United States. It is the leading cause of blindness in people between the ages of 20 and 74, the leading cause of end-stage renal disease, and a principal cause of neuropathy and peripheral vascular disease. The relative risk for stroke and heart disease is increased twofold to fourfold in patients with diabetes,

and heart disease kills approximately 650,000 Americans annually. The overall direct costs of diabetes treatment and the associated loss of productivity were estimated at $132 billion dollars in 2002 (5). Of this amount $92 billion were direct medical expenses associated with 17 million diabetes-related hospitalizations and 63 million outpatient visits (5). The indirect costs associated with lost work days, restricted activity, and the like amounted to $40 billion (5). There were about 176,000 cases of permanent disability due to diabetes in the United States in 2002 (5).

Worldwide, the prevalence of diabetes was estimated at about 30 million people in 1985. In the year 2000, the World Health Organization estimated the prevalence of diabetes at 171 million, but projected an increase in prevalence to 366 million in the year 2030 (6). This prediction appears on track, since the prevalence was estimated at 194 million in 2003 and at 246 million in 2007 (6,7). The chronicity of the disease and its myriad complications make diabetes one of the most common problems encountered by physicians everywhere.

The National Institutes of Health Diabetes Control and Complications Trial (DCCT) demonstrated unequivocally that prolonged near-normalization of blood glucose in persons with type 1 diabetes significantly reduces the development and progression of retinopathy, clinical neuropathy, abnormalities of the autonomic nervous system, albuminuria, and microalbuminuria (8–18). Most compelling has been the additional evidence that has accrued from the continued observational follow-up of the original DCCT cohort, an ongoing study known as the Epidemiology of Diabetes Interventions and Complications (EDIC). The EDIC is now reporting data confirming that intensive treatment of diabetes is associated with less cardiovascular disease (19) and atherosclerosis, specifically coronary artery calcification and carotid intima-media thickness, 6 to 12 years after completing of the 6.5 years of intensive glycemic control during the DCCT (20,21). Unfortunately, however, even though the immunological events that lead to destruction of pancreatic beta cells in type 1 diabetes begin, and can be identified, years before development of overt hyperglycemia, attempts to prevent a susceptable individual's progression to frank diabetes have proven yet unsuccessful (22).

On the other hand, eight major clinical trials carried out over the last decade have shown unequivocally that type 2 diabetes can be prevented in approximately 50% of nondiabetic obese individuals by intensive lifestyle changes that reduce caloric intake and increase physical activity, either alone or assisted by additional pharmacologic interventions (23–32). Further, early data from the NIH Look AHEAD (Action for Health in Diabetes) study has shown that intensive lifestyle intervention can decrease energy intake, increase energy expenditure, and achieve significant weight loss in obese adults who already have type 2 diabetes and improve diabetes control, reduce medication use, and reduce cardiovascular risk factors (33). The reason why type 2 diabetes can be prevented by these approaches is due to the fact that type 2 diabetes, like type 1 diabetes, has its pathophysiologic origins long before the frank development of overt diabetes. Thus, following the development of insulin resistance due to obesity (34), fasting blood sugar remains little changed as long as pancreatic beta cell insulin secretion can compensate. Eventually, beta cell function begins to fail. Even then, a 75% reduction in beta cell sensitivity to glucose is still associated with only a minor increase in blood sugar (31). Only after loss of the bulk of remaining beta cell function does frank diabetes become manifest (31). Therefore, lifestyle interventions that lead to successful weight loss during the lengthy course of pancreatic beta cell deterioration can prevent the development of diabetes by prolonging the adequacy of pancreatic beta cell insulin secretion.

Role of Dietary Management

Control of dietary intake is one of the key elements of any diabetic treatment regimen aimed at normalizing blood glucose; it is also crucial in the management of obesity, hyperlipidemia, hypertension, and impaired renal function, all, unfortunately, common comorbidities. Diet plays a major role in regulating carbohydrate, fat, and protein homeostasis in patients with diabetes. Furthermore, proper dietary management is required for the safe and effective use of insulin.

There are few randomized, controlled trials that have studied the efficacy of dietary advice in the treatment of diabetes and these do not provide convincing evidence of effectiveness (35).

However, a recent meta-analysis (36,37) demonstrated that dietary counseling can produce modest weight loss and that weight management is an essential component in the treatment of individuals with type 2 diabetes. In fact, it may be the most important therapeutic modality, since weight loss improves the control of blood sugar, and almost certainly slows the progression of complications. With respect to the latter, because the subjects enrolled in the DCCT were nonobese persons with type 1 diabetes, we do not yet know definitively whether the results of the DCCT can be extrapolated directly to the issue of the relationships among blood glucose control and selected adverse complications in obese persons with type 2 diabetes (35), although it is highly likely that the fundamental conclusions of the DCCT also apply to the latter group.

Like the results commonly observed in nondiabetic obese subjects, it is usually very difficult to achieve significant weight loss in obese diabetic individuals. However, a weight loss of only 5% to 10% body weight can lead to significant improvements in blood sugar, blood pressure, and plasma lipids (36). The likelihood of compliance is increased by adequate patient education and by intense efforts to tailor diets to the needs of individual patients in an effort to achieve prolonged compliance and a fundamental change in lifestyle. If a patient is offered no personal dietary instruction other than a preprinted guide to the diabetic diet, the chances of successful compliance are nil.

Most physicians have neither the time nor the knowledge to develop an individualized diet plan for each patient, educate each patient adequately, and follow the patient's dietary progress. Registered Dietitians, Certified Diabetes Educators, Physicians Assistants, and other properly trained medical nutritionists and educators who are either hospital-based, located in a physician's office, or in private practice in the community can formulate plans in cooperation with the physician and instruct patients. Local chapters of the American Diabetes Association (ADA) and the Juvenile Diabetes Research Foundation International can provide additional educational resources and support.

Diet Therapy

For practical purposes, the major divisions of type 1 (lean, insulin-requiring) and type 2 (overweight or obese, non-insulin-requiring) diabetes provide a means of classifying dietary management issues although the goals of medical nutrition therapy for the prevention and treatment of diabetes are similar in most respects (38).

For individuals with risk of developing diabetes, the overriding principle of medical nutrition treatment is to "decrease the risk of diabetes and cardiovascular disease by promoting healthy food choices and physical activity leading to moderate weight loss that is maintained" (38).

For persons who already have diabetes, the ADA goals of nutrition therapy (38) are to:

1. Achieve and maintain (a) blood glucose in the normal range or as close to the normal range as possible (b) a lipid and lipoprotein profile that reduces the risk of vascular disease and (c) blood pressure in the normal range or as close to normal as is safely possible.
2. To prevent, or at least slow, the rate of development of the chronic complications of diabetes by modifying nutrient intake and lifestyle.
3. To address individual nutrition needs, taking into account personal and cultural preferences and willingness to change.
4. To maintain the pleasure of eating by only limiting food choices when indicated by scientific evidence (38).

The ADA also recommends select goals that apply to specific diabetes situations. These are:

5. For youth with type 1 diabetes, youth with type 2 diabetes, pregnant and lactating women, and older adults with diabetes, to meet nutritional needs of these unique times in the life cycle.
6. For individuals treated with insulin or insulin secretagogues, to provide self-management training for safe conduct of exercise, including the prevention and treatment of hypoglycemia and diabetes treatment during acute illness (38).

The effectiveness of the individual components of a comprehensive approach to the medical nutrition therapy of diabetics has been subjected to an extensive evidence-based analysis and classification by the ADA (39). In the evidence-based hierarchy, *Level A* evidence is the highest level of evidence available and is equivalent to that which comes from well-conducted randomized controlled trials, well-conducted multicenter trials, meta-analyses that incorporate quality ratings in the analysis, and compelling nonexperimental evidence. *Level B* evidence is supportive evidence from well-conducted prospective cohort studies or meta-analyses of cohort studies, as well as well-conducted case-control studies. Levels of evidence below Level B are less carefully controlled studies, studies with potential flaws that might bias or invalidate the results, and recommendations based on expert consensus or clinical experience (39). Recommendations based on lower levels of evidence may, in fact, be correct. However, we are far less certain that this is the case and it is important to realize that not all of the ADA-specific recommendations for medical nutrition therapy of diabetes are supported by Level A or Level B evidence (38). Those recommendations that *are* made on the basis of Level A or Level B evidence are shown in Table 13-1 and discussed, along with others, below.

Strategy of Diet Therapy for Obese, Type 2 Diabetics

Although the major goals of dietary therapy for the two types of diabetes are similar, the strategies for reaching these goals differ in some important ways (Table 13-2). A recent extensive and detailed review of the principles and practice of dietary management of diabetics has been published (40).

The primary therapeutic goal for patients with non-insulin-dependent diabetes is to maintain normal glucose, lipid, and blood pressure levels. Achieving this goal is facilitated by weight loss, which is a major focus of diet therapy in obese patients with type 2 diabetes. However, current strategies for achieving significant and sustained weight loss are often ineffective. For this reason, practical therapeutic approaches emphasize pharmacologic and other supportive approaches to control serum glucose, serum lipids, and blood pressure and use moderate caloric restriction paradigms to achieve and sustain at least a modest reduction of weight, in the range of 5% to 10% of initial body weight in individuals who are overweight or have Class 1 obesity. Obviously, if additional weight loss is achievable, it is desirable. In diabetics who have body mass index (BMI) greater than 35 kg per m^2, more aggressive weight management programs are often necessary (40).

Regular clinical and biochemical monitoring is essential to evaluate the effects of various treatment regimens aimed at accomplishing the stated goals. For obese diabetics who are not taking insulin or oral hypoglycemic agents, the timing of meals, precise distribution of macronutrients, and day-to-day consistency in dietary patterns are, in general, somewhat less critical than they are in insulin-dependent subjects. However, consistency of meal content and timing is a clear adjunct to successful therapy in patients with type 2 diabetes, as it is in patients with type 1 diabetes.

Management should follow certain principles:

1. Food choices and dietary fat intake should be guided by the standards of a healthy diet as outlined in the 2005 *Dietary Guidelines for Americans* using MyPyramid (www.mypyramid.gov) as an implementation tool (see Chapter 2). As discussed in Chapter 2, these expert recommendations aim for a modest total intake of fat, with a reduction in intake of saturated plus *trans* fats to less than 10% of energy intake. This recommendation is widely used (40). The ADA recommendations are fundamentally similar, but stated somewhat differently. The ADA ascribes Level A evidence to their recommendation of limiting saturated fat intake to less than 7% of energy intake (38) while also recommending minimizing the intake of *trans* fat, although with lesser confidence in the evidence supporting this recommendation (38). Reduction in saturated and *trans* fat intake often leads to a corresponding reduction in total calorie intake because surreptitious excess energy consumption is linked to dietary intake of fat. Thus, some weight loss is often achieved as a result and *any* sustained weight loss is a beneficial goal in the management of type 2 diabetes. A sustained weight loss in the range of 10% of body weight can significantly improve the metabolic control of a type 2 diabetic patient. If, for other pressing medical reasons, weight loss is a primary therapeutic concern, a more aggressive reduction of dietary fat intake should be recommended. Despite the

TABLE 13-1. Major Nutrition Recommendations for the Medical Nutrition Treatment of Diabetics That Are Supported by Level A or Level B Evidence

Effectiveness of Medical Nutrition Treatment (MNT)

- Individuals who have pre-diabetes or diabetes should receive individualized MNT; such therapy is best provided by a registered dietitian familiar with the components of diabetes MNT. (B)

Energy balance, overweight, and obesity

- In overweight and obese insulin-resistant individuals, modest weight loss has been shown to improve insulin resistance. Thus, weight loss is recommended for all such individuals who have or are at risk for diabetes. (A)
- Structured programs that emphasize lifestyle changes, including education, reduced energy and fat (~30% of total energy) intake, regular physical activity, and regular participant contact, can produce long-term weight loss on the order of 5% to 7% of starting weight. Thus, lifestyle change should be the primary approach to weight loss. (A)
- Low-carbohydrate diets (restricting total carbohydrate to $<$130 g/day) are not recommended in the treatment of overweight/obesity. The long-term effects of these diets are unknown, and although such diets produce short-term weight loss, maintenance of weight loss is similar to that from low-fat diets and impact on CVD risk profile is uncertain. (B)
- Physical activity and behavior modification are important components of weight loss programs and are most helpful in maintenance of weight loss. (B)
- Weight loss medications may be considered in the treatment of overweight and obese individuals with type 2 diabetes and can help achieve a 5% to 10% weight loss when combined with lifestyle modification. (B)
- Bariatric surgery may be considered for some individuals with type 2 diabetes and BMI $\geq$35 kg/m^2, and can result in marked improvements in glycemia. The long-term benefits and risks of bariatric surgery in individuals with pre-diabetes or diabetes continue to be studied. (B)

Preventing diabetes

- Among individuals at high risk for developing type 2 diabetes, structured programs that emphasize lifestyle changes that include moderate weight loss (7% body weight) and regular physical activity (150 min/week), with dietary strategies (such as reduced intake of fat) to reduce calories, can reduce the risk for developing diabetes and are therefore recommended. (A)
- Individuals at high risk for type 2 diabetes should be encouraged to achieve the USDA recommendation for dietary fiber (14 g fiber/1,000 kcal) and foods containing whole grains (one-half of grain intake). (B)
- Observational studies report that moderate alcohol intake may reduce the risk for diabetes, but the data do not support recommending alcohol consumption to individuals at risk of diabetes. (B)

Controlling diabetes

Carbohydrate in diabetes management

- A dietary pattern that includes carbohydrate from fruits, vegetables, whole grains, legumes, and low-fat milk is encouraged for good health. (B)
- Monitoring carbohydrate, whether by carbohydrate counting, exchanges, or experienced-based estimation, remains a key strategy in achieving glycemic control. (A)
- The use of glycemic index and load may provide a modest additional benefit over that observed when total carbohydrate is considered alone. (B)
- Sucrose-containing foods can be substituted for other carbohydrates in the meal plan or, if added to the meal plan, covered with insulin or other glucose-lowering medications. Care should be taken to avoid excess energy intake. (A)
- As for the general population, people with diabetes are encouraged to consume a variety of fiber-containing foods. However, evidence is lacking to recommend a higher fiber intake for people with diabetes than for the population as a whole. (B)
- Sugar alcohols and nonnutritive sweeteners are safe when consumed within the daily intake levels established by the FDA. (A)

Fat and cholesterol in diabetes management

- Limit saturated fat to $<$7% of total calories. (A)
- Two or more servings of fish per week (with the exception of commercially fried fish filets) provide n-3 polyunsaturated fatty acids and are recommended. (B)

(*continued*)

TABLE 13-1. Major Nutrition Recommendations for the Medical Nutrition Treatment of Diabetics That Are Supported by Level A or Level B Evidence (*Continued*)

Protein in diabetes management
- In individuals with type 2 diabetes, ingested protein can increase insulin response without increasing plasma glucose concentrations. Therefore, protein should not be used to treat acute or prevent nighttime hypoglycemia. (A)

Alcohol in diabetes management
- In individuals with diabetes, moderate alcohol consumption (when ingested alone) has no acute effect on glucose and insulin concentrations but carbohydrate co-ingested with alcohol (as in a mixed drink) may raise blood glucose. (B)

Micronutrients in diabetes management
- There is no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes (compared with the general population) who do not have underlying deficiencies. (A)
- Routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence of efficacy and concern related to long-term safety. (A)

Nutrition interventions for type 1 diabetes
- For individuals with type 1 diabetes, insulin therapy should be integrated into an individual's dietary and physical activity pattern.
- Individuals using rapid-acting insulin by injection or an insulin pump should adjust the meal and snack insulin doses based on the carbohydrate content of the meals and snacks. (A)

Nutrition interventions for pregnancy and lactation with diabetes
- Because GDM is a risk factor for subsequent type 2 diabetes, after delivery, lifestyle modifications aimed at reducing weight and increasing physical activity are recommended. (A)

Treating and controlling diabetes complications

Microvascular complications
- Reduction of protein intake to 0.8 to 1.0 g · kg body wt $^{-1}$ · day $^{-1}$ in individuals with diabetes and the earlier stages of CKD and to 0.8 g · kg body weight $^{-1}$ · day $^{-1}$ in the later stages of CKD may improve measures of renal function (urine albumin excretion rate, glomerular filtration rate) and is recommended. (B)

Treatment and management of CVD risk
- Target A1C is as close to normal as possible without significant hypoglycemia. (B)
- In normotensive and hypertensive individuals, a reduced sodium intake (e.g., 2,300 mg/day) with a diet high in fruits, vegetables, and low-fat dairy products lowers blood pressure. (A)

Hypoglycemia
- Ingestion of 15 ro 20 g glucose is the preferred treatment for hypoglycemia, although any form of carbohydrate that contains glucose may be used. (A)
- The response to treatment of hypoglycemia should be apparent in 10 to 20 min; however, plasma glucose should be tested again in ~60 min, as additional treatment may be necessary. (B)

Acute illness
- During acute illnesses, insulin and oral glucose-lowering medications should be continued. (A)
- During acute illnesses, testing of plasma glucose and ketones, drinking adequate amounts of fluids, and ingesting carbohydrate are all important. (B)

Long-term care facilities
- In the institutionalized elderly, undernutrition is likely and caution should be exercised when prescribing weight loss diets. (B)

From American Diabetes Association. Nutrition recommendations and interventions for diabetes: A position statement of the American Diabetes Association. *Diabetes Care.* 2007;30(Suppl. 1):S48–S65.

subtle differences in the saturated fat recommendations of the ADA and the *Dietary Guidelines for Americans,* most experts would agree that, if LDL cholesterol is not normalized with a saturated fat intake of less than 10% of total energy intake, a further reduction to less than 7% of energy intake may be advisable along with pharmacologic intervention, as addressed later in this chapter. Compelling data (Level B evidence)

TABLE 13-2. Dietary Strategies for Patients with Type 1 and Type 2 Diabetes

Strategy	Obese diabetics who do not require insulin (type 2)	Nonobese, insulin-dependent diabetics (type 1)
Decrease caloric intake	Yes	No
Protect or improve pancreatic beta-cell function	Priority	Seldom important because beta cells are usually extinct
Increase frequency and number of feedings	Helpful	Yes
Maintain day-to-day consistency of intake of kilocalories, carbohydrate, protein, and fat	Not as crucial as dietary total energy and fat content	Very important
Maintain day-to-day consistency of ratios of carbohydrate, protein, and fat for each of the feedings	Helpful	Desirable
Time meals consistently	Not generally crucial	Very important
Allow extra food for unusual exercise	Not usually appropriate	Usually appropriate
Use food to treat, abort, or prevent hypoglycemia	Not generally necessary	Important
During complicating illness, provide small frequent feedings, or give carbohydrate IV to prevent starvation ketosis	Often not necessary because of resistance to ketosis	Important

Adapted from West KM. Diet and diabetes. *Postgrad Med.* 1976;60:209.

are now available indicating that replacement of saturated fats with mono- or polyunsaturated fats, especially the omega-3 fatty acids found in fish, can improve serum lipids and are likely to improve cardiovascular risk, although such substitutions *per se* have not been shown to improve glycemic control (38,40). There is considerably more controversy involving the need to reduce dietary cholesterol intake if a reduction in dietary saturated fat intake is achieved, because dietary cholesterol intake alone has a somewhat limited effect on serum cholesterol in the absence of saturated fats. Unfortunately, in the usual American diet, cholesterol is generally co-ingested with saturated fats. Thus, the ADA recommends limiting dietary cholesterol intake to less than 200 mg per day, but admits that the scientific basis for this recommendation is contingent on a lower level of evidence (38).

2. Long-term compliance with a weight loss diet is more likely if the caloric restriction is not too stringent. Moderate caloric reductions to 250 to 500 kcal less than the subject's usual intake are appropriate. An overall calorie allowance of about 25 kcal per kg of ideal body weight allows gradual weight loss (on the order of 1 to 1.5 lb per week) without being so restrictive that compliance is unlikely.
3. Adjuncts to dietary therapy often can improve both compliance and efficacy. Some patients are able to maintain a reduced dietary intake of energy if their caloric intake is spread throughout the day in the form of meals and snacks rather than three meals alone. Similarly, in addition to improving glycemic control, maintaining lean body mass, and enhancing a general feeling of well being, regular physical activity augments energy expenditure and facilitates weight management. A diabetic patient who exercises can accelerate weight loss on a fixed intake of energy; conversely, the patient can maintain the same rate of weight loss on a smaller reduction in dietary energy intake.

4. The routine use of dietary supplements is unnecessary. Except for diabetic patients on very low calorie diets that entail substantial dietary restriction under medical supervision, those with uncontrolled glycosuria, or those who are pregnant, lactating, elderly, or strict vegetarians, routine dietary vitamin and mineral supplementation is not necessary. The ADA finds that there is "no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes (compared with the general population) who do not have underlying deficiencies" (Level A) (38) and that "routine supplementation with antioxidants, such as vitamins E and C and carotene, is not advised because of lack of evidence of efficacy and concern related to long-term safety" (Level A) (38). The primary exceptions are the those that apply to special populations of non-diabetic as well as diabetic persons. Thus, folic acid supplementation or the consumption of foods fortified with folic acid may be necessary for all diabetic women of childbearing age to achieve the CDCP recommendations for a daily folic acid intake of 400 μg. Secondly, elderly persons with diabetes are advised to take supplemental vitamin B_{12} or eat foods fortified with vitamin B_{12} to achieve an adequate daily intake of that vitamin. Although no consensus recommendation has been made, diabetic women should consider taking a calcium supplement if their dietary calcium intake does not meet current recommended levels.

   Dietary deficits of chromium and zinc have been reported in diabetic persons, but little systematic evidence is available to indicate that dietary zinc or chromium supplementation is of clinical benefit. Magnesium deficiency may follow sustained polyuria secondary to hyperglycemia or the use of diuretics, but this also is not a common problem or one that requires routine supplementation. Similarly, iron replacement should be reserved for patients with demonstrable iron deficiency.
5. Use Food Exchange Lists as an aid for dietary management. The most commonly employed tool for helping type 2 diabetics manage their food intake to achieve glycemic control is the ADA food exchange list system in which common measures of various foods are ordered into groups whose individual members have approximately equal contents of carbohydrate, protein, and fat (Table 13-3). The intent is to allow flexibility of food choices within groups while keeping the overall diet contents of macronutrients, especially carbohydrates, reasonably constant. However, although the exchange system is the most extensively used aid, it is merely one guide to understanding intelligent food choices within the context of a balanced diabetic diet. Alternative approaches are available and many are widely used (40). Selected patients with type 2 diabetes may be better served by flexible diet plans if they facilitate compliance and help the patients achieve the goals outlined above. Nonetheless, the ADA exchange system remains one of the best ways to provide dietary choice and flexibility and at the same time maintain reasonably consistent energy and macronutrient intake from day to day.
6. Use the principles of the *Dietary Guidelines for Americans* to establish a prudent diet plan as discussed earlier (Chapter 2). To maintain normal blood lipid profiles, diabetic patients should aim for a diet where total fat intake does not exceed approximately 30% to 35% of dietary energy intake, although the principal focus should be on reducing the daily intake of saturated plus *trans* fats to less than 7% to 10% of total dietary energy intake, and substitution of monounsaturated and polyunsaturated fats for saturated and *trans* fats in the diet.
7. Choose dietary carbohydrates wisely. The management of dietary carbohydrate intake in diabetes had long focused on restricting the intake of simple sugars, primarily the disaccharides such as sucrose, but we now realize that this focus was misplaced. Foods containing simple sugars can generally be accommodated in a diabetic's meal plan if adequately covered with appropriate glucose lowering medications (38). In some diabetics, restriction of the intake of simple sugars can be a helpful adjunct to dietary treatment (40), but there is limited evidence to indicate that simple sugars enhance the hyperglycemic response in the context of a complete meal. Nonetheless, many experts recommend that simple sugars be consumed in moderation (40), not exceeding 40 g per day. In any case, the caloric content of the sugars consumed should be included in the total daily carbohydrate intake and care must be taken to avoid excessive calorie intake as sugars (or, for that matter, as fat or protein as well).

TABLE 13-3. Nutritional Values of the Exchange Lists

	CHO	Protein	Fat	Calories
Carbohydrate group				
Starch	15	3	≤1	80
Fruit	15	—	—	60
Vegetables	5	2	—	25
Milk				
Skim	12	8	≤1	90
Low-fat	12	8	5	120
Whole	15	Varies	Varies	Varies
Meat and meat substitutes group				
Very lean	—	7	≤1	35
Lean	—	7	3	55
Medium-fat	—	7	5	75
High-fat	—	7	8	100
Fat group	—	—	5	45
Free foods group	<5	—	—	<20
Combination foods group	Varies	Varies	Varies	Varies
Fast foods group	Varies	Varies	Varies	Varies

CHO, carbohydrate.
From the American Dietetic Association and the American Diabetes Association. *Exchange Lists for Meal Planning.* New York: American Diabetes Association, 1995, with permission.

Lately, all expert bodies have appreciated that the correct focus of dietary carbohydrate intake should be on the types of carbohydrates consumed (38,40). As discussed in the *Dietary Guidelines for Americans* (Chapter 2), the most healthful dietary carbohydrates are found in fruits, vegetables, whole grains, and legumes and these should be the basis of carbohydrate intake in the diabetic diet (38). Use of the exchange list system allows monitoring of carbohydrate intake to ensure that the total daily carbohydrate intake is similar from day to day and adequately covered by medication (41). Additionally, while there is not enough evidence to support diabetics consuming dietary fiber in a higher amount than nondiabetic individuals, the consensus recommendation is that diabetics consume at least the Dietary Reference Intake for fiber of 14 g per 1,000 kcal of dietary energy consumption.

There remains debate about whether there is a therapeutic advantage to using the glycemic index of foods as an adjunct to improving postprandial hyperglycemia in diabetics (38) (see below). Nonetheless, the ADA has concluded that there is Level B evidence for recommending that the "use of glycemic index and load may provide a modest additional benefit over that observed when total carbohydrate [intake] is considered alone" (38). A recent meta-analysis (42) concluded that low glycemic index foods offer an advantage over high glycemic index foods for improvement in circulating lipoprotein profiles in diabetics. In this context, it is important to remember that the mixed diet consumed by most Americans has a "medium" glycemic index, so that studies comparing low glycemic index foods with high glycemic index foods may overestimate the actual effects that will be found in practice.

8. In addition to diet and lifestyle interventions, employ appropriate drug therapy to ensure optimal control of hyperglycemia. The ADA and the European Association for the Study of Diabetes have recently issued consensus guidelines for the successful pharmacologic management of glycemic control in persons with type 2 diabetes (43,44).

Strategy of Diet Therapy for Type 1 Diabetics

In persons who do not have diabetes, pancreatic insulin secretion changes abruptly and appropriately in response to a change in blood sugar. After a meal, insulin secretion increases as blood sugar starts to rise. Nondiabetics can vary their caloric intakes severalfold from day to day without becoming hyperglycemic or hypoglycemic because their insulin secretion is exquisitely responsive to changes in blood glucose and the blood glucose level is, thus, tightly regulated. On the other hand, individuals with type 1 diabetes are essentially completely insulin deficient within, at most, several years after their initial diagnosis (45). Thus, type 1 diabetics are unable to secrete insulin in response to a rise in blood sugar. In an attempt to anticipate and regulate glycemia after meals and during the course of normal daily activity, most type 1 diabetics inject, more than once daily, a combination of insulins with different time courses of action. The amount and proportions of the insulin dose are determined by preceding glycemia and anticipated glycemic response. Serum insulin levels are determined largely by the types of insulin injected and by the size and timing of the injected insulin dose.

None of the currently available insulins, not even the most current so-called rapid-acting insulins, can provide a serum insulin profile to precisely match the immediate release of insulin that occurs in nondiabetic subjects following the ingestion of food and the minute-by-minute responsiveness of pancreatic insulin secretion that takes place in nondiabetic subjects. Thus, the timing of a meal following an injection of insulin is critical. Depending on the type of insulin used, meal ingestion may follow immediately (as with the use of rapid-acting insulins) or be delayed for 30 minutes or more (as with the use of short-acting insulins) in order to try to match the appearance of insulin into the systemic circulation with the absorption of glucose from the meal. Furthermore, it is imperative that the composition and distribution of meals be consistent with the composition and expected actions of the insulins injected. Because most patients with type 1 diabetes inject insulin on a relatively consistent schedule, they also consume meals on a relatively consistent schedule. Insulin doses should be adapted to the patient's lifestyle, schedule, eating preferences, and level of activity. Tailored regimens of this type are the rule for patients who monitor their blood glucose adequately. However, adjustment of the insulin dose is effective only if the caloric content is regular and the temporal distribution of food is consistent with the insulin regimen employed.

1. One should aim to achieve consistency in the composition of meals. Some regularity in the ratio of carbohydrates, proteins, and fats is necessary in each meal. The amount of insulin needed to "cover" a meal can be determined empirically, whatever the composition of the meal, and will remain fairly constant if the total number of ingested calories and ratio of macronutrients remain constant. The purpose of the dietary exchange list system is to provide consistency yet allow flexible food choices, and many type 1 diabetics (or type 2 diabetics who are taking insulin injections) use the exchange list system to achieve this consistency. However, to ensure consistency in the type, timing, and amount of carbohydrate foods consumed, most type 1 diabetics use an alternative approach called "Carbohydrate Counting" (46–50) (Table 13-4). In this scheme, emphasis is placed primarily on the total amount of carbohydrate consumed and diabetics learn what portion sizes of common foods contain approximately 15 g of carbohydrate (46–50) (Table 13-4). It should come as no surprise that the carbohydrate contents of the foods in this approach are identical to the carbohydrate contents of foods in the exchange list system. The carbohydrate "count" information is then coupled with the amount of injected insulin necessary to "cover" the glycemic response to the ingested carbohydrate. This "insulin to carbohydrate ratio" is largely determined empirically, but it is generally in the range of 1:10 (that is about 1 unit of insulin to cover about 10 g of carbohydrate). This ratio may vary as a function of body weight, physical activity, and other variables known to alter insulin sensitivity, such as selected hormones, pregnancy, and the like (46–50).
2. The degree of flexibility in the diet that is consistent with good metabolic control varies from patient to patient. Some patients can vary their caloric intake and dietary composition from day to day and still tightly regulate their blood sugar level by paying careful attention to blood sugar monitoring and insulin dose adjustment. Others require a fixed

TABLE 13-4. Carbohydrate Counting

Equivalent 15 g carbohydrate servings:
Starches: 1 slice of bread, 1/3 cup cooked pasta, 3/4 cup dry cereal, or 4–6 crackers
Fruit: 1 small piece of fruit or 1/2 cup of fruit juice
Milk: 1 cup of nonfat (skim) milk, or 3/4 cup yoghurt
Desserts: 2 small cookies or 1/2 cup ice cream

Counting the carbohydrates:

Amount of carbohydrate	Carbohydrate serving count
0–5 g	0
5–10 g	1/2 serving
11–20 g	1 serving
21–25 g	1.5 servings
2–35 g	2 servings

Compiled from references 46 through 50.

regimen to control hyperglycemia. The DCCT demonstrated an unequivocal reduction in diabetic complications following prolonged control of blood sugar, and good control should not be sacrificed for a more liberal diet.

3. The adverse consequences of rigid glycemic control include the risk for obesity because of diminished urinary loss of glucose calories and the antilipolytic effects of insulin. More importantly, however, tight control of blood glucose is associated with a large increased risk of significant, symptomatic hypoglycemia (51). Because we are unable to match plasma insulin and glucose profiles adequately, consistently, and precisely, diabetics who aim for normoglycemia are prone to episodes of serious hypoglycemia requiring the assistance of another person for resolution. Such episodes can lead to permanent detrimental consequences, both to the diabetic patient and others (e.g., auto accidents). Careful and regular monitoring for adverse effects is required, and the insulin dose and calorie intake must be adjusted as necessary. The clinical risk of hypoglycemia is increased when insulin doses are too large or not timed appropriately, when meals or snacks are missed, when physical activity is increased, and when insulin clearance is decreased as renal function declines (51).

The Dietary Prescription

It is important to individualize the diet prescription to accommodate the diabetic patient's lifestyle, eating habits, age, and concurrent disease. It is counterproductive to expect the opposite, i.e., that a patient will change their fundamental habits just to accommodate the diet prescription. The following list can be used to establish such a prescription (12):

1. In order of priority, what are the main general purposes (not strategies [52] or methods) of this patient's prescription?
2. How much does the patient weigh? How much do the doctor, dietitian, and patient think the patient should weigh? How much would the patient like to weigh?
3. What is the appropriate level of caloric consumption for the patient?
4. Does the patient require insulin? If so, is the blood glucose level relatively stable, moderately labile, or severely labile? What kind of insulin is to be given? At what time? In what amount?
5. What, when, and how much would the patient like to eat if he or she did not have diabetes? Are there any special considerations relating to economic factors or to family or cultural dietary propensities?
6. Is the level of carbohydrate to be limited? To what level or range? To what extent and under what conditions, if any, are concentrated carbohydrates to be used?
7. Are there any special requirements concerning levels of protein?

8. Are there any specific or general requirements with respect to levels of dietary fat, either saturated or unsaturated?
9. How much alcohol is to be permitted? Under what conditions? Should alcohol be exchanged for food? If so, what kind and in what amount?
10. If the temporal distribution of food is of any importance, are there specific requirements concerning the following:
    a. The relative size and timing of each of the three main meals?
    b. The timing, size, and characteristics of any extra feedings?
11. To what degree is day-to-day consistency required in
    a. Total kilocalories?
    b. Size and characteristics of specific feedings, such as lunch?
12. Are dietary adjustments to be made for exercise or marked glycosuria? Of what nature?
13. Are there any special conditions unrelated to diabetes that require a special diet (e.g., gout, hyperlipidemia, renal or cardiac failure)?
14. Can all elements of the prescription be reconciled, and how should this be done? (For example, it is usually not feasible to construct a palatable diet for a lean diabetic if the prescription restricts both carbohydrate and fat.)
15. What kind and degree of changes are to be made subsequently by the dietitian without consulting the physician?
16. What should the patient do if it becomes necessary to postpone or modify a meal (e.g., when attending a dinner meeting or social affair)?
17. Tactical questions:
    a. How much precision is required in the various elements of this prescription?
    b. What foods can be freely allowed?
    c. What foods, if any, are to be weighed or measured?
    d. Are any modifications of the standard exchange system appropriate, such as simplification?
    e. In general, is food to be unmeasured, estimated, measured, or weighed?
    f. Is it necessary or desirable to instruct the patient about the carbohydrate, protein, and fat contents of the common foods?
    g. Under what circumstances are artificial sweeteners and diet drinks to be used?
18. Has the patient's understanding of dietary principles and methods been systematically evaluated?

Setting Up the Diabetic Diet

The first step in formulating the diabetic diet is to calculate the number of calories the patient requires to achieve or maintain a healthy body weight. This is no easy task because no simple approach to the accurate and precise estimation of a specific patient's energy requirements in a clinical setting is available. Caloric requirements are related to the patient's age, level of activity, and body weight. Basal metabolic rates (BMRs) are in the range of 21 to 29 kcal per kg daily for adults below the age of 60, with women, on average, having BMRs slightly lower than those for men. Above the age of 60, the daily BMR is in the range of 19 to 23 kcal per kg. It is most appropriate to start at the low end of these ranges to estimate energy expenditure.

A lean individual's estimated energy requirement (EER) in kilocalories per day can be estimated from his or her age, body weight in kilograms, and height in meters according to the following equations (53,54):

Men:

$$EER = 662 - (9.53 \times age) + PA \times [(15.91 \times weight) + (539.6 \times height)]$$

Women:

$$EER = 354 - (6.91 \times age) + PA \times [9.36 \times weight) \times (726 \times height)]$$

PA is the subject's physical activity quotient. The value of PA assigned to the activities of usual daily living is 1.0. PA increases to 1.11 to 1.12 (for women and men, respectively) for the activities of daily life *plus* an additional 30 to 60 minutes of moderate activity daily;

to 1.25 to 1.27 for at least an *additional* 60 minutes of moderate daily activity; and to 1.45 to 1.48 for the activities of daily life plus an *additional* 180 minutes of moderate activity or at least an *additional* 60 minutes of moderate daily activity plus an *additional* 60 minutes of vigorous activity (15,16).

For overweight and obese men and women, such as most type 2 diabetics, total daily energy expenditure for weight maintenance is better estimated using the following modifications of the above equations (53).

Men:

$$EER = 1086 - (10.1 \times age) + PA \times [(13.7 \times weight) + (416 \times height)]$$

Women:

$$EER = 448 - (7.95 \times age) + PA \times [11.4 \times weight) + (619 \times height)]$$

Sedentary men and women are assigned a PA of 1.0. Low active men and women are assigned the PA values of 1.12 for men and 1.16 for women. Active men and women are given PA values of 1.29 and 1.27, respectively; and very active men and women have PA values of 1.59 and 1.44, respectively. For most obese type 2 diabetics, it is best to estimate activity level at the sedentary or low levels.

The next step in defining a diabetic diet is to determine the relative macronutrient contents. The various consensus guidelines (38,40) provide for a diet consisting of about 15% calories as protein, 50% to 60% as carbohydrate (primarily as complex carbohydrates), and 30% to 35% or less as fat, with an emphasis on restriction of saturated plus *trans* fats to 7% to 10% energy (as discussed above) and enhanced provision of monounsaturated and polyunsaturated fatty acids. In essentially all ways, this diet is the same as that recommended for all healthy adults in the 2005 *Dietary Guidelines for Americans* (Chapter 2).

The relaxed restriction on carbohydrates in current diabetic diets is a result of a better understanding of glucose homeostasis. Previous recommendations restricted carbohydrate intake because high-carbohydrate diets were thought to raise blood levels of sugar. High-starch (complex carbohydrate) diets are well tolerated by diabetics as long as the total caloric intake is controlled. A high-complex carbohydrate diet with an optimal caloric intake is better tolerated than a low-carbohydrate diet with excess calories. Furthermore, a high-complex carbohydrate diet provides the additional known nutritional benefits of a diet rich in fruits, vegetables and grains. Similarly, the reason for the more recent moderation of total fat intake is the realization that a reduction in intake of saturated and *trans* fats and the substitution of monounsaturated and polyunsaturated fatty acids for saturated fatty acids were more important that the total fat content of the diet, since an approach focusing on increasing "healthy fat" and reducing "unhealthy fat" intake provides the most appropriate dietary pattern for normalizing blood lipid profiles, a critical endpoint because the leading cause of death among diabetics is coronary artery disease.

The glycemic index (GI), discussed at length in Chapter 14, represents an attempt to classify foods according to the extent to which they raise the blood sugar level (38,55). Different foods with the same caloric value can produce markedly different elevations in the blood sugar. The GI has been defined as the area under the 2-hour blood glucose response curve for a food expressed as a percentage of the area after ingestion of the same number of calories as glucose. In general, the GIs of complex carbohydrates, especially in fiber-rich foods, are low. However, no simple algorithm can predict the GI *a priori*. Soybeans and peanuts have very low GIs, but the GIs of lentils, chick-peas, green peas, kidney beans, and pinto beans are two- to fourfold higher. The GI of fructose is equivalent to that of soybeans, the GI of honey is nearly equivalent to that of glucose, and the GI of table sugar (sucrose) is less than that of a baked potato. The blood glucose response after ingestion of a baked potato is essentially the same as that after oral glucose, but rice and pasta evoke a much lower blood glucose response. The reason for the differences in the glycemic response is not completely understood. The GI is influenced by the rate at which foods are digested and absorbed and the degree to which they raise the blood glucose level. The rate of gastric emptying and the presence of fat and protein affect the glycemic response. The glycemic response in patients with type 2 diabetes is

similar to that seen in normal persons, but the glycemic response in patients with type 1 diabetes is more variable. These individual variations limit the usefulness of the GI as a teaching tool for patients with diabetes. Also, in the context of mixed meals, the GI tends to lose its practical usefulness because the distinctions between individual foods are blurred. For this reason, many experts do not consider the GI to be a valuable adjunct to diabetes management but prefer to regulate total carbohydrate intake. However, a recent meta-analysis of low glycemic index diet studies in diabetics (56) showed that this adjunct to diet therapy led to a 0.43% decrement in hemoglobin A_1C and led the ADA to conclude that use of the glycemic index and glycemic load may provide a modest therapeutic benefit (38). In this context, it is important to emphasize that one need not go to great lengths to learn a new system to achieve this benefit, since the diet recommended in the 2005 *Dietary Guidelines for Americans* (Chapter 2) is a low glycemic index diet (55).

One must next divide the daily diet prescription into meals. The distribution of calories during the day must be adjusted to the patient's lifestyle and insulin program. A typical diet provides 20% to 30% of calories at breakfast, 20% to 35% at lunch, 25% to 40% at supper, and none to 15% as snacks. Snacks are usually taken at mid-morning, at mid-afternoon, and near bedtime. Tight control of blood sugar is easier if snacks are part of the diet regimen. Mid-morning and mid-afternoon snacks may prevent hypoglycemia by providing calories at times when levels of regular and intermediate-acting insulin reach their peak. Similarly, a bedtime snack may prevent nighttime hypoglycemia. Snacks also reduce the number of calories that are taken at meals and thus help prevent episodes of postprandial hyperglycemia.

After estimating the patient's energy requirement and determining the meal distribution, a specific meal plan is formulated using the exchange list or carbohydrate counting algorithms. The purpose of both systems is to allow a patient to vary the foods eaten from day to day and still consume a constant number of calories with a relatively fixed distribution of calories among carbohydrates, proteins, and fat and a fixed distribution of calories among the meals. The macronutrient contents of the various exchange or carbohydrate groups are shown in Table 13-3 and Table 13-4. While a thorough explanation of the exchange system is beyond the scope of this manual, it is useful to illustrate how it works. For example, an 1,800-cal diet in which the calories are distributed as 50% carbohydrate, 30% fat, and 20% protein would contain 224 g of carbohydrate, 92 g of protein, and 59 g of fat. One slice of white bread contains 15 g of carbohydrate, 3 g of protein, and no fat. This is one bread exchange with a caloric content of 80 cal. An 1,800-kcal diet might include eight bread exchanges (120 g of carbohydrate, 24 g of protein), with two of those exchanges assigned to breakfast. Thus, every breakfast would include two slices of white bread or their equivalent. Foods equivalent to two slices of bread include one cup of bran flakes or one bagel. On three successive mornings, a diabetic patient could have a breakfast that included three different items (bread, bran flakes, and bagel) while still consuming the same number of calories with the same distribution of macronutrients.

A widespread misconception among diabetics is that by spending more money for special "diabetic foods" they can eat what they like and still control their disease. Although sugar alcohols such as sorbitol have, on average, about half the calories of nutritive sweetners such as sucrose, most dietetic foods contain a significant number of calories. In fact, some products contain as many calories as the comparable regular foods. More important, however, is the fact that there is no evidence to indicate that such foods have any therapeutic advantage over regular foods in the care of, control of, or complications of diabetes. Non-nutritive sweeteners are commonly used as adjuncts in the management of both weight and glycemia. While these agents are generally recognized as safe (38), there are no convincing data that they are particularly helpful in achieving weight loss (57).

Alcohol is a component of the diet of many Americans. Most diabetics can consume limited amounts of alcohol, but several considerations peculiar to diabetes must be kept in mind. First, daily alcohol intake should be limited to fewer than two drinks daily in men and one in women (38). Because alcohol contains a significant number of calories (7 kcal per g), it is difficult to fit much alcohol into a weight loss diet and still

obtain adequate protein, vitamins, and minerals. In the obese diabetic, alcohol consumption should be minimized or eliminated until the excess weight is lost. Further, some alcoholic beverages, especially beer and sweet wines, contain a substantial number of calories in the form of carbohydrate in addition to those in alcohol. These may contribute to hyperglycemia and must be considered in the diet. When using the exchange list system, alcohol is substituted for fat exchanges: 1 oz of whiskey is the equivalent of two to three fat exchanges; 12 oz of low-calorie beer is the equivalent of two fat exchanges.

It is also important to recognize the effect of alcohol consumption on blood glucose. This effect depends on such factors as time, consumption of other foods, and type of beverage. In fasting, insulin-dependent diabetics, the ingestion of a large amount of alcohol can induce profound hypoglycemia by inhibiting the release of glucose from the liver. Alcohol can also impair counter-regulation in insulin-induced hypoglycemia. This effect may be most pronounced in tightly controlled patients with an increased incidence of hypoglycemia. Because the symptoms of hypoglycemia closely resemble those of alcohol intoxication, the hypoglycemia may go unrecognized, leading to significant detrimental consequences. To minimize the risk of nocturnal hypoglycemia when taking insulin or oral hypoglycemic agents, diabetics should only consume alcohol with food (38). Alcoholism and insulin-dependent diabetes are an unfortunate combination of diseases.

Alcohol intake can also cause an increase in circulating triglyceride concentration and diabetes is frequently accompanied by hyperlipidemia. Fortunately, control of the blood sugar and achievement of ideal body weight may return the triglycerides levels to normal, so that moderate alcohol consumption can be allowed. Finally, some patients taking sulfonylureas experience flushing, nausea, dyspnea, and palpitations when they drink alcohol. This reaction, which resembles the effect of disulfiram (Antabuse), can be prevented by taking antihistamines before alcohol, although the preferred solution is abstinence.

Modifying the Diet for Illness

In both type 1 and type 2 diabetics who are acutely ill, two general principles always apply. First, insulin or oral hypoglycemic agents should be continued (Level A) (38). Secondly, enhanced testing of plasma glucose and ketone values are necessary, as are drinking adequate amounts of fluids and ingesting sufficient amounts of carbohydrates (Level B) (38).

Acute illnesses are frequently accompanied by nausea, vomiting, and anorexia. In patients with type 2 diabetes, acute illness usually does not have a markedly adverse effect on diabetic control. For these patients, the major concern is avoiding dehydration by ensuring adequate fluid intake, usually by frequently ingesting small volumes of liquids and soft foods. Ingestion of at least 150 g of carbohydrate is recommended to reduce starvation ketosis (38). Occasionally, during an intercurrent illness such as influenza, insulin dependence develops in a patient with non-insulin-dependent diabetes; all diabetic patients should carefully monitor their blood sugar and their urine for the appearance of ketonuria during acute illness.

In individuals with type 1 diabetes, acute illness may result in profound hypoglycemia or in profound hyperglycemia and ketosis. Usually, the acute illness tends to increase insulin requirements. The only way to assess the insulin need is by frequent monitoring of blood glucose and urine ketones. The diabetic patient must take in enough carbohydrate (200 g per day) to prevent starvation ketosis. To prevent hypoglycemia during bouts of illness when appetite is depressed, adequate carbohydrate can be obtained by the frequent ingestion of sweetened fluids and soft, easily digested foods such as ice cream, juices, sweetened Jell-O, and soups. The ingestion of small amounts of fluid on a 15- to 30-minute basis helps to prevent dehydration (see Table 7-10 for selected oral rehydration solutions).

Modifying the Diet for Activity

Patients with non-insulin-dependent diabetes do not have to alter their diet to accommodate changes in exercise patterns. Exercise is a useful adjunct to caloric restriction in the attempt

to lose weight. The overweight diabetic who begins an exercise program should gradually lose weight if the caloric intake is constant. However, it should be emphasized that daily regular physical activity of all kinds is beneficial to persons with type 2 diabetes. The diabetic patient should not be led to interpret "physical activity" as traditional "exercise" (e.g., running, tennis) but made to understand that all forms of nonsedentary behavior are valuable. Brisk walking is one of the most beneficial activities for obese diabetics and has been shown to be an effective adjunct in reducing the risk for coronary heart disease.

Changes in exercise patterns in patients with insulin-dependent diabetes, however, must be accompanied by adjustments in the diet and insulin doses. Obviously, regular exercise every day at a set time, at a set level of activity, for a set length of time is easily accommodated to the person's diabetic dietary regimen. Irregular exercise is a more difficult problem. An hour of vigorous exercise (e.g., cycling, basketball) may require two extra bread exchanges or one bread and one fruit exchange. An hour of moderate exercise (walking) may require the addition of half as much carbohydrate. If the exercise is to last for less than 2 hours, the consumption of extra food can be delayed until the exercise is complete and the patient determines whether any food is necessary by measuring the blood glucose. Often, however, depending on the subject's prior history of hypoglycemia with moderate exercise for this length of time, a snack of 10 to 15 g of carbohydrate may be consumed before exercise. Among the foods that may be eaten before exercise are low-fat cottage cheese, fruit, yogurt, bread, and crackers. These should be eaten about 30 minutes before exercise. If the exercise is vigorous or of long duration, a carbohydrate-rich snack may have to be consumed every 30 minutes. The amount of food required to cover exercise depends on body size and the duration and intensity of activity.

Diabetes in Special Groups

Diabetes in Pregnant Women

Insulin-requiring diabetes is frequently more difficult to control during pregnancy, and pregnancy may cause glucose intolerance in a woman with previously normal glucose control. Special modifications of the diabetic diet are not needed to accommodate the additional requirements of pregnancy other than those recommended for pregnant women in general, as described in detail in Chapter 4. However, the normal consequences of pregnancy, such as morning sickness, may disrupt the patient's previously established eating patterns and established insulin regimens.

Weight gain during pregnancy is frequently excessive in diabetic patients and the consequences of obesity in pregnancy are substantial (58). It is preferable to control body weight before pregnancy or, if not possible, to prevent excessive weight gain during pregnancy (58) (Chapter 4). Excessive weight gain during pregnancy also magnifies the physiologic increase in insulin resistance that is a normal consequence of pregnancy. During the second and third trimesters, insulin requirements increase substantially, often as much as 50% to 100%, and additional dietary manipulations may be necessary to accommodate this increase. At the same time, the practitioner must be alert to the fact that the insulin requirement will drop immediately after delivery and the insulin dose lowered to prevent hypoglycemia.

Diabetes in Children

Diabetes is one of the most common serious chronic diseases of childhood. Whereas most adults with diabetes do not require insulin and are obese, 98% of children below the age of 10 with diabetes require insulin, and few are obese. More recently, however, as discussed earlier, the incidence and prevalence of obese type 2 diabetics has increased substantially in adolescents.

The goals of dietary therapy in children with diabetes are the same as in adults with diabetes, but in addition, dietary therapy must promote normal growth and development. The calorie requirements for children are based on sex, age, size, growth rate, and physical

activity, and age- and gender-specific energy intake recommendations are available elsewhere (53,54). Nevertheless, diets whose calculated energy intakes are constructed from these algorithms are only general guidelines, and each child's actual caloric requirement must be determined individually by trial and error. During adolescence, caloric requirements increase with the rate of growth. The energy cost of growth is about 120 kcal per day at peak growth during adolescence, although this still represents only 3% to 4% of the total energy requirement. The energy requirements of individual adolescents vary markedly. The total daily expenditure of energy in adolescent boys ranges from about 50 to 75 kcal per kg and in adolescent girls between about 50 to 65 kcal per kg, respectively, depending on their resting metabolic rate and their habitual level of physical activity. The calorie allotments for children should be modified according to their longitudinal progress on their own individual weight and height charts. Many juvenile diabetics are underweight at the time of diagnosis. A common error is to place underweight children on a diet calculated to meet the needs of children of normal weight of the same age. Underweight children may require an additional several hundred calories per day to regain lost weight and maintain growth.

Diabetes in Patients with Hypertension, Hyperlipidemia, or Renal Disease

Diabetes is frequently associated with other chronic illnesses for which the management includes diet therapy. Chronic renal failure is a common complication of diabetes. Elevated plasma cholesterol and triglyceride levels are common among diabetics. Finally, hypertension, although not directly related to diabetes, is common among the obese, middle-aged patients who comprise the majority of the diabetic population. Because each of these illnesses is treated in part by dietary measures, the formulation of a diet for patients with more than one of these illnesses requires additional planning. Fortunately, the diets used in the management of these several illnesses do not conflict with, but frequently complement, each other.

Patients with Diabetes and Chronic Kidney Disease

Recently, the National Kidney Foundation expert committee reported clinical practice guidelines for individuals with diabetes and kidney disease (59). For diabetics with kidney disease, other than end-stage renal disease, a target daily protein intake of 0.8 g per kg body weight is recommended based on Level B evidence. Specifically, two meta-analyses have demonstrated that microalbuminuria is reduced and kidney function is stabilized (60,61). Further, a recent randomized trial showed a significant reduction in relative risk (0.23 (0.07 to 0.72) of end-stage renal disease of death when dietary protein intake was modestly reduced (62). However, the results of the recently reported long-term follow up of the Modification of Diet in Renal Disease Study were inconclusive when attempting to show whether a reduction in dietary protein intake from 1.3 g per kg per day to 0.58 g per k per day would slow the progression of nondiabetic renal kidney disease (63). When consuming dietary protein intakes at the level of 0.8 g per kg per day, individuals must take care to consume dietary proteins of high biologic value, as described later in this chapter. In addition, patients must restrict their intakes of phosphorus, potassium, and sodium. None of these requirements should interfere with the recommended diabetic diet. Because the recent recommendations allow for a higher content of complex carbohydrates in the diabetic diet, a combined renal–diabetic diet is easier to devise. However, in this context, one must be aware that the Dietary Approaches to Stop Hypertension (DASH) and DASH-sodium diets that are fruit, vegetable, and grain based and have been shown to be effective in reducing blood pressure are relatively high protein diets with a daily protein intake on the order of 1.4 g per kg per day (64). Thus, applying the DASH diets to chronic kidney disease requires modification of the protein intake.

Patients with Diabetes and Hyperlipidemia

Hypertriglyceridemia occurs in about 20% of patients with type 2 diabetes. Management regimens, including appropriate blood glucose control with insulin or oral agents, reduction of alcohol intake, and caloric restriction to attain ideal body weight, should result in reduced

blood levels of both lipids and sugar. The dietary approach to hyperlipidemia is discussed in more detail later in this chapter.

Patients with Diabetes and Hypertension

The major dietary manipulations in the treatment of hypertension are caloric restriction, to help obese patients lose weight, sodium restriction (see Chapter 12) and the implementation of a healthful dietary pattern based on increased fruit and vegetable intake (64 to 73) with elimination of foods that are both high in calories and in sodium, such as processed dinners and snacks, cold cuts, sausage, French fries, salted nuts, and snack chips. In this context, to be successful it is critical to read the nutrition facts label of every purchased product. Eliminating these items helps control both diabetes and hypertension (see Chapter 12 for a discussion of the low-sodium diet). Regular exercise and a reduced alcohol intake are also useful proven adjuncts in the treatment of hypertensive diabetics.

RENAL DISEASE

General Principles

Diet therapy is an essential component of the management of renal disease. Although the overall evidence points to the fact that low protein diets will retard the progression of chronic renal disease, unequivocal demonstration of this thesis remains elusive (60–63,74,75).

The goals of diet therapy are to (a) provide adequate nutrition, (b) minimize uremia and other metabolic derangements, (c) reduce the risk factors for cardiovascular disease, and (d) delay the progression of renal failure (74). Improvement in the patient's metabolic status reduces the symptoms associated with uremia, including fatigue, nausea, pruritus, and anorexia.

A wasting syndrome in uremic patients is secondary to inadequate dietary intake of protein and energy, altered protein metabolism, and the endocrine abnormalities associated with renal failure (hyperparathyroidism, insulin resistance). In addition, patients on dialysis lose nutrients into the dialysate, which further contributes to wasting. A major factor contributing to malnutrition in chronic renal failure is the *anorexia* caused by uremia. Uremia also diminishes taste acuity, so that food seems bland and unappealing. Proper nutrition may help reverse the wasting syndrome. For example, the correct manipulation of dietary protein can reduce the degree of uremia; if the patient's appetite improves, the caloric intake increases and wasting is reversed. Total parenteral nutrition (TPN) can be used in patients with chronic renal failure, whether they are managed conservatively or on dialysis, although this represents a management aid in complex rather than routine situations. The use of TPN in the renal patient is covered in Chapter 11.

The dietary management of chronic renal disease depends on the degree of renal failure and the need for dialysis. The National Kidney Foundation divides chronic renal disease into five stages (75):

Stage 1: Kidney damage with normal or increased glomerular filtration rate (GFR) $\geq$90 mL per min 1.73 m^2
Stage 2: Kidney damage with mildly decreased GFR between 60 and 89 mL per min 1.73 m^2
Stage 3: Moderately decreased GFR (30 to 59 mL per min 1.73 m^2)
Stage 4: Severely decreased GFR (15 to 29 mL per min 1.73 m^2)
Stage 5: Renal failure (GFR $<$15 mL per min 1.73 m^2)

While nutritional modifications are important in every stage of declining renal function, clearly the most stringent attention to nutrient intake must take place in Stage 5 renal disease when every aspect of nutrient ingestion and excretion is under conscious control of both the patient and the physician.

Phases of Management

Chronic Kidney Disease in Nondiaylzed Patients

Protein Quantity. In the predialysis phases of chronic kidney disease, renal function has not progressed to the point at which dialysis is indicated, but conservative dietary therapy is critically important. Dietary protein intake is generally not restricted in people with Stage 1 renal disease. For individuals who have Stage 2 and Stage 3 renal disease, dietary protein restriction, in the range of 0.75 g protein per kg per day is generally the rule (74,75), although patients who are willing to tolerate more stringent dietary protein restriction are offered the option of restricting dietary protein intake to 0.60 g protein per kg per day (74). When renal disease progresses to Stage 4, dietary protein intake should be reduced to 0.60 g protein per kg per day for individuals who can accept this difficult limitation (75). However, if the patient cannot comply with this level of restriction, or if the severely restricted protein intake compromises dietary energy intake, the diet should be liberalized to an intake of 0.75 g protein per kg per day (75). Available evidence supports the fact that this dietary approach can maintain good nutritional status and good metabolic status, and limit symptoms of renal disease and its secondary effects (e.g., renal osteodystrophy), while possibly slowing the progression of renal failure (60–63,74,75). This level of dietary protein restriction is also recommended for persons with nephritic syndrome, but with the very important modification that an additional 1.0 g of high biologic value protein per day be consumed for each gram of urinary protein lost above 5 g per day (74).

Protein Quality. As renal disease progresses, the ability of the kidneys to excrete urea diminishes. The load of urea presented to the kidneys is usually proportional to the amount of protein in the diet; however, even patients on a zero-protein diet produce some urea as a result of the breakdown of tissue proteins. If too much protein is included in the diet, the level of blood urea nitrogen (BUN) rises and symptoms of uremia develop. However, when dietary protein intake is restricted too much as a therapeutic or preventive strategy, the supply of essential amino acids required for the synthesis of necessary proteins becomes inadequate and protein malnutrition is the consequence. Further, it is not only important for a patient to consume an adequate *amount* of protein; it is also important that the protein be of the right *type* or *quality*. Dietary amino acids are classified as either nonessential or essential. Because the body cannot synthesize essential amino acids, they must come from the diet. Nonessential amino acids can be ingested or synthesized. In chronic renal failure, endogenous synthesis of the nonessential amino acids is preferable to ingestion for two reasons: The synthesis of an amino acid uses up an amino nitrogen that would otherwise go into urea and the synthesis of an amino acid reduces the amount of amino acid that must be consumed in dietary protein. The net effect of both processes is diminished substrate for urea production. An alternative to this approach is the use of dietary α-ketoacid analogues of essential amino acids. Via transamination, these ketoacids are converted into the respective essential amino acids, so that an amino acid group is salvaged while simultaneously an essential amino acid is provided. However, there is lack of evidence that this option can retard the progression of renal failure, and diets containing ketoacid supplements are not recommended (74).

Essential amino acids, on the other hand, must largely be present in the diet (as protein) in quantities adequate to allow the required level of body protein synthesis. Additionally, in uremia, the conversion of phenylalanine to tyrosine is impaired and uremics appear unable to synthesize enough histidine to meet their needs. Thus, two amino acids that are not normally essential in healthy individuals become additional, conditionally essential amino acids in patients with chronic kidney disease. The need to supply a sufficient amount of essential amino acids in the diet can become problematic in patients with chronic kidney disease since, to reduce generation of urea, they must restrict dietary protein intake. To accomplish both goals (sufficient essential amino acids and limited urea production) while maintaining adequate synthesis of body proteins, it is essential that the proteins these individuals consume have the maximum amounts of essential amino acids per gram of protein. Proteins of *high biologic value* meet this requirement because most of the nitrogen is in the form of essential amino acids, all essential amino acids are present in

the protein, and the essential amino acids are present in concentrations proportional to the minimum daily requirements. Eggs are the food with proteins of the highest biologic value. Other foods with proteins of high biologic value include fish, poultry, lean meat, and dairy products. Proteins of low biologic value are found in some grains, nuts, seeds, and legumes.

Other Diet and Lifestyle Recommendations. With few exceptions, such as dietary protein intake discussed above and the others discussed below, overall nutrition and lifestyle guidelines for individuals with Stages 1 through 4 chronic kidney disease (76) are fully consistent with those recommended in the 2005 *Dietary Guidelines for Americans* (Chapter 2), the DASH diet plan (64–69), the American Heart Association dietary guidelines (77), and the report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) (78). These are fundamentally the same as those discussed for people with diabetes earlier in this chapter and more extensively in Chapters 2 and 3. They are aimed at reducing cardiovascular risks by maintaining a healthy body weight, enhancing physical activity, limiting alcohol intake, and stopping smoking.

In addition to the restricted protein intake above, the specific exceptions are recommendations for dietary intakes of potassium and phosphorus. Because the kidney is the predominant route for potassium excretion, it is necessary to limit potassium intake in persons with chronic renal disease as the glomerular filtration rate declines. In persons with Stage 3 chronic kidney disease, potassium intake is restricted to under 4 g of potassium daily (74,76), while individuals who have progressed to Stage 4 or 5 chronic kidney disease should not consume more than 2 to 3 g of potassium daily (74,76). Serum phosphorus control is a significant clinical issue in patients with chronic kidney disease because hyperphosphatemia can lead to the development of hyperparathyroidism as well as calcium phosphate deposits in soft tissues and arteries (74). There is lack of consensus on the optimal intake of phosphorous in Stage 3 and Stage 4 chronic renal disease and recommended intakes range from 0.8 to 1.2 g phosphorus per day (74,76).

Table 13-5 shows a summary of the major nutritional recommendations for individuals with chronic kidney disease who do not require dialysis.

Chronic Kidney Disease Requiring Dialysis

Protein Intake. When the GFR falls to approximately 5 mL per 1.73 m^2 min (advanced Stage 5 chronic kidney disease), dietary manipulation alone can no longer control the metabolic abnormalities associated with renal failure, and transplantation or dialysis is required. Even if the subject's GFR is in the upper ranges of Stage 5 chronic kidney disease, dialysis should be considered if nutritional status and body weight are difficult to maintain. The goals of diet therapy for patients on dialysis are to minimize metabolic abnormalities, correct for nutrients lost during dialysis, and provide sufficient nutritional support to prevent the protein–energy malnutrition that is commonly seen in patients undergoing maintenance dialysis (74,79,80).

In the absence of dialysis, the argument for limiting dietary protein intake is far more compelling in Stage 5 chronic renal disease. In this circumstance, a reduction in dietary protein intake not only reduces the generation of deleterious nitrogenous metabolic products but also leads to a concomitant reduction in the intake of both phosphorus and potassium, which generate additional deleterious metabolites. However, since these patients are at high risk of malnutrition and the long-term consequences of uremia, and since there is no evidence that withholding dialysis and limiting protein intake leads to a better outcome than instituting dialysis and providing a more liberal diet, most nephrologists recommend that maintenance dialysis (or renal transplantation) commence at this stage of deterioration of renal function.

When dialysis is successfully established, protein intake can be liberalized somewhat because of the nitrogen removed during dialysis. For patients undergoing maintenance hemodialysis, the recommended daily dietary protein intake is 1.2 g protein per kg body weight and for those undergoing peritoneal dialysis it is 1.2 to 1.3 g protein per kg body weight (74,75) (Table 13-5). At least half of the dietary proteins consumed should be high biologic value proteins. This level of protein intake avoids the protein–energy malnutrition

TABLE 13-5. Nutritional Requirements for Patients with Chronic Renal Failure (74)

	Chronic kidney disease prior to dialysis	Chronic renal failure requiring maintenance dialysis
Dietary nutrients		
Protein	0.6–0.75 g/kg/day (of which ≥0.35 g/kg/day is protein of high biologic value)	Hemodialysis: 1.0–1.2 g/kg/day (≥50% high biologic value) Peritoneal dialysis: 1.2–1.3 g/kg/day
Energy	>35 kcal/kg/d[a]	>35 kcal/kg/day[a]
Fat	30%–35% Energy	30%–35% Energy
P:S fat ratio	1:1	1:1
Carbohydrate	Rest of nonprotein calories	Rest of nonprotein calories
Fiber	14 g/1,000 kcal	14 g/1,000 kcal
Fluids	Up to 3 L/day[b]	Usually 750–1,500 mL/day[b]
Sodium	1–3 g/day[b]	0.75–1.0 g/day[b]
Potassium	40–70 mEq/day	40–70 mEq/day
Phosphorus	5–10 mg/kg/day	8–17 mg/kg/day
Calcium	1.4–1.6 g/day	1.4–1.6 g/day
Magnesium	200–300 mg/day	200–300 mg/day
Iron	≥10–18 mg/day[c]	≥10–18 mg/day[c]
Zinc	15 mg/day	15 mg/day
Vitamin supplements		
Thiamine	1.5 mg/day	1.5 mg/day
Riboflavin	1.8 mg/day	1.8 mg/day
Pantothenic acid	5 mg/day	5 mg/day
Niacin	20 mg/day	20 mg/day
Pyridoxine HCl	15 mg/day	5–10 mg/day
Vitamin A	0	0
Folic acid	1 mg/day	1 mg/day
Vitamin B_{12}	3 μg/day	3 μg/day
Vitamin C	60 mg/day[d]	60 mg/day[d]
Vitamin D	See text	See text
Vitamin E	8 mg/day[e]	8 mg/day[e]
Vitamin K	0	0

[a] Unless patient is overweight, obese, or is gaining unwanted weight.
[b] Can be higher in patients with greater urinary or dialysis losses.
[c] Ten milligrams for men and nonmenstruating women; 18 mg for menstruating women.
[d] Recommended amount is less than the RDA because ascorbic acid can be metabolized to oxalate and increased oxalate levels can be a problem in chronic kidney disease (74).
[e] As α-tocopherol (includes *RRR*-α-tocopherol and the 2*R*-stereoisomeric forms). Amount is less than the RDA because additional vitamin E supplementation is not clearly necessary (74).
Adapted from Kopple JD. Renal disorders and nutrition. In: Shils ME, Shike M, Ross AC, et al., eds. *Modern Nutrition in Health and Disease,* 10th ed. Baltimore: Williams & Wilkins, 2006:1475–1509.

that can occur at lower intake levels due to the reduced capacity of these patients to conserve body proteins, amino acids, and other biologically important nitrogenous compounds that are lost in the dialysate (80). In hemodialysis, losses are estimated to be as high as 1 g of free amino acids per hour and 3 g of total (free plus protein-bound) amino acids per hour. Thus, a standard 4-hour session of hemodialysis results in losses equivalent to 5 to 10 g of protein. Because a large proportion (30% to 40%) of the amino acids lost in the dialysate is essential amino acids, it is critical that at least half of the dietary protein be of high biologic value, as noted above. For similar reasons, patients undergoing long-term peritoneal dialysis may require even a greater intake of protein than patients on hemodialysis. The "pores" of the peritoneum are larger than those of dialysis tubing and so allow even larger proteins to be lost into the dialysate. On average, these patients lose 10 to 14 g of protein, peptides, and amino acids daily into the dialysate fluid.

Energy Intake. Daily maintenance energy intake in dialyzed patients is set at 35 kcal per kg body weight for those who are less than 60 years of age and 30 to 35 kcal per kg body weight. These are target values. If an individual is obese, overweight, or gaining weight at an accelerated rate, energy intake should be reduced. Likewise, individuals who are losing weight may require a higher energy intake.

An adequate intake of calories in the form of carbohydrates and fats is required to prevent the use of dietary or tissue protein as a source of energy. The catabolism of proteins results in increased urea production. The ideal calorie intake is whatever is required to achieve and maintain an ideal body weight. Patients who are below their ideal body weight need more calories. Unfortunately, the average calorie intake of dialysis patients is frequently lower than 30 kcal per kg per day and patients with chronic renal failure are often energy deficient as manifested by weight loss, diminished adipose tissue, and loss of muscle mass. Because these patients also tend to be volume expanded, their muscle mass and fat stores may be even lower than their weight might suggest.

Dietary instructions for renal patients must be complete, given by professionals, and reinforced regularly. Achieving an adequate caloric intake is a major problem in the management of patients with chronic renal failure. In some cases, compliance with other dietary restrictions must be sacrificed to attain an adequate caloric intake. The vigorous pursuit of perfect metabolic balance may result in a diet that is totally unpalatable and a patient with an inadequate calorie intake.

Because they are frequently anorectic and have difficulty in maintaining an adequate calorie intake, patients with chronic renal failure may require nutritional supplements that supply energy. Many commercial nutritional supplements are now available that are especially appropriate for patients with renal failure. In some supplements, the calories are all carbohydrate (e.g., Polycose) (Table 11-9). Other supplements are more specific to renal failure; they contain a mixture of fat and carbohydrate and are designed to be low in protein, phosphorus, sodium, and potassium for readily apparent reasons (e.g., Nepro). Table 9-4 lists the supplements specifically intended for patients with renal disease, and Table 9-5 provides the detailed nutritional content of some of them.

Water Intake. Water requirements are not usually a major problem for patients with chronic renal failure who are not receiving dialysis. Fluid intake should equal insensible loss (water lost from skin and lungs, which is usually 400 to 600 mL per day) plus urine volume. Most conservatively managed patients do well on 1.5 to 3.0 L per day (74). The goal of fluid (and salt) management in patients who are receiving dialysis is to limit the rate of weight gain between dialysis treatments to 1 lb per day. This can be achieved with a diet containing 750 to 1,000 mg of sodium plus a water intake in the range of 750 to 1,000 mL daily (Table 13-5). A daily fluid allotment of 1,000 mL includes 500 mL for insensible losses and 500 mL for a 1-lb weight gain. Fluid in food must be subtracted from the fluid allotment. Any food that is liquid at room temperature (e.g., gelatin, ice cream) is counted as a fluid. Fruits and vegetables are 85% to 90% water, cooked cereals are 70% to 85% water, and meat is 45% to 60% water. It should be readily apparent that 1,000 mL per day is a severe fluid restriction; compliance is difficult for many patients.

In patients undergoing long-term peritoneal dialysis and in those on hemodialysis who have greater urinary losses, water and sodium intakes may be increased. Thus, in the absence of anuria, urinary salt and water losses can be added to the restrictive allowances above. Stringent salt restrictions may improve metabolic control but make the diet unpalatable. Nonetheless, patients with hypertension and congestive heart failure may have to reduce their salt intake.

Sodium Intake. Recommendations for dietary sodium intake are outlined in Table 13-5, and sodium-restricted diets are readily available (81). Little sodium is excreted in the feces, and as chronic renal disease progresses, the ability of the kidneys to respond to variations in sodium intake diminishes. The normal kidney responds to a low-sodium diet by reabsorbing virtually all the filtered sodium and responds to a high-sodium diet by reabsorbing less. The failing kidney progressively filters and reabsorbs less sodium and cannot adapt to changes in sodium intake. When this happens, edema, hypertension, and congestive heart

failure may ensue. On the other hand, too little dietary sodium intake can result in dehydration, a reduced GFR, and acceleration of the deterioration in renal function. The goal is to have the daily sodium intake equal the fixed daily loss.

One approach to determining the sodium requirement is to put the patient on moderate sodium restriction (3 to 6 g of salt per day; 1 g of salt equals 410 mg of sodium) and measure the 24-hour urinary sodium. The dietary intake can be adjusted on the basis of the urinary sodium. The patient's sodium status is also roughly reflected by changes in weight. Weight gain reflects sodium intake in excess of sodium excretion, and weight loss reflects net sodium loss. Most patients with renal disease require 2 to 8 g of salt (1 to 3 g or 40 to 130 mEq of sodium) per day, although variation among individual patients is significant. As renal function deteriorates, the requirement may diminish. Patients with renal disease are often placed on diets in which the sodium restrictions are excessively stringent. A rising BUN may reflect dehydration instead of excessive protein intake. Further, not all forms of chronic renal failure affect sodium homeostasis in the same way. Pyelonephritis and polycystic kidney disease tend to be salt-wasting conditions requiring increased dietary sodium and glomerulonephritis is associated with hypertension that might require a lower salt intake.

In any case, dietary sodium requirements change with nonurinary salt losses, primarily those in sweat. Sodium restrictions must be liberalized in warm climates for patients whose homes are not air conditioned. Some patients require sodium bicarbonate for the treatment of acidosis. In such cases, dietary sodium must be reduced to compensate for the sodium in the sodium bicarbonate. Two grams of sodium bicarbonate contain the same amount of sodium as 1.5 g of salt.

Potassium Intake. Foods high in protein are usually also high in potassium, and if they are given to patients with a low GFR, hyperkalemia may develop (74). Thus, diets for individuals with chronic kidney disease are restricted in potassium as discussed above and shown in Table 13-5. Specific diets for potassium restriction are available (81).

The standard American diet contains 50 to 100 mEq of potassium per day. Patients with a GFR of less than 15 mL per min usually require potassium restriction to 40 to 70 mEq per day. Hyperkalemia is less likely in those with a urine output of 1,000 mL or more per day. A 40-g protein diet (0.6 g protein per kg per day for a 70-kg person) provides 50 to 60 mEq of potassium per day. Excessive dietary potassium can lead to hyperkalemia and the danger of cardiac arrhythmias. Patients with renal failure should not use salt substitutes that contain large amounts of potassium (Table 7-16). Similarly, they should not be given potassium supplements when treated with thiazides or furosemide. Hyperkalemia is exacerbated by acidosis and catabolic stress with muscle protein breakdown. These conditions should be prevented by proper medical management and corrected expeditiously when they occur. In some patients, potassium restriction may not be necessary because, despite nearly normal serum potassium levels, the total body potassium is frequently low in chronic renal failure as most potassium is located intracellularly. Thus, dietary potassium should not be appreciably restricted unless hyperkalemia is a problem and the urine output is below about 1,000 mL per day.

Phosphorus, Calcium, and Vitamin D Intakes. Renal osteodystrophy, a major problem in chronic renal disease, results from the abnormalities in calcium, phosphorus, parathyroid hormone (PTH), and vitamin D homeostasis brought on by renal failure. As the kidney fails, its ability to clear phosphate diminishes, and the serum phosphate level rises. Hyperphosphatemia is accompanied by hypocalcemia, which causes the release of PTH. Elevated levels of PTH result in increased renal phosphate clearance and bone resorption. The goals of therapy in renal osteodystrophy are to supress secondary hyperparathyroidism and normalize osteoid mineralization by reducing phosphate absorption by decreasing dietary phosphate intake and using phosphate-binding gels, and by supplementing the diet with calcium and vitamin D. Table 13-3 shows the recommended phosphorus intakes for individuals with chronic kidney disease requiring dialysis.

PTH levels rise with the loss of as little as 25% of renal function. Thus, one of the earliest interventions required in renal failure is the reduction of phosphate absorption.

Phosphate absorption is reduced by lowering the dietary intake of phosphate using specialized diets for that purpose (81) and by administering phosphate-binding gels. The usual American diet contains 1.0 to 1.8 g of phosphorus per day. The elimination of milk, milk products, cheese, colas, and instant powdered beverages combined with protein restriction (40 g per day) will reduce intake to 600 mg per day (81). Nonetheless, when the GFR falls below about 25 mL per min per day, this level of dietary phosphorus restriction is still not adequate to prevent hyperphosphatemia. The diet of patients on dialysis is higher in protein than that of conservatively managed patients, so that their dietary intake of phosphorus is also usually higher. The need for phosphate binders is just as great for dialysis patients as for nondialysis patients, and several commercial phosphate binders are available. The goal in using phosphate binders is to keep the serum phosphorus level in the range of 4 to 5 mg per dL. Most clinicians use phosphate-binding gels early in the course of renal disease before imposing any dietary restrictions.

Calcium Intake. Although chronic renal failure causes a positive phosphorus balance, it results in a negative calcium balance. Several factors contribute to the negative calcium balance—hyperparathyroidism, calcium malabsorption secondary to vitamin D deficiency, and a diet low in calcium because phosphorus-rich dairy products are restricted. Oral calcium supplements are recommended for the reasons that have been outlined; approximately 1.5 g of elemental calcium per day should be given to patients with a GFR below 25 mL per min. Because a diet with 40 g of protein provides about 300 to 400 mg of calcium daily, these subjects require approximately 1.0 to 1.4 g of calcium supplements daily (74,82).

Before calcium supplementation is started, it is important that the serum phosphorus be under control. If calcium supplements are given in the face of hyperphosphatemia, calcium phosphate is deposited in the soft tissues. For patients with Stages 3 and 4 chronic kidney disease, the goal is to maintain serum calcium within the normal range (corrected for serum albumin level). For patients with Stage 5 chronic kidney disease, the goal is to keep the corrected serum calcium level near the lower end of the normal range for the laboratory used (74).

Vitamin D Intake. The reduction in functioning renal mass in chronic renal failure is accompanied by a decreased conversion of 25-hydroxycholecalciferol (25-OHD) to 1,25-dihydroxycholecalciferol (1,25-OHD), the active metabolite of vitamin D. The decreased levels of 1,25-dihydoxycholecalciferol result in a decreased absorption of dietary calcium.

Vitamin D status can be monitored by measuring the plasma levels of 25-OHD and intact parathyroid hormone (PTH). Current guidelines for individuals with Stage 3 and Stage 4 chronic kidney disease recommend vitamin D supplementation when serum 25-OHD levels are less than 30 ng per mL and plasma intact PTH levels are greater than the target range for the stage of chronic kidney disease, but only in patients who also have a corrected total calcium level of less than 9.5 mg per dL and serum phosphorus level of less than 4.6 mg per dL (82). Patients with Stage 5 chronic kidney disease who are receiving dialysis and who have serum levels of intact PTH greater than 300 pg per mL should receive a vitamin D supplement to reduce serum PTH to within a target range of 150 to 300 pg per mL (82). In this case, intermittent, intravenous administration of calcitriol (1,25-OHD) is more effective than oral administration. It is possible to induce hypercalcemia by giving calcium and vitamin D supplements. Therefore, the serum calcium level should be monitored carefully and regularly. Vitamin D increases the absorption of both phosphate and calcium; thus, serum phosphorus levels also must be monitored during vitamin D therapy.

Iron Intake. Twenty-five percent of nontransfused patients on long-term hemodialysis are deficient in iron. Iron intake (especially heme iron intake) is frequently low. A major cause of iron deficiency in these patients is the loss of 5 to 20 mL of blood left in the dialyzer after each treatment, which can amount to a loss of several hundred milligrams to a gram of iron per year. In addition, the heparin used as an anticoagulant may increase gastrointestinal and uterine blood loss. For these reasons, many dialysis patients receive supplementation with ferrous sulfate (Table 13-5).

Requirements for Other Vitamins. Patients with chronic renal failure are frequently vitamin-deficient because of their poor dietary intake. However, the alterations in vitamin requirements caused by chronic renal failure are poorly defined, and the systematic data are insufficient to set new dietary reference intakes (DRIs) for vitamins. Supplementation with vitamin A should be avoided because chronic renal disease is associated with elevated levels of vitamin A. Vitamin K supplementation is not routinely required but may be necessary in patients who are receiving TPN and antibiotics. The loss of water-soluble vitamins into the dialysate in hemodialysis creates an additional demand. Nonetheless, although no consensus recommendations regarding the increased needs are available, many experts advise prudent supplementation of water-soluble vitamins (Table 13-5). One standard multivitamin plus 1 mg of folic acid per day should meet the requirements. The recommended vitamin supplementation is the same for both conservatively managed patients and those on dialysis.

Dietary Management of Concomitant Hyperlipoproteinemia and Hypertension. In chronic kidney disease, the catabolism of triglyceride-rich lipoproteins is diminished, leading to an increase in the circulating levels of the atherogenic apolipoprotein-B containing very-low-density lipoproteins and intermediate-density lipoproteins, as well as a decrease in circulating high-density lipoproteins (see later in this chapter). Clinical practice recommendations have been published for the management of hyperlipidemias in renal disease (83). The expert committee issuing these recommendations adopted the recommendations made by the National Cholesterol Education Task Force, Adult Treatment Panel III (ATP III) (84) as will be discussed later in this chapter. Hypertension is a common comorbidity in chronic kidney disease. The National Kidney Foundation has provided practice guidelines on nutrition and antihypertensive medication use in persons with chronic kidney disease (76). These are fundamentally similar to those issued by other expert committees on hypertension management (64,66,68,70–73,77,78,85–89). The nutrition guidelines are those discussed previously, namely, lifestyle change that includes maintaining a healthy body weight and increasing physical activity; a reduction of alcohol intake, a reduction in dietary sodium intake to less than 2.4 g per day (or lower, if necessary according to the stage of kidney disease); a focus on the DASH dietary intake pattern with an increased intake of fruits, vegetables, low-fat dairy products, whole grains, poultry, fish and nuts; but modification of the high protein, potassium, and phosphorus intakes of the DASH diet pattern to accommodate the needs of patients with chronic kidney disease (76).

Practical Management Issues

1. In chronic renal failure, caloric intake is more likely to be inadequate than excessive; thus, caloric restriction is usually not appropriate. On the other hand, the proper dietary management of chronic renal failure is quite compatible with a diet low in sugars and alcohol and high in polyunsaturated fats.
2. A brief physical examination in addition to standard blood chemistry studies should make it possible to determine patient compliance and any needed changes in the diet. Various laboratory tests and other criteria assist in monitoring the adequacy of specific nutrients.
3. In patients who undergo dialysis three times a week, a reasonable goal is a BUN of 60 to 80 mg per dL after the longest interval between dialysis sessions (3 days). A higher BUN suggests excessive protein intake if weight is maintained or gained. It suggests protein catabolism if associated with recent weight loss.
4. Inability to achieve or maintain ideal body weight is a sign of poor caloric intake. A rising BUN may reflect protein catabolism in a patient with inadequate caloric intake.
5. Excessive weight gain between dialysis sessions with a normal serum sodium level reflects excess salt and water ingestion. Excessive weight gain with a low serum sodium level suggests excessive ingestion of fluids but not salt. Edema, congestive heart failure, and increasing blood pressure may be signs of excess sodium intake. Weight loss, diminished urine output, and a rising BUN all point to inadequate salt ingestion.
6. An elevated potassium level reflects increased potassium ingestion or acidosis.
7. An elevated phosphorus level may reflect either failure to take phosphate binders or excessive dietary phosphorus intake, usually in the form of dairy products.

Acute Renal Failure

There is no uniformly agreed upon practice plan for nutrition therapy of patients with acute renal failure (74). The goals of diet in acute renal failure are to provide adequate calories to maintain body weight and minimize catabolism of tissue proteins. The major difficulty in managing patients without dialysis is providing adequate calories without fluid overload. Whenever possible, the patient should receive nutrition via the enteral route, but extensive recommendations for total parenteral nutrition in patients with acute renal failure are available elsewhere (74).

The following are suggested guidelines for approaching the nutritional needs of patients with acute renal failure (74):

1. Fluids should be given in an amount totaling the sum of all measured sources of losses plus an additional 400 mL per day to account for contributions from insensible water loss and the water produced through metabolism. The goal is a normal serum sodium level and no weight gain.
2. Energy expenditure is often elevated in patients with acute renal failure. The proper amount of energy intake is that amount necessary to maintain body weight. Desirable energy intake is 30 to 40 kcal per kg per day, of which 10% to 30% is given as liquid emulsions. At least 150 to 200 g of carbohydrate should be supplied to minimize protein breakdown.
3. The protein requirement in acute renal failure is a highly debated topic (74). If patients are otherwise adequately nourished and expected to regain renal function within a few weeks, 0.3 to 0.5 g of high-biologic-value protein or essential amino acids per kilogram per day is used. For patients who are highly catabolic, who have high levels of urinary nitrogen, or who are not expected to recover for more than 2 weeks, additional protein intake is advisable, up to 1.2 g per kg per day.
4. Salt intake should equal salt losses (urine, stool, gastric aspirate).
5. Because acute renal failure may be accompanied by substantial tissue destruction and acidosis, the possibility of rapidly developing hyperkalemia is greater than in chronic renal failure. Serum potassium should be monitored carefully and dietary potassium minimized.
6. In acute renal failure, dialysis makes it possible to control hyperkalemia, fluid overload, acidosis, and uremia. After the initiation of dialysis, less stringent restriction of protein, fluids, and potassium may be possible.

HYPERLIPOPROTEINEMIA

Introduction

According to recent estimates (90), nearly 80 million Americans have one or more forms of cardiovascular disease. Seventy-two million are hypertensive and nearly 16 million have coronary heart disease, including nearly 8 million with myocardial infarction, nearly 9 million with angina, and almost 6 million with stroke (90). Even though deaths from cardiovascular diseases have declined substantially (91), they still claimed more than 870,000 lives in 2004, accounting for 36.3% of deaths. Coronary heart disease is the single leading cause of death in the United States today, taking nearly a half-million lives yearly. This year, more than one million Americans will have a heart attack and one-third of these will die.

More than 200 risk factors for cardiovascular disease have been identified, but the major factors are far fewer in number. Some, like male sex, increasing age, and genotype, cannot be modified. Others, such as increased plasma LDL cholesterol, increased circulating triglycerides, low plasma high density lipoprotein (HDL) cholesterol, cigarette smoking, hypertension, obesity, and reduced physical activity, are theoretically reversible. Reductions in LDL cholesterol, hypertension, and cigarette smoking have been conclusively shown to lower risk. Increases in HDL cholesterol and physical activity are highly likely to lower risk. Because many of these risks are related to diet and lifestyle, a highly significant reduction in the risks for cardiovascular disease can be achieved through the

nutritional practices outlined in this volume (see Chapter 2) and presented in detail elsewhere (64,66,68,70–73,77,78,85–89).

Definitions

Lipoproteins

By definition, lipids are insoluble in water. In order to be transported in the aqueous solution, plasma, triglycerides and cholesterol are complexed with apoproteins and phospholipids to form solubilized particles, now called *lipoproteins*. The major lipoprotein classes are outlined in Table 13-6 and the metabolism of the lipoprotein classes is extensively reviewed elsewhere (92–98).

Chylomicrons

The major function of chylomicrons is to carry exogenous dietary fat from the intestine to peripheral tissues (92,94). Chylomicrons are formed in the endoplasmic reticulum of enterocytes. During transit through the Golgi apparatus, they acquire apoproteins (apo) A-I, A-II, A-IV, and B-48. After passing through the lacteals of the intestinal villi, the chylomicrons are transported through the thoracic duct into the bloodstream, where they acquire the additional apoproteins apo C-II and apo E via transfer from HDLs. Thereafter, the chylomicrons interact with the enzyme lipoprotein lipase, located on the endothelial surface of blood capillaries in many organs. Apo C-II is a required cofactor in the activation of lipoprotein lipase. Lipoprotein lipase hydrolyzes the chylomicron triglycerides into unesterified fatty acids and glycerol. At the same time, the apo A peptides are transferred to HDLs. The remaining, much smaller chylomicron particle, still containing apo B-48 and now called a *chylomicron remnant*, is taken up by a specific hepatic receptor that recognizes the apo E peptide on its surface.

Very Low Density Lipoproteins

Very low density lipoproteins (92), or VLDL, are synthesized by the liver. Their principal role is to transport endogenously synthesized triglycerides of hepatic origin to peripheral tissues. VLDL resemble chylomicrons in that they are rich in triglycerides (albeit somewhat smaller in size), receive small amounts of apo E and apo C-II from HDL, and lose their triglycerides via lipoprotein lipase-catalyzed hydrolysis. VLDL are unique in that they acquire apo B-100 during intrahepatic assembly. Although they are primarily triglyceride containing particles, VLDL also contain a modest amount of circulating cholesterol (VLDL cholesterol), and when VLDL concentrations are abnormally high, they may contribute significantly to the total circulating cholesterol level. VLDL triglyceride hydrolysis proceeds more slowly than that of chylomicrons and results in two lesser

TABLE 13-6. The Principal Plasma Lipoprotein Classes

		Composition (%)			
Class	**Size (Å)**	**Protein**	**Cholesterol**	**Triglycerides**	**Phospholipids**
Chylomicrons	750–10,000	2	5	90	3
VLDLs	300–800	10	12	60	18
IDLs	250–400	10	30	40	20
LDLs	200–220	25	50	10	15
HDLs	75–100	50	20	5	25

VLDL, very low density lipoprotein; IDL, intermediate density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein.
From Kuo PT. Prevention and treatment of hyperlipidemia. In: Halpern SL, ed. *Quick Reference to Clinical Nutrition.* Philadelphia: JB Lippincott Co, 1979:137.

VLDL particles, the larger of which is called a *VLDL remnant* (removed by the hepatic LDL receptor) and the smaller of which is called an *intermediate-density lipoprotein* (IDL). Because VLDL remnants are VLDL particles that have had much of their triglyceride removed, they are relatively enriched in cholesterol and are atherogenic. About half of IDL are also taken up by hepatic receptors, but the remaining half are further converted to LDL, with apo B-100 as the predominant remaining peptide. In practice, IDL are included in the LDL fraction because they are small particles that are depleted in triglyceride, contain apo B-100, and are highly enriched in cholesterol, in other words, much more like LDL than VLDL.

Low Density Lipoproteins

Low density lipoproteins (92,93,96), or LDLs, are the principal carrier of plasma cholesterol, accounting for approximately 60% to 70% of the total serum cholesterol level in normal persons (LDL cholesterol). Half of the LDL particle is cholesterol; only 10% is triglyceride, and most of its protein is apo B-100 (Table 13-6). In normal individuals, more than 90% of apo B is found in LDL and the rest is associated with VLDL. LDL are the vehicles whereby cholesterol synthesized in the liver is delivered to peripheral tissues and to hepatocytes via the hepatic LDL receptor that clears about 60% to 80% of circulating LDL. The remaining LDLs are cleared by other specific receptors and oxidized LDL can be taken up by scavenger receptors on macrophages and vascular smooth muscle cells. When these macrophages become lipid laden, they are called foam cells, and are a major component in the development of atherosclerosis. LDL are metabolized slowly over several days and are the major atherogenic lipoprotein. Additionally, when the little lipid in LDL is removed, they become a lipoprotein particle known as small dense LDL. This dense cholesterol-containing particle has a lower affinity for the LDL receptor and is more readily oxidized and removed by macrophages. Thus, small dense LDLs are believed to be even more atherogenic than native LDL.

High Density Lipoproteins

High density lipoproteins (92,97), or HDLs, are secreted in an immature, disc-like, nascent form largely by the liver but also by the intestine, containing apo A-I as their principal apoprotein. These disc-like particles can absorb free cholesterol from cells through the action of ATP binding cassette transporter 1 and the apopeptides A-I and A-IV. Thereafter, through the action of a circulating cholesteryl ester transfer complex containing lecithin-cholesterol acyltransferase (LCAT) (98), an enzyme activated by apo A-I, HDL cholesterol is esterified and carried back to the liver where it is removed by the LDL receptor or the hepatic scavenger receptor. Additionally, through the action of cholesteryl ester transfer protein (CETP), some cholesterol ester is transferred from HDL to apo B-100 containing triglyceride-rich lipoproteins. The net effect is that cholesterol in peripheral tissues is transported back to the liver (so-called reverse cholesterol transport) and eventually removed by the liver. The liver, in turn, ultimately disposes of the cholesterol by excreting it in bile. The cholesterol content of HDL (HDL cholesterol) is normally about 20% to 30% of the total serum cholesterol level.

Non-HDL Cholesterol

This term applies to a calculated value that is the difference between total plasma cholesterol and HDL cholesterol. In other words, it represents the cholesterol content of LDL plus VLDL and includes all the lipoproteins that contain apo B, the atherogenic lipoproteins. Because it is easy to compute, this value has become a practical indicator of total atherogenic lipoproteins and is used as a surrogate for measuring apo B directly, a practical benefit because apo B measurements are not routinely available in clinical laboratories. Another advantage of calculating non-HDL cholesterol is that the subject does not have to be fasting for the measurement, as neither total plasma cholesterol nor HDL cholesterol changes appreciably after a meal.

Lipoprotein-Associated Cardiovascular Risks

Total and LDL Cholesterol

The U.S. population distributions of serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride are given in Table 13-7 (84). An elevated serum LDL cholesterol

TABLE 13-7. Serum Total Cholesterol Levels (mg/dL) for Persons 20 Years of Age or Older in the United States

	Percentile				
	5th	25th	50th	75th	95th
Men					
≥20	139	173	200	228	273
20–34	131	161	183	209	253
35–44	143	180	205	232	267
45–54	154	191	214	242	283
55–64	154	189	214	243	282
65–74	149	186	209	237	284
75+	145	176	203	230	273
Women					
≥20	143	175	201	233	284
20–34	132	158	181	205	248
35–44	144	171	192	215	257
45–54	157	187	212	243	298
55–64	167	204	229	261	307
65–74	170	204	232	258	308
75+	161	198	228	258	305
Hispanic					
Men	137	171	197	224	272
Women	139	167	193	223	274
Non-Hispanic Black					
Men	136	169	195	222	275
Women	136	170	196	226	284
Non-Hispanic White					
Men	141	174	201	229	272
Women	144	177	203	235	284
Serum LDL cholesterol levels (mg/dL) for persons 20 years of age or older in the United States					
Men					
≥20	76	105	128	153	194
20–34	72	97	119	139	170
35–44	82	111	132	156	205
45–54	76	117	140	164	195
55–64	82	115	135	162	200
65–74	83	113	133	158	196
75+	86	109	128	151	194
Women					
≥20	69	98	121	147	
20–34	63	90	109	130	170
35–44	70	96	115	137	171
45–54	70	106	129	153	190
55–64	80	121	143	167	209
65–74	76	119	144	166	203
75+	83	119	144	167	209
Hispanic					
Men	71	98	121	144	188
Women	67	93	115	137	178
Non-Hispanic Black					
Men	71	100	124	149	200
Women	63	97	119	145	193
Non-Hispanic White					
Men	79	106	129	154	194
Women	70	98	122	149	189
Serum HDL cholesterol levels (mg/dL) for persons 20 years of age or older in the United States					
Men					
≥20	28	37	44	53	72
20–34	28	38	45	53	69

(*continued*)

TABLE 13-7. Serum Total Cholesterol Levels (mg/dL) for Persons 20 Years of Age or Older in the United States (*Continued*)

	Percentile				
	5th	25th	50th	75th	95th
Serum HDL cholesterol levels (mg/dL) for persons 20 years of age or older in the United States					
35–44	28	36	43	52	73
45–54	26	35	42	52	75
55–64	28	36	42	51	71
65–74	28	36	43	54	73
75+	28	37	44	54	75
Women					
≥20	34	44	53	64	83
20–34	34	45	53	64	83
35–44	34	44	53	64	79
45–54	36	45	55	65	84
55–64	33	44	53	65	89
65–74	33	45	54	65	84
75+	32	44	55	65	86
Hispanic					
Men	28	37	44	52	67
Women	33	42	51	60	77
Non-Hispanic Black					
Men	32	41	50	60	85
Women	35	46	55	66	86
Non-Hispanic White					
Men	27	36	43	52	71
Women	34	45	54	64	84
Serum triglyceride levels (mg/dL) for persons 20 years of age or older in the United States					
Men					
≥20	53	83	118	173	318
20–34	46	70	94	139	256
35–44	53	82	126	180	307
45–54	62	100	135	201	366
55–64	64	101	144	228	396
65–74	64	99	137	190	319
75+	64	96	125	175	304
Women					
≥20	48	72	102	152	273
20–34	43	61	84	117	226
35–44	46	67	93	132	288
45–54	49	76	114	163	277
55–64	62	96	135	203	396
65–74	70	99		182	283
75+	64	94	130	178	274
Hispanic					
Men	53	83	120	184	361
Women	55	85	118	170	293
Non-Hispanic Black					
Men	45	64	89	135	245
Women	41	58	79	113	207
Non-Hispanic White					
Men	55	85	123	181	319
Women	49	75	104	156	274

From National Cholesterol Education Program. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final Report. *Circulation.* 2002;106:3143–3421. U.S. adult population data collected during the Third National Health and Nutrition Survey (NHANES III), 1988–1994.

TABLE 13-8. ATP III Classification Total and LDL Cholesterol (84) Modified to Account for the Results of More Recent Clinical Trials (92)

Classification	Total cholesterol (mg/dL)	LDL cholesterol (mg/dL)
Optimal		<100 < 70 (optional)
Near optimal/ above optimal		100–129
Desirable	<200	
Borderline high	200–239	130–159[a] < 100 (optional)
High	≥240	160–189[a]
Very High		≥ 190[a]

LDL, low density lipoprotein.
[a] More properly called "borderline high-risk," "high risk," and "very high risk."
From National Cholesterol Education Program (84) as modified by Havel and Kane (92).

is the most significant lipoprotein risk factor associated with the development of cardiovascular disease. The relationship between LDL cholesterol and cardiovascular risk, a relationship verified in numerous population studies and clinical trials, is a log-linear one, even at the lowest serum LDL cholesterol levels tested, with the relative risk = 1.0 level set at 40 mg per dL (99). From observational studies, people with LDL cholesterol levels less than 100 mg per dL have very low risks of cardiovascular disease, thus these lower levels have been traditionally labeled as "optimal" (84). This position was supported by numerous early clinical trials that that lowered LDL cholesterol using lifestyle modification and drug therapy, but the most recent aggressive drug trials have convincingly demonstrated the additional direct beneficial effect of reducing serum cholesterol to levels even lower than 100 mg per dL (84,99–108).

Table 13-8 shows the current classification of serum total and LDL cholesterol levels based on the ATP III recommendations (84) as recently modified by the availability of new data since the original ATP III recommendations were issued (99). The equivalent non-HDL cholesterol recommendations are 30 mg per dL higher than the values shown for LDL cholesterol, because this is the approximate contribution of the cholesterol content of VLDL when triglyceride levels are normal. Because the risk for coronary artery disease decreases with serum cholesterol over the entire range of cholesterol levels found in the American population, it is difficult to define a "normal" cholesterol level, and the lowest cholesterol levels are optimal ones. Based on the data shown in Table 13-7, approximately half the U.S. population has a cholesterol level above the desirable range and about an equal number have LDL cholesterol levels that categorize them as being at borderline-high or high risk of coronary heart disease.

Triglycerides

Over the past decade or so, it has become increasingly clear that circulating triglyceride levels are also an independent risk factor for coronary heart disease (109–112) and it has recently been confirmed that elevated nonfasting triglyceride levels are independently associated with an increased risk of cardiovascular events (110–112). Table 13-9 shows the ATP III classification of triglycerides for risk assessment and management. As discussed above, when triglyceride levels rise, VLDL remnants containing a significant amount of cholesterol contribute to the atherogenicity of plasma lipoproteins as estimated using the calculated non-HDL cholesterol. The most prevailing view is that this cholesterol is the mechanism by which triglyceride-rich particles contribute to coronary heart disease risk. Thus, in the circumstances of hypertriglyceridemia, non-HDL cholesterol is a better indicator of circulating atherogenic lipoproteins than is LDL cholesterol.

TABLE 13-9. Clinical Classification of Serum Triglyceride Levels

Triglyceride category	ATP III levels (mg/dL)
Normal	<150
Borderline-high	150–199
High	200–499
Very high	≥500

Modified from National Cholesterol Education Program. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final Report. *Circulation.* 2002;106:3143–3421.

HDL Cholesterol

There is extensive epidemiologic evidence linking low HDL levels to coronary heart disease (84,97,113), and population studies show that coronary heart disease risk rises as HDL cholesterol levels fall. Based on population data, ATP III has defined a low serum HDL level as a value below 40 mg per dL (84,113). The 5th percentile values in the U.S. population are closer to 30 mg per dL (Table 13-7), but 40 mg per dL (approximately the 25th percentile) was chosen as a more desirable coronary health-based limit. However, as with LDL cholesterol, there is a continuous inverse relationship between HDL cholesterol and cardiovascular risk. Therefore, it is somewhat arbitrary to refer to a "low" or "normal" HDL, when one might more appropriately classify an HDL level as "better" or "worse" (113). An average of 45 to 55 mg of cholesterol per deciliter of plasma is carried by HDL and, since cardiovascular risk declines as HDL cholesterol increases, HDL cholesterol is commonly called "good cholesterol." Nevertheless, although it is now abundantly clear from many well-controlled, randomized studies that lowering LDL cholesterol decreases cardiovascular disease risk, we do not yet have conclusive evidence that increasing HDL, *per se*, will likewise diminish the risk of coronary heart disease. For this reason, there is no specific HDL cholesterol-raising goal that is set for clinical management, and LDL cholesterol reduction remains the principal initial goal.

The Hyperlipoproteinemias

The term *hyperlipoproteinemia* describes a group of disorders in which serum lipoproteins are elevated on the basis of genetic abnormalities in lipoprotein metabolism (92–98,101,103,114–119). Because the concentrations of plasma lipids are continuous variables, any definition of hyperlipoproteinemia is somewhat arbitrary. Traditionally, these disorders were classified into six clinically useful phenotypes according to physical and biochemical presentation and the distribution of lipoprotein classes that were elevated (Table 13-10). Following identification of the genetic defects that led to the clinical phenotypes, this classification has fallen somewhat out of favor. However, because of its clinical practicality, the traditional method of classification remains in general use (92,101) because the specific molecular bases for a large fraction of the familial hyperlipoproteinemias, particularly the primary triglyceridemias (116), remain unknown and the identified mendelian disorders account for only a very small fraction of the variance in atherosclerosis disease susceptibility (118).

Each type of hyperlipoproteinemia is not a single disease, but rather a group of "genotypic" disorders marked by similar "phenotypic" abnormalities in circulating lipoproteins. Each type includes identified primary genetic defects and various secondary disorders. When the latter occur because of a specific underlying disease state, such as uncontrolled diabetes, treatment of the underlying disorder frequently corrects the lipid abnormality. Similarly, when the primary disorder is aggravated by obesity, alcohol consumption, or estrogen or glucocorticoid treatment, elimination of the aggravating factor facilitates diet therapy. Because obesity and excessive consumption of cholesterol, total fat, and saturated

TABLE 13-10. Patterns of Lipid Abnormalities in the Traditional Approach to Classifying the Genetic Hyperlipoproteinemias

Type	Cholesterol	Triglycerides	Atherogenicity
I Chylomicronemia	Normal or slightly elevated	Very high	Uncertain
IIa Hypercholesterolemia	Elevated LDL cholesterol	Normal	+++
IIb Familial combined hyperlipemia	Elevated LDL cholesterol	Elevated	+++
III[a] Dsybetalipoprotinemia	Elevated	Elevated	+++
IV Hypertriglyceridemia	Normal or slightly elevated	Elevated	++
V Mixed hypertriglyceridemia	Moderately elevated	Markedly elevated	+

[a]Increased VLDL remnants or intermediate density lipoproteins. A definitive diagnosis of type III requires lipoprotein ultracentrifugation and characterization of apo E isoforms.

fat increase plasma lipoprotein concentrations in many people, diet is an important component of the management of hyperlipidemia.

Type I Hyperlipoproteinemia

Type I hyperlipoproteinemia (94) is characterized by fasting chylomicronemia. Plasma cholesterol is usually normal and plasma triglycerides are markedly elevated, generally to values well above 1,000 mg per dL. Because chylomicrons do contain a small amount of cholesterol, when the chylomicron concentration is extremely high, a slight secondary elevation of plasma cholesterol may be found as well. The classic form of this disease is an autosomal recessive disorder caused by more than 60 identified mutations in the gene for the enzyme lipoprotein lipase (94,101,114–116,119). It is usually identified in childhood by symptoms of eruptive xanthomata and pancreatitis. Chylomicronemia is less frequently caused by autosomal recessive defects in the gene for the apo C-II peptide activator of lipoprotein lipase and 10 defects in the apo CII gene have been identified (94). Familial hepatic lipase deficiency (94) is a rare autosomal recessive disorder where chylomicrons may accumulate in plasma, although these subjects have additional dyslipidemia with accumulation of additional apo B-containing lipoproteins representing incompletely metabolized VLDL (94).

Type IIa Hyperlipoproteinemia

Type IIa hyperlipoproteinemia (93,96), or familial hypercholesterolemia, is an autosomal dominant condition marked by high LDL levels and normal VLDL levels. Thus, plasma cholesterol is elevated but triglycerides are normal. Familial hypercholesterolemia results from a variety of genetic defects in the LDL cell surface receptor that controls the plasma removal of LDL (117). More than 400 different LDL receptor gene abnormalities have been found (96) in about half to three-quarters of the subjects with the phenotype of familial hypercholesterolemia (103,117) and a small number of additional patients have this phenotype on the basis of a defective apo B or other very rare abnormalities (103,117). The carrier frequency for this group of LDL receptor gene defects taken as a whole is approximately 1 in 500. Nevertheless, in about 20% to 30% of patients with a clinical diagnosis compatable with these monogenic hypercholesterolemias, no gene defect has been found (103).

Type IIb Hyperlipoproteinemia

Type IIb hyperlipoproteinemia (93) is the most common pattern found in families with premature coronary heart disease, is an autosomal dominant condition with variable

penetrance, with a population prevalence of 1% to 5.0% (93,116). It is characterized by increases in both circulating VLDL and LDL; thus, plasma cholesterol and triglycerides are both elevated. Additionally, HDL levels tend to be reduced. No single gene defect has yet been found that results in this phenotype, called *familial combined hyperlipidemia*, and it is not clear whether or not this is a monogenic or polygenic disorder, although various mutations that might contribute the phenotype have been identified (93). The type IIb phenotype is aggravated by obesity or glucocorticoid treatment and also can be seen as a secondary consequence of the nephrotic syndrome.

Type III Hyperlipoproteinemia

Type III hyperlipoproteinemia (95) is characterized by an accumulation of IDL, resulting in a combined cholesterolemia and triglyceridemia, usually to about the same degree. This condition is also called *remnant hyperlipoproteinemia, dysbetalipoproteinemia,* or *broad-beta disease* because the accumulated IDLs are remnants of incompletely metabolized triglyceride-containing lipoproteins with a relatively high cholesterol content that migrate beyond the usual "beta" or LDL cholesterol band during electrophoresis.

Type III hyperlipoproteinemia is relatively uncommon, with a prevalence between 1 in 10,000 and 1 in 20,000 (116). Clinically, it is characterized by unusual xanthomata, called *planar xanthomata,* in the creases of the palms of the hand and by tuberous xanthomata over the elbows and knees. Diagnosis of this disorder requires identification of IDL by ultracentrifugation and confirmation of the homozygosity for the mutant apolipoprotein E_2 genotype, because more than 90% of people with type III hyperlipoproteinemia are homozygous for this apo E isoform that cannot bind effectively with the hepatic receptor responsible for removing apo E-containing lipoprotein remnant particles from plasma. The pathogenesis of dyslipidemia in type III hyperlipoproteinemia, however, is not completely understood since most people who are homozygous for apo E_2 are not hyperlipidemic. Thus, the development of clinical hyperlipidemia must be the result of interaction with other genes or environmental factors. Some of these are known and include obesity, diabetes, and hypothyroidism.

Type IV Hyperlipoproteinemia

Type IV hyperlipoproteinemia is more commonly called *familial hypertriglyceridemia*. It is a relatively common problem, with a prevalence of about 5% to 10% (109), and is characterized principally by an isolated increase in plasma triglycerides secondary to elevated VLDL, but HDL levels may be low. Neither the principal genetic defect(s) nor the pathogenic mechanisms of type IV hyperlipoproteinemia have been fully elucidated. It is not clear whether this is a monogenic or polygenic disorder (103). Hepatic VLDL overproduction appears to be the primary pathophysiologic mechanism, although some evidence for diminished removal has also been found. Elevated VLDL levels are seen commonly secondary to diabetes, uremia, nephrotic syndrome, alcohol ingestion, and glucocorticoid or estrogen treatment. Familial hypertriglyceridemia is associated with obesity, and obesity may aggravate VLDL elevations in subjects with primary hyperlipidemia. Nonetheless, obesity usually does not cause significant hypertriglyceridemia in persons with normal lipoprotein metabolism.

Type V Hyperlipoproteinemia

Type V hyperlipoproteinemia is a rare pattern marked by elevations in both chylomicrons and VLDL. Thus, triglycerides are significantly elevated, and the phenotype is often called *mixed hypertriglyceridemia* because the triglycerides are contained in both VLDL and chylomicrons. Mild elevations in cholesterol may be secondary to the cholesterol content of VLDLs and chylomicrons. The underlying mechanisms and genetics of this phenotype are unknown, but it does not generally appear until later in life. Most patients have diabetes, renal failure, or other disorders, abuse alcohol, or are on various medication regimens. The common feature in this disorder appears to be an inherent or acquired defect in the capacity to metabolize triglyceride-rich lipoproteins that have been produced in excess quantity by the liver in response to excessive fatty acid release by adipose tissue (101).

Atherogenic Dyslipidemia

Atherogenic dyslipidemia is a particularly important constellation of lipoprotein abnormalities of great clinical significance appearing to result from the coexistence of several defects, lipoprotein or otherwise, of lipid metabolism (101,120). The specific findings are (a) mild hypercholesterolemia, (b) mild to moderate hypertriglyceridemia, (c) the presence of circulating small, dense LDL particles, and (d) a low serum concentration of HDL cholesterol. Although genotype and aging are strong contributors, three additional lifestyle factors are also apparently contributory or causative. These include obesity, physical inactivity, and diets high in fatty acids that increase serum cholesterol (101,120). Naturally, the latter three factors are clinically relevant because they are potentially modifiable. In this regard, the central pathophysiologic link is the presence of insulin resistance and the patient can improve insulin sensitivity by increasing physical activity and losing weight, two goals of almost every medical and public health recommendation for maintaining a healthy weight (see Chapters 2 and 14).

Diagnosis

Because of the association of hyperlipidemia with coronary heart disease, it is generally recommended that plasma cholesterol and triglycerides be measured periodically during adult life. If a family has a history of hyperlipidemia or, especially, premature deaths due to coronary heart disease, children should also be tested because familial hypercholesterolemia is an autosomal dominant disease.

Total serum cholesterol and serum HDL levels are relatively unaffected by eating. This is one of the reasons why the calculation of non-HDL cholesterol is a particularly useful tool, as discussed above. However, a recent meal can cause a marked elevation of plasma triglycerides, due to the appropriate postprandial presence of chylomicrons in plasma. Triglycerides should be measured only after a 12- to 14-hour fast. Remember, too, that VLDL contain about 1 mg of cholesterol for every 4 mg of triglyceride, so that a person with significant hypertriglyceridemia may have a modestly increased total serum cholesterol value on the basis of the cholesterol content of his or her VLDL. A simple clinical approach to estimating VLDL cholesterol is to divide the triglyceride level by five, but the resulting quotient is only accurate when total serum triglycerides are less than 400 mg per dL. Thus, the calculation is not particularly helpful when it is most needed, i.e., in the case of severe hypertriglyceridemia. Plasma lipid values are best determined while patients are maintaining a steady weight and have been on their usual diet for several weeks. If abnormal values are found, before a firm diagnosis is made that may permanently affect the future course of a person's life, repeat fasting lipid levels should be measured on two or three occasions separated by 2- to 3-week intervals.

There are no routine clinical laboratory tests for the presence of chylomicrons in plasma, but a simple, practical approach to their detection is simply refrigerating the plasma overnight at 4°C. If chylomicrons are present, they will form a creamy layer on top of the plasma. The presence of chylomicrons in plasma drawn after a 12-hour fast is abnormal and indicative of familial chylomicronemia (type 1 lipoproteinemia), type V hyperlipoproteinemia, or a secondary abnormality caused by other diseases such as severe, insulin deficient diabetes. Fasting chylomicronemia is usually seen only when plasma triglyceride levels are above 1,000 mg per dL.

The implications of elevated plasma cholesterol depend on the lipoprotein class with which the cholesterol is associated. As noted earlier, a risk for coronary heart disease is associated with an elevated level of apolipoprotein B containing particles carrying cholesterol. These are principally LDL and the various VLDL remnant particles. Both LDL and HDL cholesterol can be measured specifically and directly in the clinical laboratory and this is the preferred approach. Nonetheless, this is not done in every hospital, and often LDL cholesterol is estimated by taking the measured total cholesterol value and subtracting HDL cholesterol and VLDL cholesterol (serum triglyceride concentration divided by 5). As discussed above, this approach can be problematic when serum triglyceride values are significantly elevated (either as VLDL or as chylomicrons). Further, the calculation is incorrect if VLDL remnants are elevated as in type III hyperlipoproteinemia.

All of the lipoprotein apopeptides, such as apo B, can be measured directly and specifically as well, but these measurements are not readily available in most routine clinical laboratories. However, determining the apo E genotype is absolutely necessary for the diagnosis of type III hyperlipoproteinemia and for discriminating lipoprotein lipase deficiency from apo CII deficiency in the diagnosis of familial chylomicronemia (type 1 hyperlipoproteinemia).

THERAPEUTIC APPROACHES

Nonlipid Risk Factors

In addition to the risk conferred through lipoproteins (high LDL and/or low HDL), the risk of coronary heart disease is changed by a number of other well-documented, nonlipid risk factors (84–87,99,101). Three of these, age (>45 years in men and >55 years in women), male gender, and a family history of premature coronary heart disease, are not modifiable by the patient or physician. The remaining factors that increase cardiovascular risk, on the other hand, are theoretically modifiable. These include obesity, physical inactivity, a diet pattern that promotes atherogenesis, cigarette smoking, diabetes, hypertension, and conditions that promote thrombogenic states (84). For the purposes of calculating a clinical risk algorithm (84), obesity is not included because it operates through the other risk factors (i.e., hypertension, hyperlipidemia, diabetes). Physical activity level is also not included because its principal beneficial effect is not on lowering LDL cholesterol, the primary lipoprotein goal (84). A person is considered at high risk if he or she has two or more of the remaining risk factors (including the lipoprotein risk factors of elevated LDL and reduced HDL cholesterol) that are known to increase the likelihood of coronary heart disease (84). A subject-specific 10-year coronary heart disease risk (<10%, 10% to 20%, and >20%) is then calculated according to the Framingham scoring system (84), readily accessible from the National Heart, Lung and Blood Institute at www.nhlbi.nih.gov/guidelines/cholesterol/ risk_tbl.htm.

The overall goal is to reduce LDL cholesterol. In high-risk persons (>2 risk factors and 10-year CHD risk of >20%), the recommended LDL cholesterol goal is <100 mg per dL (84), with the therapeutic option of lowering it even further, to below 70 mg per dL, if desired and achievable (99) (Table 13-8). For those who have a moderately high risk, defined as having the presence of more than two risk factors and a 10-year CHD risk of 10% to 20%, the recommended LDL cholesterol goal is <130 mg per dL (84) with the option to lower it further to <100 mg per dL, if desired. For those whose risk is moderate (more than two risk factors, but 10-year CHD risk <10%), the LDL cholesterol goal is <130 mg per dL. Finally, for persons of lower risk (0 to 1 risk factors), an initial acceptable goal is to reduce LDL cholesterol to less than 160 mg per dL (84).

The first goal of a therapeutic approach is to attempt to reduce the modifiable, nonlipid risk factors by convincing the patient to cease smoking, controlling blood pressure, and improving nutrition and physical activity to accomplish weight reduction (84). The foundation for this approach is behavior-change-mediated lifestyle intervention (38,40,64,66,68,71,77,78,84,86,87,89,101) (see Chapter 14). Lifestyle intervention should continue throughout the person's lifetime, even if it becomes necessary to introduce pharmacologic treatment when the LDL cholesterol goals are not met (84,99). It should come as no surprise that the recommended nutrition and lifestyle recommendations are precisely those found in the 2005 *Dietary Guidelines for Americans* and discussed at length in Chapter 2.

There is now an extensive array of effective lipid lowering drugs. Discussion of their use is beyond the scope of this book and detailed reviews can be found elsewhere (84). Our discussion will focus on the aspects of reducing LDL cholesterol through nutritional means.

Dietary Therapy

General Principles

Dietary therapy is the mainstay of lifestyle-altering treatment of all the hyperlipoproteinemias, and nutritional approaches to serum lipoprotein reduction have been an active area

of nutrition research and practice for decades. Although the responses of serum lipids to dietary manipulations are known, the biochemical mechanisms for the observed responses are not always clear. Despite the fact that most (two-thirds to three-fourths) of the serum cholesterol is endogenous rather than of dietary origin, alterations in dietary cholesterol and saturated fat intakes can change serum cholesterol levels. However, the effect of dietary alterations on serum cholesterol varies greatly from person to person. Dietary changes that cause a marked fall in cholesterol in one person may have little or no effect in another. The reduction in serum cholesterol is most marked when dietary cholesterol is reduced to a very low level (<100 mg per day). In severe dietary cholesterol restriction, the diet consists largely of cereals, legumes, fruits, and vegetables, with only small allowances of meat and dairy products. Additionally, the fall in serum cholesterol is not directly proportional to the degree of dietary restriction. A substantial reduction in dietary cholesterol (e.g., from 600 to <300 mg per day) usually results in only a modest reduction in serum cholesterol.

Increasing the ratio of dietary polyunsaturated to saturated fats (P:S ratio) in the diet reduces serum cholesterol levels. Reducing dietary cholesterol intake and simultaneously increasing the dietary P:S ratio reduces serum cholesterol more than does reducing dietary cholesterol alone. The mechanism by which an increased P:S ratio decreases serum cholesterol is not established, but a decrease in the synthesis of endogenous cholesterol has been postulated. Monounsaturated fatty acids, such as are found in olive and peanut oils, have cholesterol-lowering effects similar to those of polyunsaturated oils. Irrespective of the mechanism, controlled clinical trials have shown conclusively that substitution of dietary saturated fats by polyunsaturated fats reduces coronary heart disease risks (84).

The major determinant of chylomicron production and VLDL production is the rate of synthesis of triglycerides in the enterocytes and hepatocytes, respectively. The rate of triglyceride synthesis in enterocytes is determined by the intake of fat. The rate of triglyceride synthesis in hepatocytes is determined by total caloric intake and fat intake. Thus, caloric restriction reduces both chylomicron and VLDL production by reducing the synthesis of triglycerides. In this context, elevated triglyceride levels are associated with obesity. Weight loss usually reduces the hypertriglyceridemia associated with obesity. In many patients with hypertriglyceridemia, a pronounced rise in triglyceride levels occurs after alcohol ingestion. Elimination or marked curtailment of alcohol results in decreased triglycerides.

The guiding principles of the ATP III nutrition approach to reducing LDL cholesterol-associated coronary heart disease risk are shown in Table 13-11 (84). In every respect, other than a somewhat more stringent reduction in saturated fat intake than some recommendations, the ATP III recommendations are essentially identical to those of every other expert body that has provided specific guidelines for a healthy diet (38,64,66,71,77, 78,86,87,89), including the 2005 *Dietary Guidelines for Americans* detailed in Chapter 2. Various aspects of specific recommendations have been discussed extensively throughout this book.

Saturated and trans *Fats*

For every 1% increase in saturated fat intake (as a percent of total energy intake), LDL cholesterol rises about 2% and vice versa when saturated fat intake is reduced (84). Thus, reduction of saturated fat intake is a cornerstone of risk reduction through diet (121). Similarly, *trans* fats raise serum LDL cholesterol levels and their intake should be kept as low as possible.

Dietary Cholesterol

Controlled studies indicate that high cholesterol intakes raise serum cholesterol, although there is significant interindividual variation in response (84). Estimates are that serum cholesterol increases about 10 mg per dL for every 100 mg increase in dietary cholesterol per 1,000 calories of energy intake. Dietary cholesterol intake has been declining steadily in the United States for decades and now averages about 331 mg per day in men and 213 mg per day in women, of which one-third comes from egg consumption (84). The ATP III goal is to reduce cholesterol intake to less than 200 mg per day

TABLE 13-11. Essential Dietary Component of the Therapeutic Lifestyle Change Necessary to Achieve a Sustained Reduction in LDL Cholesterol

Dietary component	Recommendation
Energy	Adjust to maintain desirable body weigh
Total fat	25%–35% of total calories
Saturated fats	Less than 7% of total calories
Polyunsaturated fats	Up to 10% of total calories
Monounsaturated fats	Up to 20% of total calories
Cholesterol	Less than 200 mg/day
Protein	Approximately 15% of total calories
Carbohydrate	50%–60% of total calories, predominantly as complex carbohydrates; whole grains, fruits, and vegetables
Soluble fiber	14 g per 1,000 kcal of energy
Plant stanols/sterols	2 g/day

Adapted from National Cholesterol Education Program. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final Report. *Circulation.* 2002;106:3143–3421. Fiber recommendation adjusted for compatability with the Dietary Reference Intake recommendation for fiber (Chapter 2).

cMono- and Polyunsaturated Fatty Acids

Substantial experimental evidence supports the statement that both mono- and polyunsaturated fatty acids reduce LDL cholesterol when substituted for saturated fatty acids, including the recently reported OmniHeart randomized trial (88). Olive oil is the principal source of monounsaturated fat and the principal sources of polyunsaturated fats are the liquid vegetable oils. Because unsaturated fats do not increase LDL cholesterol when substituted for dietary carbohydrates, it is not necessary to stringently restrict total fat intake if the predominant fats in the diet are unsaturated.

Omega-3 polyunsaturated fatty acids appear to be a unique class of polyunsaturated fats. The omega-3 fatty acid, alpha-linolenic acid, is found in flaxseed, soybean, and canola oils (and in walnuts) while walnuts which fish oils contain the longer chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-3 fatty acids from fish oils have been shown repeatedly to decrease the risks of cardiovascular disease (122,123), and the American Heart Association recommends that all adults eat fish at least two times a week and that individuals with documented coronary heart disease consume about 1 g of EPA and DHA daily as a supplement (123). Additionally, some have suggested that omega-3 fatty acid supplements will complement therapy with statins, particularly when the patient has elevations in both cholesterol and triglycerides (124).

Carbohydrates

Carbohydrate intake should be limited to less than 60% of energy intake and the majority of carbohydrates consumed as the complex carbohydrates in whole grains, fruits, and vegetables. This will also ensure an adequate intake of dietary fiber that should be consumed at an intake level of about 14 g of fiber for each 1,000 calories of energy.

Plant Stanols/Sterols

Recent studies indicate that plant sterols and plant-derived stanols or stanol esters can reduce LDL cholesterol when consumed in the amounts of 2 to 3 g daily (84). These are found naturally in fruits, vegetables, seeds, nuts, and some oils like soybean oil. However, they are now added to several margarines and to at least one brand of orange juice. Similarly, several manufacturers sell SoftGel capsules that contain these compounds.

Soy Protein

There are some data suggesting that soy protein can cause small reductions in LDL cholesterol (84). However, the average effect is only 3% and this small reduction requires considerable consumption of soy protein (50 g, on average) (125). Thus, there is little compelling reason

to recommend increasing soy protein intake or substituting soy protein for other dietary proteins on the basis of cardiovascular health (125).

Wine

In populations, light to moderate alcohol intake is associated with a reduced cardiovascular risk although it is not clear whether there is any particular benefit of wine compared to other forms of alcohol (126). On the other hand, there is also considerable epidemiologic evidence that more substantial alcohol intakes are associated with increased risks of hypertension and stroke (126). Because of the potential for excess consumption, there is no way to calculate the risk/benefit ratio for a public health recommendation. For this reason, the American Heart Association recommends that "alcohol use should be an item of discussion between physician and patient" (126).

Vitamin and Mineral Supplements

Other than a routine daily multivitamin taken for "nutrition insurance," the use of vitamin B_{12} supplements in elderly individuals, the recommendation for calcium supplements in women unable to achieve an adequate intake of calcium, and the public health recommendation for folic acid supplements in women of childbearing age, there is no evidence that any dietary supplements have benefit in preventing cardiovascular disease (127,128). In fact, there is some evidence that beta-carotene, vitamin A, and vitamin E supplements may actually increase, rather than decrease, mortality (128). Additionally, there is no evidence that herbal or other botanical supplements have any beneficial effect in reducing the risk for coronary heart disease (84).

Other comorbidities must be taken into account when a cholesterol-lowering diet is designed. For example, as described earlier in this chapter, if renal disease is present, it may be necessary to lower dietary protein, potassium, and phosphorus intakes, and if the patient has hypertension, further limitation of the salt intake may be required. The DASH diet plan accomplishes both blood pressure reduction and lipid reduction and can improve body weight (66). However, as discussed earlier in this chapter, the DASH diet plan must be modified if applied to individuals with renal disease.

An important component of dietary therapy for patients with hyperlipoproteinemia is an attempt to achieve a desirable body weight. All overweight patients should receive dietary counseling, including behavior modification for lifestyle change, in conjunction with the caloric restriction necessary to achieve weight reduction (see Chapter 14). Even a small weight reduction on the order of 5% to 10% of body weight may improve triglyceridemia and lower LDL cholesterol. Weight reduction is especially important for individuals who exhibit the characteristics of atherogenic dyslipoproteinemia, as described earlier.

Obesity (with or without diabetes) and alcohol consumption both commonly precipitate hypertriglyceridemia. Thus, weight-reduction diets and elimination of alcohol are essential steps in managing hypertriglyceridemia (116). Weight loss reduces VLDL production and thus lowers triglycerides. When high plasma levels of triglycerides are secondary to other diseases, therapy should be directed first toward the underlying disorder. Non-insulin-dependent diabetes, when poorly controlled, is a common cause of hypertriglyceridemia; treatment with caloric restriction, exercise, or insulin often normalizes triglyceride concentrations. When hypothyroidism is associated with hypertriglyceridemia, patients usually are obese and may have a familial form of hyperlipidemia; with this combination of disorders, thyroid hormone therapy alone may not correct the hypertriglyceridemia completely. An additional approach in severe hypertriglyceridemia is to restrict fat intake to 10% to 15% of energy intake (116). This is a temporizing measure and can be problematic in the long term, both from the standpoint of compliance and because the necessarily increased carbohydrate content of the diet might lead to increased synthesis of VLDL triglycerides. Along with a restriction in dietary saturated fat and energy intakes, omega-3 fatty acid supplements may improve plasma triglyceride levels significantly (116).

Practical Dietary Management

Decreasing Cholesterol and Saturated Fat Intakes

The average American consumes between 300 to 400 mg of cholesterol daily. Cholesterol intake can be reduced to less than 300 mg by eliminating foods very high in cholesterol and

in saturated and *trans* fatty acids (organ meats, butter fat, lard, certain margarines), and by substituting skim milk for whole milk (Table 13-12). The cholesterol contents of some common foods are as follows: a large egg, 215 mg; 1 tbs of butter, 30 mg; a hamburger made with a quarter of a pound of beef, 85 mg; one strip of bacon, 16 mg; and 1 cup of whole milk, 34 mg. Although eggs contain a significant amount of cholesterol, they are relatively "poor" in saturated fatty acids and studies show that, by themselves, they raise LDL cholesterol considerably less than might be anticipated. In any case, cholesterol-free egg substitutes are widely available in supermarkets. A further reduction of cholesterol intake, to about 200 mg of cholesterol per day, can be achieved by significantly reducing the amount of animal fats consumed. Fish, shellfish, and poultry intakes are encouraged. Athough the cholesterol content of shrimp is high, they contain many noncholesterol sterols (e.g., sitosterol) that compete for absorption, and the amount of shrimp eaten is generally considerably less than the amount of beef consumed. The consumption of beef, lamb, ham, and pork should be limited. Meat substitutes, made from a variety of vegetable sources, are now available in virtually every supermarket and in almost every meat product configuration, including "bacon," "sausage," "ground beef," and "turkey." Surimi, a form

TABLE 13-12. Lipid Content of Selected Foods

Specific food (100 g)	Total fat (g)	P:S ratio[a]	Cholesterol (g)
Beef, lean, cooked	14.9	0.1	80
Beef, fatty, cooked	29.8	0.1	85
Chicken and turkey (light meat, no skin)	3.9	0.8	77
Frankfurter, all beef, cooked	28.5	0.1	61
Bologna, salami, cold cuts	30.0	0.1	85
Bacon, regular, cooked	49.0	0.3	85
Fish (cod)	1.5	1.7	68
Shrimp	1.1	1.54	195
Clams, mussels, cooked	1.9	2.9	67
Tuna, canned, water-packed	0.8	1.5	30
Eggs (equivalent to 2 whole)	10.5	0.4	425
Egg, yolk	30.9	0.4	1,281
Egg, white	0	—	0
Milk, whole	3.5	0.1	13.6
Milk, 1% fat	1.1	0.1	4
Milk, skim	0.2	0.1	2
Cheese, cheddar, American	33.1	0.1	105
Cheese, cottage, low-fat	1.9	0.1	8
Ice cream, regular (11% fat)	11	0.1	44
Butter	81.0	0.1	219
Oils			
Corn	100.0	4.6	0
Cottonseed	100.0	2.0	0
Safflower	100.0	8.2	0
Sesame	100.0	2.9	0
Soybean, partially hydrogenated	100.0	2.5	0
Olive	100.0	0.6	0
Peanut	100.0	1.9	0
Coconut	100.0	0.1	0
Peanut butter	50.6	1.6	0

[a]P:S ratio is the ratio of polyunsaturated fatty acids to saturated fatty acids; values less than 0.1 have been rounded to 0.1. For dairy products, the values average closer to 0.05, and for coconut oil, the P:S ratio is closer to 0.02.

Adapted from Grundy SM. Nutrition in the management of disorders of serum lipids and lipoproteins. In: Shils ME, Shike M, Ross AC, et al., eds. *Modern Nutrition in Health and Disease,* 10th ed. Baltimore: Williams & Wilkins, 2006:1076–1094.

of processed pollock that is low in fat and cholesterol, is sold as imitation crab meat and is a reasonably priced substitute for meat protein.

Reduce dietary intake of whole milk and cheese. Except for cottage cheese and farmer's cheese, most cheeses are high in cholesterol and their consumption should be limited. Fat-modified cheeses are now commonly available in supermarkets. The calorie content of low-fat or nonfat cheeses is reduced in comparison to that of regular cheese, and cheeses made from vegetable fats rather than animal fats have no cholesterol and a high P:S ratio, although their caloric content is about the same as that of natural cheese. Some whole milk substitutes, made for lactose-intolerant patients, are composed entirely of vegetable products and oils (e.g., soy "milk") and are acceptable substitutes. However, in the context of weight maintenance, it is important to remember that these products may contain as many calories as whole milk.

Many homemade and commercially prepared baked goods contain significant amounts of saturated fat in the form of butter, lard, and whole milk in addition to the cholesterol of egg yolks. These products include waffles, pancakes, muffins, pastries, French toast, potato chips, cakes, and pies. Low-cholesterol baked goods can be made at home, with either egg whites or egg substitutes used instead of whole eggs, skim milk instead of whole milk, and soft margarine instead of butter and lard. A variety of low-fat, low-cholesterol bakery products is now available commercially.

Increasing the Intakes of Healthy Fats and Modifying the P:S Ratio

The P:S ratio in the standard American diet is less than 1.0. Most polyunsaturated fats come from vegetable oils, whereas most saturated fat comes from meat and dairy products. Traditional margarines were all made by partially hydrogenating vegetable oils that increases fatty acid saturation and therefore reduces the P:S ratio. During the hydrogenation process, some fatty acids are converted to *trans* fatty acids. Substantial evidence now indicates that *trans* fatty acids are as atherogenic, or even more atherogenic, as saturated fats. All expert bodies recommend reducing the intake of *trans* fats to as low as possible. This goal is being made easier every day, because most manufacturers are striving to remove all *trans* fats from their products. When buying margarine, it is critical to read the label, as *trans* fats are listed. Many margarine products are now *trans* fat free and others have added healthy fats and unsaturated oils to decrease the atherogenic properties. In particular, these use vegetable oils and are, thus, soft margarines, generally sold in tubs, rather than the stick margarines. Further, given the listing of grams of saturated and unsaturated fats on the label, one can calculate the P:S ratio, which is best when above 2.0. Also, when reading the label, pay attention to the type of vegetable fat, because this term may refer to coconut oil or other oils that are high in saturated fats. Of all the vegetable oils, safflower oil has the highest P:S ratio. Other vegetable oils with a high P:S ratio are corn, soybean, and sunflower oils. The P:S ratio for olive oil (0.6) is lower than that for most other vegetable oils because olive oil is predominantly a monounsaturated oil; however, monounsaturated oils lower cholesterol as effectively as polyunsaturated oils. The P:S ratios for palm oil (0.2) and coconut oil (0.2) are even lower, and these are not effective cholesterol-lowering oils.

Most regular commercially prepared baked goods, including crackers for snacks, cookies, cakes, and pies, have low P:S ratios because they are made with animal fats or hydrogenated vegetable fats. Commercial cake mixes have low P:S ratios for the same reason. At least in part, this is due to the fact that baked goods of this type require some fats that are solid at room temperature in order to rise properly when baked and to maintain their shape and final form after baking.

The P:S ratios for vegetable products are generally high and fish and poultry have higher P:S ratios than do other animal products. To raise the P:S ratio of the diet, one must reduce the consumption of meat, eggs, butter, and whole milk and increase the consumption of foods and oils with a high P:S ratio. The dietary changes that decrease cholesterol intake also generally lower the intake of saturated fat because, in the American diet, the foods that are high in cholesterol tend to be high in saturated fat (e.g., meat, butter, and dairy products made from whole milk). Many recipes call for saturated fats; Table 13-13 provides a list of polyunsaturated substitutes for these saturated fats but, for the reasons stated above, such substitutions will change the character of baked goods.

TABLE 13-13. Polyunsaturated Substitutes for Saturated Fats Useful in Changing a Recipe That May Be High in Saturated Fat to One That Is High in Polyunsatured Fat

Saturated fat	Polyunsaturated fat
1 oz chocolate	= 2 tbs cocoa + 2 tsp margarine
1 egg	= 1 tbs flour for thickening
1 egg	= 2 egg whites
1 cup butter	= 1 cup margarine
1 cup sour cream	= 1 cup yogurt
1 cup whole milk	= 1 cup skim milk + 2 tsp margarine
1 tbs butter	= 3/4 tbs oil
1 1/4 cup butter	= 1 cup oil

From the Washington University Lipid Research Center.

ADDITIONAL RESOURCES

The following government-sponsored website can serve as an additional resource for patient and professional information on diet, healthy weight, hypertension, cholesterol, and coronary heart disease: www.nhlbi.nih.gov/subsites/index.htm.

References

1. National Institutes of Health. National Institute of Diabetes, Digestive and Kidney Diseases. Diabetes Information Clearinghouse. National Diabetes Statistics. Total prevalence of diabetes in the United States, all ages, 2005. http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm. Accessed on June 10, 2007.
2. Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion. National Diabetes Surveillance System. Number (in millions) of persons with diagnosed diabetes, United States, 1980–2005. http://www.cdc.gov/diabetes/statistics/prev/national/tablepersons.htm. Accessed on June 10, 2007.
3. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health and Nutrition Examination Survey 1999–2002. *Diabetes Care*. 2006;29:1263–1268.
4. The Writing Group for the SEARCH for Diabetes in Youth Study Group. Incidence of diabetes in youth in the United States. *JAMA*. 2007;297:2716–2724.
5. American Diabetes Association. Direct and indirect costs of diabetes in the United States. http://www.diabetes.org/diabetes-statistics/cost-of-diabetes-in-us.jsp. Accessed June 10, 2007.
6. World Health Organization. Diabetes Programme. Country and regional data. http://www.who.int/diabetes/facts/world_figures/en/ Accessed on June 10, 2007.
7. International Diabetes Federation. *Diabetes Prevalence*. http://www.idf.org/home/index.cfm?node=264 Accessed on June 10, 2007.
8. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977.
9. The Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the diabetes control and complications trial. *Ophthalmology*. 1995;102:647.
10. The Diabetes Control and Complications Trial Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the diabetes control and complications trial. *Kidney Int*. 1995;47:1703.
11. The Diabetes Control and Complications Trial Research Group. Influence of intensive diabetes treatment on quality-of-life outcomes in the diabetes control and complications trial. *Diabetes Care*. 1996; 19:195.
12. The Diabetes Control and Complications Trial Research Group. Lifetime benefits and costs of intensive treatment as practiced in the diabetes control and complications trial. *JAMA*. 1996;276:1409.
13. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the diabetes control and complications trial. *Diabetes*. 1997;46:271.

14. The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the diabetes control and complications trial. *Diabetologia*. 1998;41:416.
15. The Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive diabetes treatment on carotid artery wall thickness in the epidemiology of diabetes interventions and complications. *Diabetes*. 1999;48:383.
16. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med*. 2000;342:381.
17. The Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. *Diabetes Care*. 2000;23:1084.
18. The Diabetes Prevention Program. Baseline characteristics of the randomized cohort. *Diabetes Care*. 2000;23:1619.
19. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643–2653.
20. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med*. 2003;348:2294–2303.
21. Cleary PA, Orchard TJ, Genuth S, et al. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes*. 2006;55:3556–3565.
22. Eisenbarth GS. Update in type 1 diabetes. *J Clin Endocrinol Metab*. 2007;92:2403–2407.
23. Tuomilehto J, Lindström J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343–1350.
24. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
25. Chiasson J-L, Josse RG, Gomis R, et al. Acarbose for prevention of type 2 diabetes mellitus: The STOP-NIDDM randomised trial. *Lancet*. 2002;359:2072–2077.
26. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes*. 2002;51:2796–2803.
27. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes*. 2002;51:2796–2803.
28. Torgerson JS, Hauptman J, Boldrin MN, et al. Xenical in the prevention of diabetes in obese subjects (XENDOS) study: A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27:155–161.
29. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997;20:537–544.
30. Ramachandran A, Snehalatha C, Mukesh MS, et al. Indian Diabetes Prevention Programme (IDOO): the Indian Diabetes Prevention Program shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia*. 2006;49:289–297.
31. Buchanan TA. Perspectives in diabetes: (How) can we prevent type 2 diabetes? *Diabetes*. 2007;56:1502–1507.
32. Hussain A, Claussen B, Ramachandran A, et al. Prevention of type 2 diabetes: A review. *Diabetes Res Clin Practice*. 2007;76:317–326.
33. The Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: One-year results of the Look AHEAD trial. *Diabetes Care*. 2007;30:1374–1383.
34. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. 2006;444:840–846.
35. Nield L, Moore HJ, Hooper L, et al. Diet advice for the treatment of type 2 diabetes mellitus in adults (review). *Cochrane Database Syst Rev*. 2007;18:CD004097.
36. Anderson JW, Kendall CWC, Jenkins DJA, et al. Importance of weight management in type 2 diabetes: Review with meta-analysis of clinical studies. *J Am Coll Nutr*. 2003;22:331–339.
37. Dansinger ML, Tatsioni A, Wong JB, et al. Meta-analysis: the effects of dietary counseling for weight loss. *Ann Intern Med*. 2007;147:41–50.
38. American Diabetes Association. Nutrition recommendations and interventions for diabetes: A position statement of the American Diabetes Association. *Diabetes Care*. 2007;30(Suppl. 1):S48–S65.
39. American Diabetes Association. Introduction. *Diabetes Care*. 2005;28 (Suppl. 1):S1–2.
40. Anderson JW. Diabetes mellitus: Medical nutrition therapy. In: Shils ME, Shike M, Ross AC, et al., eds. *Modern Nutrition in Health and Disease,* 10th ed. Baltimore: Williams & Wilkins, 2006:1043.
41. Holler HJ, Pastors JG. *Diabetes Medical Nutrition Therapy: a Professional Guide to Management and Nutrition Education Resources*. Alexandria: American Dietetic Association and American Diabetes Association, 1997.

42. Anderson JW, Randles KM, Kendall CWC, et al. Carbohydrate and fiber recommendations for individuals with diabetes: A quantitative assessment and meta-analysis of the evidence. *J Am Coll Nutr*. 2004;23.
43. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2006;29: 1963–1972.
44. Nathan DM. Response to comments on: Nathan DM, Buse JB, Davidson MB et al. (2006) Management of hyperglycaemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 49:1711-1721. *Diabetologia*. 2007;50:231–233.
45. Sherry NA, Tsai EB, Herold KC. Natural history of β-cell function in type 1 diabetes. *Diabetes*. 2005;54 (Suppl. 2):S32–S39.
46. American Diabetes Association. Carbohydrate counting: the basics. *Clin Diabetes*. 2005;23:123–124.
47. Kulkarni KD. Carbohydrate counting: a practical meal-planning option for people with diabetes. *Clin Diabetes*. 2005;23:120.
46. Daly A, Bolderman K, Franz M. et al. *Basic Carbohydrate Counting*. Alexandria: American Diabetes Association, 2003.
49. Daly A, Bolderman K, Franz M, et al. *Advanced Carbohydrate Counting*. Alexandria: American Diabetes Association, 2003.
50. Gillespie SJ, Kulkarni KD, Daly AE. Using carbohydrate counting in diabetes clinical practice. *J Am Diet Assoc*. 1998;98:897–905.
51. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care*. 2003;26:1902–1912.
52. West KM. Diet and diabetes. *Postgrad Med*. 1976;60:209.
53. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academies Press, 2005.
54. Institute of Medicine, National Academy of Sciences. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington, DC: National Academies Press, 2006.
55. Barclay AW, Brand-Miller JC, Woelever TM. Glycemic index, glycemic load, and glycemic response are not the same. *Diabetes Care*. 2005;28:1839.
56. Brand-Miller J, Petocz P, Hayne S, et al. Low-glycemic index diets in the management of diabetes. *Diabetes Care*. 2003;26:2261–2267.
57. Raben A, Vasilaras TH, Moller AC, et al. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. *Am J Clin Nutr*. 2002;76:721–729.
58. Catalano PM. Management of obesity in pregnancy. *Obset Gynecol*. 2007;109:419–433.
59. National Kidney Foundation. K/DOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *Am J Kidney Dis*. 2007;49:S1–S179.
60. Kaisiske BL, Lakatua JD, Ma JC, et al. A meta-analysis of the effects of protein restriction on the rate of decline of renal function. *Am J Kidney Dis*. 1998;31:954–961.
61. Pedrini MT, Levey AS, Lau J, et al. The effect of dietary protein restriction on the progression of diabetic and non-diabetic renal diseases. A meta-analysis. *Ann Intern Med*. 1996;124:627–632.
62. Hansen HP, Tauber-Lassen E, Jensen BR, et al. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. *Kindey Int*. 2002;62:220–228.
63. Levey AS, Greene T, Sarnak MJ, et al. Effect of dietary protein restriction on the progression of kidney disease: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am J Kidney Dis*. 2006;28:879–888.
64. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-sodium collaborative research group. *N Engl J Med*. 2001;344:3–10.
65. Obarzanek E, Proschan MA, Vollmer WM, et al. Individual blood pressure responses to changes in salt intake: Results from the DASH-Sodium Trial. *Hypertension*. 2003;42:459–467.
66. Obarzanek E, Sacks FM, Vollmer WM, et al. Effects on blood lipids of a blood pressure-lowering diet: The Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr*. 2001;74:80–89.
67. Lin P-H, Aickin M, Champagne C, et al. Food group sources of nutrients in the dietary patterns of the DASH-Sodium trial. *J Am Diet Assoc*. 2003;103:488–496.
68. Vollmer WM, Sacks FM, Ard J, et al. Effects of diet and sodium intake on blood pressure: Subgroup analysis of the DASH-Sodium Trial. *Ann Intern Med*. 2001;135:1019–1028.
69. Akita S, Sacks FM, Svetkey LP, et al. Effects of the dietary approaches to stop hypertension (DASH) diet on the pressure-natriuresis relationship. *Hypertension*. 2003;42:8–13.
70. Adrogué HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. *N Engl J Med*. 2007;356:1966–1978.
71. Writing group of the PREMIER collaborative research group. Effects of comprehensive lifestyle modification on blood pressure control. Main results of the PREMIER clinical trial. *JAMA*. 2003;289:2083–2093.

72. He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev.* 2004, Issue I. Art. No.: CD004937, DOI: 10.1002/14651858.CD004937. Date of most recent substantive amendments 09 May 2005. Published in *The Cochrane Library* 2007, Issue 1.
73. He FJ, MacGregor GA. How far should salt intake be reduced? *Hypertension*. 2003;42:1093–1099.
74. Kopple JD. Nutrition, diet, and the kidney. In: Shils ME, Shike M, Ross AC, et al., eds. *Modern Nutrition in Health and Disease,* 10th ed. Baltimore: Williams & Wilkins, 2006:1475–1509.
75. National Kidney Foundation. K/DOQI Clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis*. 2000;35[Suppl]:S1–S140.
76. National Kidney Foundation. K/DOQI Clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004; 43[Suppl]:S1–S290.
77. Krauss RM, Eckel RH, Howard B, et al. AHA Scientific Statement: AHA dietary guidelines: Revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation*. 2000;102:2284–2299.
78. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42:1206–1252.
79. Kopple JD. Therapeutic approaches to malnutrition in chronic dialysis patients: the different modalities of nutritional support. *Am J Kidney Dis*. 1999;33:180.
80. Lim VS, Kopple JD. Protein metabolism in patients with chronic renal failure: role of uremia and dialysis. *Kidney Int*. 2000;58:1.
81. Schiro-Harvey K. *National Renal Diet: Professional Guide*, 2nd ed. Chicago: American Dietetic Association, 2002.
82. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42 [Suppl]:S1–S201.
83. National Kidney Foundation. K/DOQI clinical practice guidelines for managing dyslipidemias in chronic kidney disease. *Am J Kidney Dis*. 2003;41[Suppl]:S1–S91.
84. National Cholesterol Education Program. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final Report. *Circulation*. 2002;106:3143–3421.
85. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA*. 2003;289:2560–2572.
86. Goldstein LB, Adams R, Alberts MJ, et al. AHA/ASA Guideline: Primary Prevention of Ischemic Stroke: A guideline from the American Heart Association/American Stroke Association Stroke Council: Cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. The American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37:1583–1633.
87. Appel LJ, Brands MW, Daniels SR, et al. Dietary approaches to prevent and treat hypertension: A scientific statement from the American Heart Association. *Hypertension*. 2006;47:296–308.
88. Appel LJ, Sacks FM, Carey VJ, et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids. *JAMA*. 2005;294:2455–2464.
89. Appel LJ, Champagne CM, Harsha DW, et al. Effects of comprehensive lifestyle modification on blood pressure control: Main results of the PREMIER clinical trial. *JAMA*. 2003;289:2083–2093.
90. Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics–2007 update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2007;15:e69–e171. Summary statistics available online at http://www.americanheart.org/downloadable/heart/1166712318459HS_StatsInsideText.pdf
91. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med*. 2007;356:2388–2398.
92. Havel RJ, Kane JP. Structure and metabolism of plasma lipoproteins. In: Scriver CR, Beaudet AL, Valle D, et al., eds. *The Metabolic and Molecular Bases of Inherited Disease,* 8th ed. New York: McGraw Hill, 2001:270–2716.
93. Kane JP, Havel RJ. Disorders of the biogenesis and secretion of lipoproteins containing the B apoproteins. In: Scriver CR, Beaudet AL, Valle D, et al., eds. *The Metabolic and Molecular Bases of Inherited Disease,* 8th ed. New York: McGraw Hill, 2001:2717–2752.
94. Brunzell JD, Deeb SS. Familial lipoprotein lipase deficiency, apo C-II deficiency, and hepatic lipase deficiency. In: Scriver CR, Beaudet AL, Valle D, et al., eds. *The Metabolic and Molecular Bases of Inherited Disease,* 8th ed. New York: McGraw Hill, 2001:2789–2816.
95. Mahley RW, Rall SC Jr. Type III hyperlipoproteinemia (dysbetalipoproteinemia): the role of apolipoprotein E in normal and abnormal lipoprotein metabolism. In: Scriver CR, Beaudet AL, Valle D, et al., eds. *The Metabolic and Molecular Bases of Inherited Disease,* 8th ed. New York: McGraw Hill, 2001: 2835–2862.
96. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Valle D, et al., eds. *The Metabolic and Molecular Bases of Inherited Disease,* 8th ed. New York: McGraw Hill, 2001:2863–2912.

97. Tall AR, Breslow JL, Rubin EM. Genetic disorders affecting high-density lipoproteins. In: Scriver CR, Beaudet AL, Valle D, et al., eds. *The Metabolic and Molecular Bases of Inherited Disease,* 8th ed. New York: McGraw Hill, 2001:2915–2936.
98. Santamarina-Fojo S, Hoeg JM, Assmann G, et al., Lecithin cholesterol acyltransferase deficiency and fish eye disease. In: Scriver CR, Beaudet AL, Valle D, et al., eds. *The Metabolic and Molecular Bases of Inherited Disease,* 8th ed. New York: McGraw Hill, 2001:2817–2832.
99. Grundy SM, Cleeman JI, Merz CN, et al., for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110:227–239.
100. Thavendiranathan P, Bagai A, Brookhart MA, et al. Primary prevention of cardiovascular diseases with statin therapy: A meta-analysis of randomized controlled trials. *Arch Intern Med.* 2006;166:2307–2313.
101. Grundy SM. Nutrition in the management of disorders of serum lipids and lipoproteins. In: Shils ME, Shike M, Ross AC, et al., eds. *Modern Nutrition in Health and Disease,* 10th ed. Baltimore: Williams & Wilkins, 2006:1076–1094.
102. Garg A, Simha V. Update on dyslipidemia. *J Clin Endocrinol Metab.* 2007;92:1581–1589.
103. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high risk individuals: a randomized placebo-controlled trial. *Lancet.* 2002;360:7–22.
104. Shepherd J, Blauw GJ, Murphy MB, et al., on behalf of the PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *Lancet.* 2002;360:1623–1630.
105. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA.* 2002;288:2998–3007.
106. Sever PS, Dahlof B, Poulter NR, et al., for the ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandanavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial. *Lancet.* 2003;361:1149–1158.
107. Cannon CP, Braunwald E, McCabe CH, et al. Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350:1495–1504.
108. Deedwania P, Barter P, Camena R, et al., for the New Targets Investigators. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. *Lancet.* 2006;368:919–928.
109. Sacks F. The apolipoprotein story. *Atherosclerosis Suppl.* 2006;7:23–27.
110. McBride PE. Triglycerides and risk for coronary heart disease. *JAMA.* 2007;298:336–338.
111. Nordestgaard BG, Benn M, Schnohr P, et al. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA.* 2007;298:299–308.
112. Bansal S, Buring JE, Rifai N, et al. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA.* 2007;298:309–316.
113. Friedewald Jr. VE, Brewer Jr. HB, Grundy SM, et al. The editor's roundtable: High-density lipoprotein cholesterol. *Am J Cardiol.* 2007; 99:1698–1705.
114. Breslow JL. Genetics of lipoprotein abnormalities associated with coronary heart disease susceptibility. *Annu Rev Genet.* 2000;34:233–254.
115. Denke MA. Nutrient and genetic regulation of lipoprotein metabolism. In: Shils ME, Shike M, Ross AC, et al., eds. *Modern Nutrition in Health and Disease,* 10th ed. Baltimore: Williams & Wilkins, 2006: 1067–1075.
116. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. *Can Med Assoc J.* 2007;17:1113–1120.
117. Soutar AK, Naoumova RP. Mechanisms of disease: genetic causes of familial hypercholesterolemia. *Nature Clin Prac Cardiovascular Med.* 2007;4:214–225.
118. Lusis AJ, Mar R, Pajukanta P. Genetics of atherosclerosis. *Annu Rev Genomics Hum Genet.* 2004;5:189–218.
119. Gotto A, Pownall H. *Manual of Lipid Disorders,* 2nd ed. Baltimore: Williams & Wilkins, 1999.
120. Bamba V, Rader DJ. Obesity and atherogenic dyslipidemia. *Gastroenterology.* 2007;132:2181–2190.
121. Mead A, Atkinson G, Albin D, et al. Dietetic guidelines on food and nutrition in the secondary prevention of cardiovascular disease—evidence from systematic reviews of randomized trials (second update, January 2006). *J Hum Nutr Diet.* 2006;19:401–419.
122. Wang C, Harris WS, Chung M, et al. n-3 fatty acids from fish or fish-oil supplements, but not α-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr.* 2006; 84:5–17.
123. Kris-Etherton PM, Harris WS, Appel LJ, for the AHA Nutrition Committee. Omega-3 fatty acids and cardiovascular disease. New recommendations from the American Heart Association. *Atheroscler Thromb Vasc Biol.* 2003;23:151–152.
124. Nambi V, Ballantyne CM. Combination therapy with statins and omega-3 fatty acids. *Am J Cardiol.* 2006;98[suppl]:34i–38i.

125. Sacks FM, Lichtenstein A, Van Horn, L, et al. Soy protein, isoflavones, and cardiovascular health. A summary statement for professionals from the American Heart Association Nutrition Committee. *Atheroscler Thromb Vasc Biol.* 2006;26:1689–1692.
126. Goldberg I, Mosca L, Piano MR, et al. Wine and your heart. A science advisory for healthcare professionals from the Nutrition Committee, Council on Epidemiology and Prevention, and Council of Cardiovascular Nursing of the American Heart Association. *Circulation.* 2001;103:472–475.
127. Bleys J, Miller III ER, Pastor-Barriuso R, et al. Vitamin-mineral supplementation and the progression of atherosclerosis: A meta-analysis of randomized controlled trials. *Am J Clin Nutr.* 2006;84:880–887.
128. Bjelakovic G, Nikolova D, Gluud, LL, et al. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention. Systematic review and meta-analysis. *JAMA.* 2007;297:842–857.

OBESITY 14

DEFINITION OF OBESITY

Obesity is an excess amount of body fat. For decades, a variety of methods have been available for measuring body fat in humans. Nonetheless, there is no uniformly accepted range of normal body fat in man. Therefore, there is no standard of human obesity based on a quantitative value for excessive accretion of body fat. Additional confusion results from the fact that the presence of abnormal amounts of total body fat alone is not the only degree of fat accumulation associated with medical complications. Thus, abnormal distribution of body fat, particularly intra-abdominal fat, is also distinctly associated with increased morbidity.

Because both an individual's height and weight are readily measured with good accuracy and precision, guidelines for assigning risks due to obesity have generally used a surrogate variable called the body mass index (BMI) that is calculated by dividing a person's weight (in kilograms) by the square of his or her height (in meters). Thus, for an 80-kg man who is 180 cm tall,

$$\text{BMI} = 80/(1.80)^2 = 24.7$$

Since the BMI is a very practical way of estimating relative body mass, it has become the *de facto* standard for characterizing overweight and underweight for size. However, it is important to again emphasize that the BMI does not measure body fat directly, and in the normal range of BMI, body fat content among individuals can vary widely (see Chapter 5 under the section titled Longitudinal Measures of Growth or Body Weight for additional discussion of BMI). For example, at the same BMI, women and elderly individuals have more body fat than young men. Similarly, even among individuals of the same age or gender, a person with a lower BMI may have more body fat than a person with a higher BMI. However, within the obese BMI range, BMI is primarily an estimate of increased body fat, and incremental changes in BMI principally indicate an accumulation of body fat, not the accretion of lean tissue.

In adults, a BMI between 18.5 and 24.9 is classified as normal based on the J-shaped relationship between the BMI and diseases that are a consequence of obesity (1) (Figure 14-1), although caveats concerning this relationship are discussed below in more detail. Table 14-1 is a BMI table for adults that can be downloaded from the National Heart, Lung and Blood Institute (NHLBI) at www.nhlbi.nih.gov/guidelines/obesity/bmi_tbl.pdf, and an adult BMI calculator from the NHLBI can be found at www.nhlbisupport.com/bmi/bmicalc.htm.

In children, the BMI normal range changes with age and, therefore, no single, normal BMI range is applicable throughout childhood. The National Center for Health Statistics age- and gender-specific BMI tables for children between the ages of 2 and 20 years

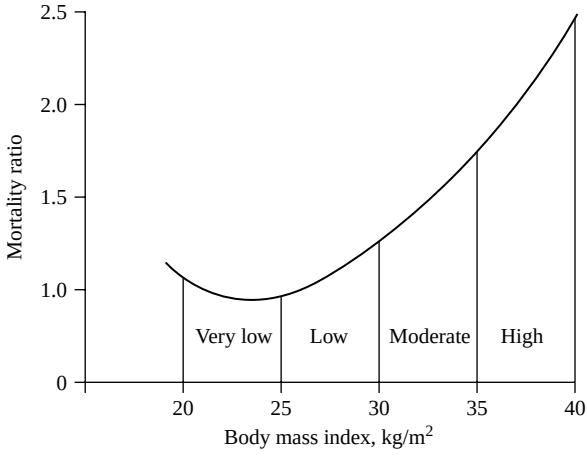


FIGURE 14-1. General relationship between body mass index and mortality risk in adults. Use of body mass index to estimate excess mortality risk from obesity in persons ages 20 to 29 years and 30 to 39 years. (Based on data from Les EA, Garfunkel L. Variation in mortality by weight among 750,000 men and women. *J Chron Dis* 1987;32:563, as adapted by Bray GA. Obesity: basic considerations and clinical approaches. *Dis Mon* 1989;18:449.)

can be downloaded at www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm, and an age- and gender-specific BMI calculator for children can be found at www.kidsnutrition.org/bodycomp/bmiz2.html (see Table 5-14 for BMI values calculated from height in centimeters and weight in kilograms).

From the recommended normal BMI range between 18.5 and 24.9, it is possible to "back-calculate" combinations of heights and weights that yield healthful BMI values. Based on this calculation, Table 14-2 shows healthful weight ranges for adults that are offered as guidelines for persons of given heights. For comparison, median weights and heights for children and adults reported in the 2005 DRI report are provided in Table 5-8.

The U.S. National Center for Health Statistics, Centers for Disease Control and Prevention, classifies persons with BMI values in the 25 to 29.9 range as overweight, while the World Health Organization (WHO) calls such individuals "preobese." Both organizations classify individuals whose BMI is equal to, or greater than, 30 as obese (1,2). The WHO further categorizes class I obesity as a BMI between 30.0 and 34.9, class II obesity as a BMI between 35.0 and 39.9, and class III obesity as a BMI above 40 (1) while the National Center for Health Statistics defines the category of BMI greater than 40 as "extreme obesity" (2). Based on these definitions, in 2003–2004 more than 66% of American adults were either overweight or obese; 32.2% of the adult population was obese and extremely obese individuals accounted for 4.8% of adults. Most distressingly, the prevalence of obesity continues to rise. Between 1960 and 1962, the prevalence of obesity in the United States was only 13.3% and extremely obese individuals accounted for only 0.9% of the population (3). In 1995, no state had an obesity prevalence of greater than 20%, but in the year 2000, only 28 states had an obesity prevalence rate of less than 20%. In 2005, only 4 states had a prevalence of obesity less than 20%, while 17 states had obesity prevalence rates equal to or greater than 25%. Three states had obesity prevalence rates of greater than 30% (Figure 14-2). Further, the distribution of BMI has changed and become more skewed to the right, indicating that people with high BMI are become fatter at a greater rate than those whose BMI is within the normal or overweight ranges (3).

TABLE 14-1. Adult Body Mass Index

	Normal						Overweight					Obese										Extreme obesity																
BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Height (inches)	Body weight (pounds)																																			
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167	172	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173	178	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179	184	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185	190	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191	196	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197	203	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204	209	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210	216	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216	223	229	235	241	247	253	260	266	272	278	284	291	297	303	309	315	322	328	334
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223	230	236	242	249	255	261	268	274	280	287	293	299	306	312	319	325	331	338	344
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230	236	243	249	256	262	269	276	282	289	295	302	308	315	322	328	335	341	348	354
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236	243	250	257	263	270	277	284	291	297	304	311	318	324	331	338	345	351	358	365
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243	250	257	264	271	278	285	292	299	306	313	320	327	334	341	348	355	362	369	376
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250	257	265	272	279	286	293	301	308	315	322	329	338	343	351	358	365	372	379	386
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258	265	272	279	287	294	302	309	316	324	331	338	346	353	361	368	375	383	390	397
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265	272	280	288	295	302	310	318	325	333	340	348	355	363	371	378	386	393	401	408
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272	280	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279	287	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287	295	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

Source: National Institutes of Health, National Heart, Lung, and Blood Institute, http://www.nhlbi.nih.gov/guidelines/obesity/bmi_tbl.pdf

TABLE 14-2. U.S. Weight Guidelines for Adult Men and Women[a]

Height[b]	Weight[c] (lb)
4′10″	91–119
4′11″	94–124
5′0″	97–128
5′1″	101–132
5′2″	104–137
5′3″	107–141
5′4″	111–146
5′5″	114–150
5′6″	118–155
5′7″	121–160
5′8″	125–164
5′9″	129–169
5′10″	132–174
5′11″	136–179
6′0″	140–184
6′1″	144–189
6′2″	148–195
6′3″	152–200
6′4″	156–205
6′5″	160–211
6′6″	164–216

[a] Calculated from the "low-risk" BMI range: 19–25 kg/m^2.
[b] Without shoes.
[c] Without clothes.
From Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med.* 1999;341:427, with permission.

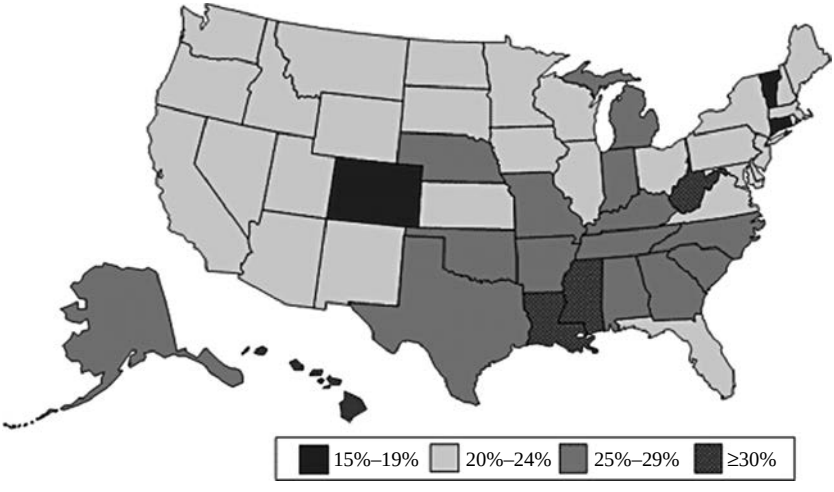


FIGURE 14-2. U.S. Obesity Prevalence Rates by State in 2005. From the National Centers for Health Statistics, Centers for Disease Control and Prevention, www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/

RELATIVE DISEASE RISKS IN OBESITY

The BMI cutoff values for the healthy weight range are based on large epidemiologic studies correlating BMIs and mortality rates (4–23). Nonetheless, recent detailed analysis of the National Health and Nutrition Examination Surveys has not been able to demonstrate excess deaths due to obesity in individuals who were overweight (BMI 25.0 to 29.9) (8,9,15), and the relative mortality risks of gender and social class exceed the relative mortality risks of overweight individuals (23,24). Further, although the prevalence of obesity has increased dramatically over the last several decades, life expectancy has, likewise, also increased. In large part, this has been the result of a simultaneous, approximately 50% decline in cardiovascular deaths (11,25). About half of this decline has been attributed to improved therapies and about half to reduction of risk factors including reductions in serum cholesterol, blood pressure, and smoking (11,25). Others, however, have argued that the principal concern of elevated BMI is not the mortality risk but, rather, the "living risk" associated with the increased incidence of the diseases that are associated with obesity and lead to mortality (i.e., diabetes, hypertension, coronary artery disease), comorbidities that increase in the overweight BMI range (26). Additionally, the relationships among increased body fat and both morbidity and mortality may be confounded by the use of BMI as a surrogate for measurement of body fat. Thus, in many epidemiologic studies, a subject's BMI is self-reported and this may lead to an error in calculation of true BMI based on measured height and weight (27,28). Further, as mentioned earlier, body fatness varies at any given BMI (29) and the J-shaped relationship between BMI and mortality is linearized when body fat is determined directly (5,22). Finally, as discussed below, BMI does not provide an indication of the anatomical location of the excess body fat, and risk of both comorbidities and mortality are increased within each BMI unit value when excessive visceral fat is present (21).

Thus, the BMI should be considered as only one component of risk assessment in patients of various heights and weights. In general, especially when the BMI exceeds 30, the higher the BMI, the greater the risk for obesity-related comorbidities and accompanying mortality. Other important factors in assessing the risks associated with obesity include the following:

Age

The relative rates of death associated with increasing BMI values decrease with advancing age and, above the age of about 75, individuals with BMI in the overweight or obese range no longer have an increased risk of mortality (30–34), although increased abdominal fat may remain an indicator of increased risk (32,33).

Fat Distribution

Morbidity is greater in persons with excess intraabdominal or subcutaneous truncal fat (android or "apple-shaped" distribution) than in those with excess gluteofemoral fat (gynoid or "pear-shaped" distribution), and the risk for diabetes, hypertension, dyslipidemia, and ischemic heart disease is greater in the former group (35–42). Waist circumference is often used as a surrogate marker for abdominal obesity because it is correlated with abdominal fat mass. Waist circumferences of 102 cm (40 in.) in men and 88 cm (35 in.) in women correspond to the approximately 95th percentiles of waist circumferences in the United States (43), and waist circumferences above these values are associated with an increased disease risk.

Weight Gain during Adulthood

Weight gain of more than 5 kg after ages 18 to 20 increases obesity-related disease risk in both men and women (42). Unfortunately, this risk factor applies even in lean adults.

State of Fitness

Subjects with better oxygen consumption during exercise had lower rates of diabetes and cardiovascular mortality across a range of body weight values (44–47).

Ethnic Background

At the same BMI values as Caucasians, Asian-Pacific populations are at increased risk for the development of diabetes and cardiovascular disease (48–50).

RECOMMENDED WEIGHT

To interpret energy balance or weight change, other measurements of recommended body size have been used. For the application or interpretation of such tables, it is important to emphasize the following:

1. The use of terms such as "recommended" or "desirable" weight implies that we know what the criteria for normal or optimal weight should be. We do not, and no uniform agreement has been reached on otherwise arbitrary definitions.
2. The so-called "normal" distribution of weight in adults gradually increases with age. A consensus exists that this increment is not a "normal," healthful effect of aging but rather the potentially detrimental consequence of inactivity and loss of lean body mass with aging.
3. Total weight alone does not permit an estimate of body composition (i.e., how much fat and how much lean tissue are present). A person can be overweight but not overly fat. No convenient "field" method is available for reliably determining a person's body composition.

Weight Tables for Children

Population reference values for the weights of American infants and children, recently revised by the National Center for Health Statistics, can be downloaded from the Centers for Disease Control and Prevention website (51). It is very important to realize that these weight charts are not the true current weight distributions of American children 6 years of age or older. The height data at all ages and the weight data for infants and children below the age of 6 years are the most currently available. However, because of the increasing prevalence of overweight children, the advisory group that developed the current tables chose to exclude weight data from the most recent, Third National Health and Nutrition Examination Survey and use earlier, age-normalized weight values for children 6 years of age or older (52).

Weight Tables for Adults

Many commonly used tables for desirable adult weights were derived from data compiled by the Society of Actuaries and Association of Life Insurance Medical Directors (53). It is important to realize that these tables refer to weights at ages 25 to 29 that were associated with minimal mortality rates at later ages. It is also important to realize that the subjects were not representative of the population as a whole but, rather, were self-selected from persons eligible to be insured, were largely Caucasian, were predominantly from the middle or upper class, and tended to be healthier and weigh less than the general population. Further, they were weighed in their clothes with their shoes on. There is no reason to continue to use these tables today, and the statistics from which they were derived cannot be relied on to provide advice about healthy weights for all adults.

Adults should use currently available BMI charts derived from very large, representative data sets to determine their healthy or desirable weight ranges. These tables and corresponding BMI calculators are widely available on the Web.

PATHOGENESIS OF OBESITY

Genetic, endocrine, neurologic, psychologic, behavioral, developmental, and environmental factors are all involved in the pathogenesis of obesity to differing degrees among

different individuals. The factors contributing to obesity in a specific individual may be difficult to define, but it is clear that obesity is not a single disease but rather a heterogeneous group of disorders, each of which is manifested by the phenotypic expression of excess body fat.

Genetics

Genes clearly influence the development of body size, and heredity plays a definite role in human obesity (54–67). If neither parent is obese, the offspring have a 10% chance of becoming obese. Having one obese parent increases the risk for obesity to 40%. If both parents are obese, the risk rises to 80%. The roles of heredity and childhood environment have been separated by studies of adopted children with obese biologic parents. The incidence of obesity is higher in children with obese biologic parents and normal-weight adoptive parents than in children with normal-weight biologic parents and normal-weight adoptive parents, so that a role for heredity in human obesity is indicated. Furthermore, convincing evidence of the importance of genetic factors in the pathogenesis of obesity comes from multiple studies of monozygotic twins reared together or apart, which shows that variability in BMI is largely independent of shared environment. The data in these and other studies show that genes account for as much as 64% to 84% of the variability observed in BMI and body fat mass (54,57–59,67).

More than 200 genes are now linked with the human obesity phenotype and more than 250 quantitative trait loci for obesity-related phenotypes have been identified from more than 60 genome-wide scans (60). Genetic loci associated with obesity have been found on every chromosome except the Y chromosome (60). Further, more than 50 loci related to mendelian obesity syndromes, such as the Prader-Willi and Bardet-Biedl syndromes, have been mapped (60,61), and hundreds of individuals have been identified whose obesity is the consequence of single-gene mutations in 11 different genes (60–92) (Table 14-3).

Nonetheless, other than for defects in the melanocortin-4 receptor that appear to account for perhaps 1% of obesity in the general population and to be responsible for obesity in up to 5% of obese individuals screened (64), single-gene defects have been identified in only a very tiny number of obese people and, in population screening studies, there were no associations of the leptin or leptin receptor genes with obesity (93–95). Recently, however, genome-wide scons have identified the FTO gene as the gene possibly responsible for common variations in fat mass in the genomal population.

Further, while many investigators have attempted to find polymorphisms in genes likely to be associated with the pathophysiology of obesity, these searches have, by and large, been either unrewarding or have identified genetic polymorphisms that are responsible for only a small fraction of the variance in body weight (62,65). Thus, for example, two meta-analyses of the relationship between the $Trp^{64}Arg$ polymorphism in the β_3-adrenergic receptor

TABLE 14-3. Single-Gene Defects That Result in a Human Obesity Phenotype

Gene	Reference
Corticotropin-releasing hormone receptor-1	69
Corticotropin-releasing hormone receptor-2	69
G-protein-coupled receptor 24	70
Leptin	64, 65, 68
Leptin receptor	64, 71
Melanocortin 3 receptor	72–74
Melanocortin 4 receptor	7–85
Neurotrophic tyrosine kinase receptor type 2	65,86
Pro-opiomelanocortin	87–89
Proprotein convertase subtlisin/kexin type 1	90–91
Single-minded homolog 1	92–93

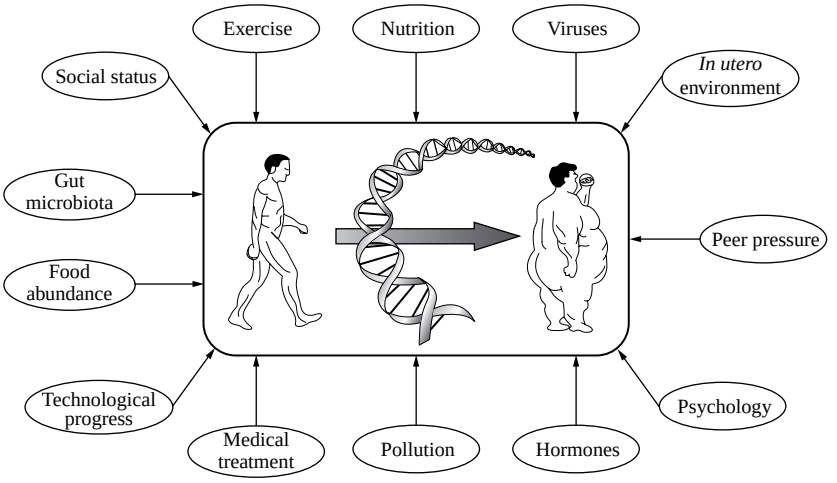


FIGURE 14-3. Gene-environment interactions that contribute to obesity. (From Mutch DM, Clément K. Unraveling the genetics of human obesity. *PLoS Genetics*, 2006;2:e188, with permission.)

gene and obesity were able to demonstrate a 0.2-6 to 0.30-BMI unit increase associated with that of the polymorphism, a difference that likely contributes little to the major increase in BMI observed over the last few decades (97,98).

Thus, it is widely recognized that obesity is a polygenic disorder, but the combinations of genes and their interactions that underlie the common forms of human obesity remain largely unknown. Furthermore, while it is critical to emphasize that the prevalence of obesity in the United States has approximately doubled in the last two decades, a period inconsequential in the context of genetic changes, this does not indicate, as is commonly stated, that genes have not contributed to the temporal increase in body weight. The evidence that genes are responsible for the majority of the variance in body weight is incontrovertible. Genes set the range of distribution of body weights within a population. An individual's position within that range is determined by the person's own genotype. This "genotypic weight" position, in turn, determines the person's relative susceptibility to those environmental factors that disturb energy balance, resulting in an increased "phenotypic weight." These factors are those that increase energy intake or decrease energy expenditure (Figure 14-3) (66,99–101).

Regulation of Food Intake

The last two decades have witnessed dramatic advances in our understanding of the biochemical and hormonal systems that regulate food intake and satiety by defining how both the gut and the adipocyte signal the brain about the status of food intake and body energy stores (102–115), firmly establishing the endocrine roles of both systems.

The Adipocyte as an Endocrine Organ (102–105,107,109,112,115) (Figure 14-4). Leptin is released from fat cells and circulates in the plasma in proportion to body fat mass, interacting within the arcuate nucleus of the hypothalamus with two principal neuronal cell types, one in which neuropeptide Y (NPY) and agouti-related (AGRP) proteins co-localize, and a second that contains pro-opiomelanocortin (POMC). Leptin signaling in the former neurons inhibits NPY and AGRP gene expression and leads to a decrease in the release of NPY and AGRP. Because these peptides normally cause an increase in food intake, inhibition of their secretion by leptin causes a decrease in food intake. In the second family of neurons, leptin signaling causes an increase in POMC gene expression

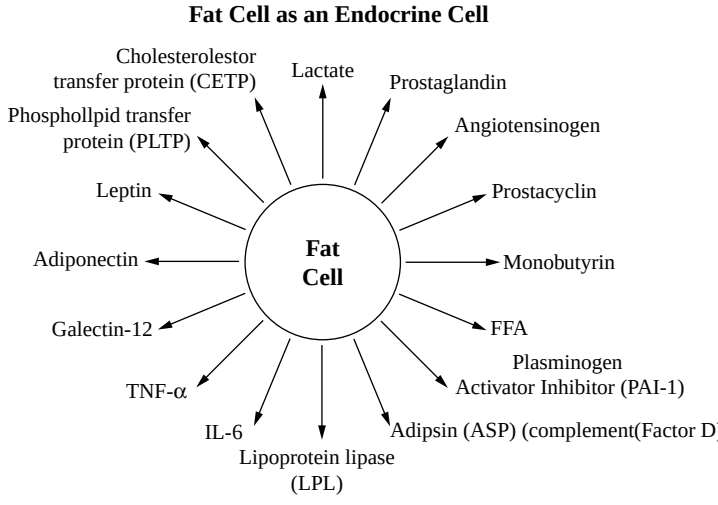


FIGURE 14-4. The adipocyte as an endocrine organ. (From Bray GA. The epidemic of obesity and changes in food intake: the Fluoride Hypothesis. *Physiol Behav* 2004;82:115, with permission.)

and, consequently, increased generation of the peptide α-MSH (α-melanocyte-stimulation hormone) that is produced from the cleavage of POMC by prohormone convertase-1. Released MSH, in turn, binds to the melanocortin-4 receptor and inhibits food intake. Other hypothalamic neuropeptides have been identified as additional mediators of the effects of leptin on appetite and satiety. These include the appetite-stimulating (orexigenic) peptides hypocretin-1 and -2, orexin A and B, and galanin, which are down-regulated by leptin or insulin, and the anorexigenic (appetite-suppressing) peptides corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), and cocaine- and amphetamine-regulated transcript (CART), which are up-regulated by leptin or insulin.

Further, it is now clear that adipose tissue also releases a variety of inflammatory mediators (Figure 14-5) that disrupt insulin action and mediate the insulin resistance that accompanies obesity, providing the link between obesity and the development of diabetes, cardiovascular disease, and the metabolic syndrome (116,117).

The Gastrointestinal Tract as an Endocrine Organ (106,108–111,113,114). Murphy and Bloom have described the gastrointestinal tract as the body's largest endocrine organ that releases more than 20 regulatory peptides (110). Ghrelin, produced predominantly by the stomach and upper small intestine, is the gut's unique orexigenic or appetite-stimulating hormone. Ghrelin is, in fact, the only hormone that we know that stimulates appetite. Ghrelin is an endogenous ligand for the growth hormone–secretagogue receptor in the brain, but it is not necessary for growth hormone secretion. Precisely how ghrelin stimulates appetite and hunger is not yet known unequivocally, but evidence suggests that it acts by stimulating NPY- and AGRP-producing neurons and inhibiting POMC- and CRH-producing neurons in the hypothalamus, with the combined net effect of stimulating feeding (109,110,114).

As opposed to the unique nature of ghrelin, the gut produces a variety of anorexigenic hormones, notably pPeptide YY (PYY), cholecystokinin (CKK), pancreatic polypeptide (PP), glucagon-like peptide-1 (GLP1), and oxyntomodulin (OXM). These hormones have a more complex variety of mechanisms of action, but PPY, GLP1, and OXM can directly inhibit NPY and AGRP neurons while stimulating POMC-producing neurons in the hypothalamus, the net effect of which is to decrease feeding (110,111,113,114) (Figure 14-6).

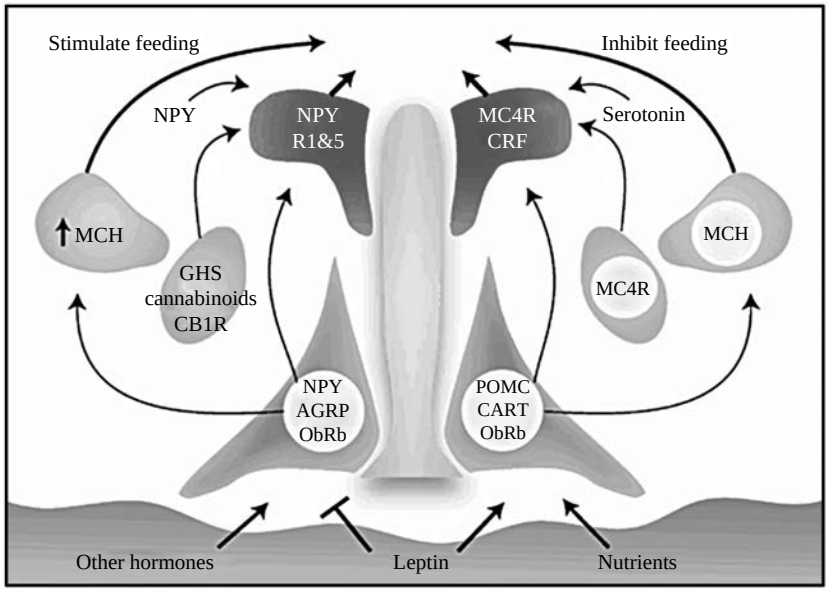


FIGURE 14-5. How the fat cell signals the brain to regulate energy balance. (From Friedman JM. Modern science versus the stigma of obesity. *Nature Med* 2004;10:563, with permission.)

Perhaps the most recent intriguing discoveries about gastrointestinal function and the development of obesity deal with the role of the gut microbiota in energy balance. In a series of elegant studies, investigators in Dr. Jeffrey Gordon's laboratory have shown that the gut microflora have the ability to extract more energy from the diet and to both increase the storage of dietary fat and reduce fat oxidation in the host (118–121). Further, in humans there is a correlation between weight loss and the composition of gut microflora, irrespective of whether weight loss was achieved by a low-fat or a low-carbohydrate diet (121).

Energy Expenditure

Energy expenditure varies considerably from person to person and resting metabolic rate varies more between individuals and families than within individuals and families on the basis of genetic determinants of energy expenditure. Likewise, there is similar evidence showing that energy intake also clusters within families, either on the basis of genes or familial environmental influences (122).

The nature of the changes in energy expenditure in obesity is well studied and the results have put to rest various myths about energy metabolism in obese individuals (123). First, basal metabolic rate, accounting for 65% to 70% of total daily energy expenditure in people who do not engage in significant physical activity, is not decreased in obese individuals. On the contrary, it is higher than that of lean people, because obese individuals have more lean body mass than lean people (123). Likewise, because they must move more weight during weight-bearing physical activities, obese individuals also expend more, not less, energy in physical activity (123). Finally, obese people have no clear evidence of abnormalities in energy expenditure following a meal or in the ability to regulate thermogenesis when adapting to changes in energy intake or environmental conditions (123). Thus, the total daily energy expenditure in obese people is greater than that in lean individuals. This fact has been confirmed repeatedly in every carefully done study measuring total daily energy expenditure in room calorimeters or using the doubly-labeled water method for

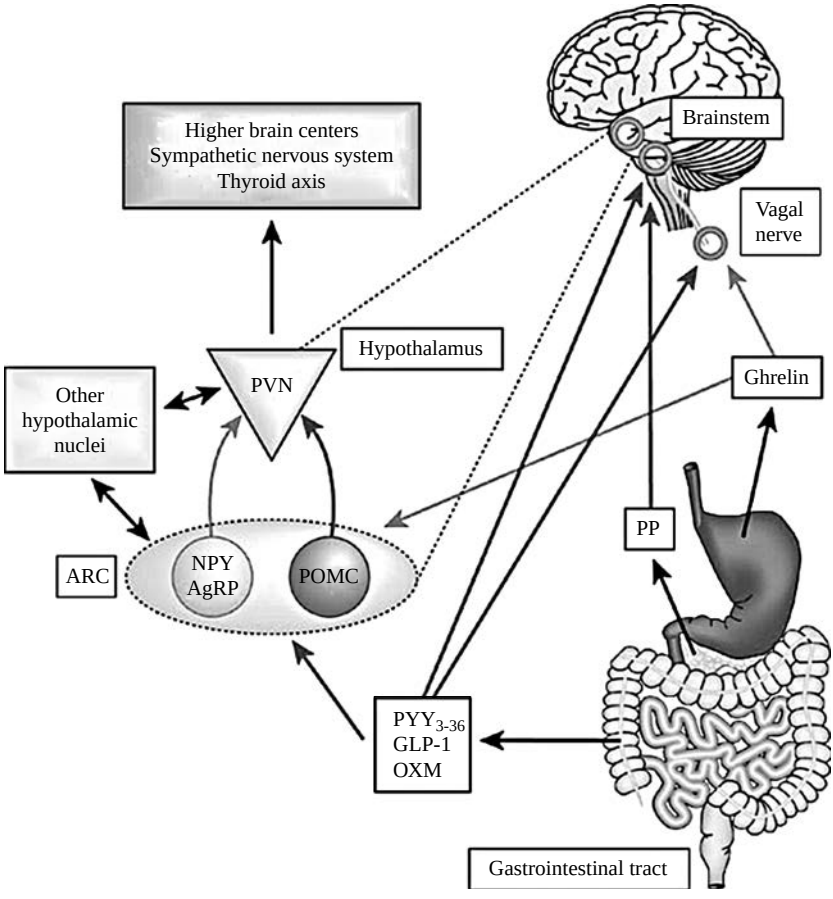


FIGURE 14-6. How the gut signals the brain to regulate appetite and satiety. (From Murphy KG, Bloom SR. Gut hormones and the regulation of energy homeostasis. *Nature*, 2006;444:854, with permission.)

determining energy expenditure in the free-living state. The consequence of this observation is likewise clear. If an obese individual is maintaining his or her body weight while his or her energy expenditure is greater than that of corresponding lean individuals, the obese person *must* have a higher dietary energy intake. In other words, there are no obese individuals who maintain their excess body weight by consuming fewer calories than lean people. Finally, irrespective of whether an individual has a more or less efficient system of energy expenditure, he or she has an energy cost of maintaining basal metabolic processes and carrying out physical activities. If calorie consumption is less than the sum of these energy costs, a person will lose weight. There are no exceptions to this basic law of energy balance. Apparent failures are invariably due to underestimating energy intake or overestimating energy expenditure.

Energy Intake and the Macronutrient Content of Foods

There is no method that is capable of accurately or precisely measuring energy intake in free-living subjects. The best approaches entail uncertainties greater than the precision

required to answer basic questions of energy balance in humans. Studies have shown repeatedly that adults tend to underestimate their energy intake, and that overweight persons tend to underestimate their dietary intake more than subjects of normal body weight. On average, the best methods for estimating energy intake underestimate actual intake by about 20% (124).

Further, when calculating energy intake, "a calorie is a calorie," irrespective of differences in dietary composition (125,126). Although there is some evidence supporting a role for high fat intakes in promoting body weight gain, the data that specific dietary components favor the development of obesity (or help prevent it) are not convincing (127–129). However, there is a significant genetic contribution to the individual variability that accompanies alterations in dietary intake (130).

Maintenance of Body Weight

It is important to realize that the energy balance system is very tightly controlled by the hormonal regulatory systems described above. Over the course of a year, an adult consumes approximately one million calories. Yet, during the course of several decades of adult life, body weight is maintained essentially constant in most people, implying an efficiency of the energy balance system of greater than 99.5%. Over the course of human history, the energy balance system has evolved to protect individuals during periods of caloric deprivation. The range of protection is largely defined by one's genotype. Therefore, when one attempts to lower one's body weight below a threshold determined by one's genetic constitution, counter-regulatory events are brought into play to return body weight to the expected range. Thus, basal metabolic rate declines when an obese person loses weight on a calorie-restricted diet. This adaptation contributes to the difficulty in maintaining weight loss. On most conventional weight-loss programs, an obese person loses weight fairly rapidly for a few weeks, and then the rate of weight loss declines markedly or even stops, even though the person still adheres to the weight-loss program. Several factors contribute to this pattern. First, the initial weight loss may involve a significant loss of tissue glycogen and protein, which is associated with loss of water. Later, most of the weight loss involves fat, and fat loss is not associated with water loss. Second, as weight declines, fat-free mass is also lost and there is less lean tissue to support, so basal metabolic rate declines concomitantly (131). Thyroid hormone function also diminishes to conserve energy loss. Taken together, these changes lead to a reduction in the rate of weight loss, and both discouragement and diminished compliance ensue. Dieters should be warned that the rate of weight loss will decrease. More importantly, when the rate of weight loss declines, a dieter should not be accused of noncompliance in the absence of strong evidence for this behavior. A major unfortunate issue that plagues all dieters is that they regain lost weight. Even though this is a well appreciated problem, the factors that are responsible for regaining lost weight are not well understood. Clearly, one factor is a gradual loss of compliance with the changes in energy intake and energy expenditure that were responsible for losing weight in the first place. However, almost certainly, a large fraction of the regained weight is the result of the tightly regulated counter regulatory system that aims to restore an individual's body weight to the range defined by the individual's genotype. The latter is not under the individual's own volitional control.

MANAGEMENT OF OBESITY

The management of obesity is difficult, and the rate of success, defined as adequate weight loss followed by a prolonged period in which the lost weight is not regained, is low. Obesity can be managed by diet, exercise, surgery, drugs, behavior modification, or combinations of these modalities. The most effective approaches employ a program of lifestyle modification that includes helping a person control his or her external food environment, thus decreasing exposure to foods and food cues, an appropriate restriction of dietary energy intake, and institution of an integrated plan of increased physical activity (132,133). Behavioral modification is an integral part of such programs, because changing

behavior is essential to changing lifestyle. The cornerstone principles of behavioral modification are

1. self-monitoring or the systematic observation and recording of food intake and physical activity behaviors in order for the patient to become more aware of the behaviors themselves and the environmental factors that influence these behaviors;
2. stimulus control or the identification and modification of environmental cues associated with overeating or limiting activity;
3. cognitive restructuring, a process by which subjects increase their awareness of their own body weight perceptions in order to institute change; and
4. tools for stress management (134).

Here, we focus primarily on diet, with the recognition that the long-term results of obesity treatment by diet alone have, on the whole, been less effective than programs that employ lifestyle modification and enhanced physical activity (135–139).

Dietary Management

A realistic goal in the dietary management of obesity is to have the patient lose 5% to 10% of body weight and then maintain this reduced weight. Ideally, one should lose weight down to one's ideal body weight, but this goal is unrealistic for most patients. Many more dieters achieve an initial significant weight loss than maintain such weight loss. In fact, 80% to 90% of dieters regain some or all lost weight. In prescribing a diet, it is important to choose one that the patient will comply with long enough to lose the necessary amount of weight. The more weight that must be lost, the longer the diet will have to be maintained and the more carefully the diet should be designed. For patients with a BMI above 35 who have demonstrated an ability to lose weight and maintain a lower weight and for whom further weight loss is advisable for medical or social reasons, treatment with pharmacologic agents should be considered.

The patient must understand that the process is long (Figure 14-7). To lose a modest amount of weight within a short period of time, patients will comply with almost any diet. However, when a large amount of weight must be lost over a long period, compliance is better when the diet is nutritionally balanced and palatable. The longer an unbalanced weight loss diet is continued, the greater the risk for the development of nutritional deficiency. Thus, it is important that markedly obese patients be placed on diets that fulfill the requirements for vitamins and minerals. Properly constructed diets in the 1,200-kcal range are nutritionally adequate without supplements. Equally important is the need for patients to establish new eating habits so that they will be able to maintain a lower weight after the desired weight loss has been achieved. This is one goal of behavior modification, as discussed earlier and also later in this chapter. A major problem with many weight loss programs is that they are designed to help patients lose weight but are not constructed so that the subjects make permanent changes in their eating habits and physical activity behaviors. In fact, many weight loss diets are so monotonous or unpalatable that it is impossible to continue them for many months. As a result, after losing weight, patients discontinue the hypocaloric diet and resume the diet that led to obesity. This is one reason for the low success rate in keeping off lost weight. Successful diet programs require an energy intake below the subject's level of energy expenditure and a level of compliance that maintains this hypocaloric intake for a period sufficiently long enough to achieve the desired amount of weight loss.

Low-Calorie, Nutritionally Balanced Diets

The most direct and reasonable approach to weight loss is a nutritionally balanced diet that is low enough in calories to result in weight loss, developed according to the principles outlined by the National Heart, Lung and Blood Institute (NHLBI) (132). The NHLBI suggests that persons who desire to lose weight should reduce their calorie intakes by 500 to 1,000 kcal per day, a decrement that will produce a weight loss of 1 to 2 pounds per week. This rate of weight loss can be achieved in women consuming a diet of 1,000 to 1,200 kcal per day and in men consuming 1,200 to 1,500 kcal daily. Many experts recommend limiting weight loss to less than 1.5 pounds per week, because an increased incidence of gall stones is seen in individuals who lose more than 1.5 pounds per week.

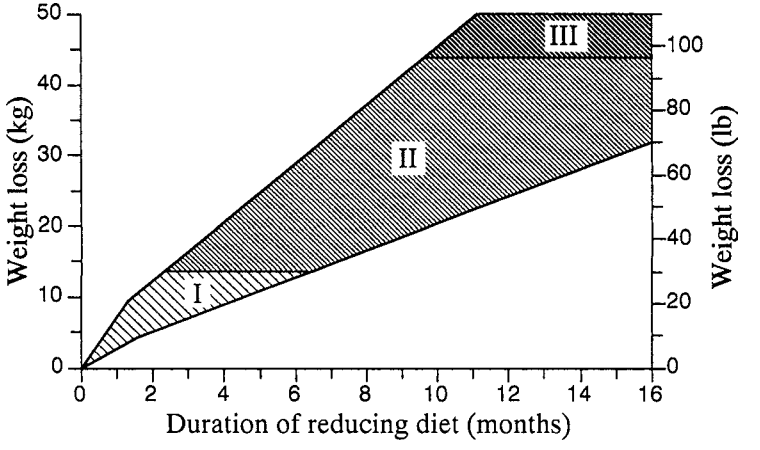


FIGURE 14-7. Duration of reducing diets calculated to achieve weight losses of approximately 75% fat and 25% fat-free tissue at acceptable rates of weight reduction. *Shaded areas* show length of treatment required for patients with grade I, II, or III obesity according to body mass index. (From Garrow JS. *Obesity and Related Diseases.* Edinburgh: Churchill-Livingstone, 1988.)

It is not particularly useful to attempt to calculate a specific caloric deficit from the subject's diet history because individuals invariably underreport their true energy intake. A representative 1,200-kcal nutritionally balanced diet is given in Table 14-4. The composition of the diet should be constructed according to the principles defined by the *Dietary Guidelines for Americans* (see Chapter 2). A balanced diet with this caloric content should supply the required amounts of proteins, vitamins, and minerals, although women may need to consume a calcium supplement to meet the recommended intake of calcium. However, even balanced diets in the range of 1,000 kcal may provide inadequate amounts of niacin, thiamine, folate, pyridoxine, iron, zinc, and calcium and diets less than 1,000 kcal must be supplemented with essential vitamins and minerals. Untrained health care providers should never prescribe diets of less than 1,000 kcal per day. Such very-low-calorie diets (VLCD) should only be used as part of a structured weight loss program monitored closely by individuals trained in the conduct and management of VLCD and, then, only used primarily as treatment for individuals who are morbidly obese (see below).

Caloric restrictions in the range of 1,200 to 1,400 kcal can be achieved by following several principles.

Eliminate or Markedly Limit Concentrated Sources of Calories. Certain foods are energy dense (high in caloric content per volume) but contribute little to the daily nutrient needs. These include potato chips, cream sauces, pastries, and doughnuts. Alcoholic beverages also have a high caloric content (168 kcal for a 12-oz beer, 172 kcal for 2 oz of whiskey). Many people consume 10% to 20% of their calories as alcoholic beverages. Eliminating alcoholic beverages without making other dietary changes leads to significant weight loss in such persons. Diets that achieve reductions in dietary energy density are associated with improved weight loss and diet quality, the latter because energy density reductions are achieved primarily by increasing fruit and vegetable intake while reducing dietary fat intake (140,141).

Reduce the Portions of Foods with Significant Caloric Content. Fats have a higher caloric content (9 kcal per g) than carbohydrates (4 kcal per g) or protein (4 kcal per g). Thus, reducing the portions of foods high in fat (meat, butter, margarine, salad oil) has a greater effect on caloric intake than reducing the portions of foods high in

TABLE 14-4. Sample Meal Plan for a 1,200-kcal Diet

Kilocalories	Exchanges	Carbohydrate (g)	Protein (g)	Fat (g)
Breakfast				
1 cup skim milk	1 nonfat milk	12	8	0
90				
1/2 cup orange juice	1 fruit	15	0	0
60				
3/4 cup corn flakes	1 bread	15	3	0
80				
1 slice white toast	1 bread	15	3	0
80				
Coffee	—	0	0	0
0				
Lunch				
2 oz chicken	2 lean meat	0	14	6
110				
2 slices white bread	2 bread	30	6	0
160				
1/2 cup tomato	1 vegetable	5	2	0
25				
1 tsp mayonnaise	1 fat	0	0	5
45				
1 apple	1 fruit	15	0	0
60				
Diet soda	—	0	0	0
0				
Dinner				
2 oz broiled beef	2 medium-fat meat	0	14	10
150				
1/2 cup carrots	1 vegetable	5	2	0
25				
1/2 cup asparagus	1 vegetable	5	2	0
25				
Lettuce	—	0	0	0
0				
1 tbs French dressing	1 fat	0	0	5
45				
1/4 cup strawberries	1 fruit	15	0	0
60				
1 plain dinner roll	1 bread	15	3	0
80				
1 cup skim milk	1 nonfat milk	12	8	0
90				
Snack				
2 graham crackers	1 bread	15	3	0
80				
Totals				
1,265		174	68	26

carbohydrates (fruits and vegetables, breads, potatoes, pasta). It is difficult to design a successful low-calorie diet if the proportion of calories coming from fat is in the range of the typical U.S. diet. It is also important to recognize that the portions of foods eaten in America have become absurdly large. In fact, "small" portions have virtually disappeared from restaurants and fast-food establishments. Even when portions are small, they are invariably larger than the portions recommended in the U.S. Department of

Agriculture MyPyramid system. The research data on energy consumption has consistently shown that people will eat more when presented with large portions that when given smaller portions.

Change the Methods of Food Preparation. The caloric content of food can be greatly affected by the method of preparation. The caloric content of fried chicken is greater than that of baked chicken. Significant calorie (and fat) reduction can be achieved simply by removing the skin from chicken. Similarly, the caloric content of French fries is much greater than the energy content of an equivalent weight of baked potato. The way food is treated at the table also affects its caloric content. The salad dressing has more calories than the salad, the gravy may have more calories than the biscuit, and the sour cream may have more calories than the potato.

Add High-Fiber, Low-Calorie Foods to the Diet. High-fiber foods frequently take longer to chew and can contribute to a sense of satiety (presumably by increasing gastric distension) without contributing much to caloric intake. High-fiber, low-calorie foods include bran, most nonstarchy vegetables (carrots, celery, green beans, asparagus, cabbage), and many fruits. The Dietary Reference Intake for fiber in adults is 14 g per 1,000 kcal per day (see Chapter 2). Most Americans consume far less, and people can easily tolerate the modest increase required to achieve the Dietary Reference Intake.

Be Aware of Calories. If weight is to be lost with a low-calorie, nutritionally balanced diet, the dieter must be aware of the caloric content of food. The dieter should be encouraged to buy and use one of the pocket calorie counters that are available at all major bookstores. Table 14-4 provides a representative 1-day meal plan for a 1,200-calorie diet, and Table 14-5 is a partial list of portion sizes that contain 100 calories (see Table 5-9 for additional food portions and their caloric content). Table 14-4 also shows how the caloric content and macronutrient composition of a meal plan can be calculated by using the exchange lists described for the diabetic diet. The diet shown contains two nonfat milk exchanges, six bread exchanges, three fruit exchanges, three vegetable exchanges, two fat exchanges, two lean meat exchanges, and two medium-fat meat exchanges. Knowing that carbohydrates and proteins contain 4 cal per g and that fats contain 9 cal per g, we can calculate the caloric distribution for this meal plan as 55% carbohydrate, 22% protein, and 18% fat.

By using the same number and distribution of exchanges, a large number of meal plans can be developed, each with the same number of calories and macronutrient distribution. These simple dietary modifications are safe and reasonable and, if followed for a long enough period of time, should lead to significant weight loss. The rate of weight loss is a function of the caloric deficit (the difference between the number of calories in the new diet and the number in the patient's original diet). Thus, a 1,200-kcal diet results in more rapid weight loss in a person who previously consumed 3,000 kcal per day (caloric deficit of 1,800 kcal per day) than in someone who previously consumed 2,000 kcal per day (caloric deficit of 800 kcal per day). For each pound of weight lost, a caloric deficit of 3,400 kcal is required, rounded off to 3,500 kcal for ease of calculation. A woman on a 1,700-kcal diet whose weight was constant on a diet of 2,200 kcal per day has a caloric deficit of 500 kcal per day or 3,500 kcal per week. On this diet, she should lose a pound a week (Table 14-6) (see Energy Balance in Chapter 5 for the derivation of 3,500 kcal per pound of body weight). This rule of thumb must be modified for some circumstances. At the beginning of a period of dieting, a mild diuresis frequently develops resulting in a more rapid weight loss than that projected by the caloric deficit. After a few weeks, the rate of weight loss becomes slower. The reason for this change in the rate of weight loss is that the basal metabolic rate and caloric cost of exercise both diminish as weight decreases. A 70-kg man jogging a mile in 9 minutes expends 18 fewer calories than an 80-kg man.

Only Use Nutritionally Sound Weight Loss Programs. Some of these programs are listed in Table 14-7. Few of the commercial weight loss programs have been subjected to unbiased studies of effectiveness (142–146) and, in general, these programs are associated with high costs, high attrition rates, and weight regain in a significant fraction of

TABLE 14-5. 100-kilocalorie Portions

Food (oz)	Portion	Weight/volume
Apple		
Fresh	1 (3-in. diameter)	8
Juice	3/4 cup	6
Pie	1/2 part (9-in. pie)	2
Sauce	1/2 cup	4
Bacon, broiled	2 slices	2/3
Banana, fresh	1 medium	3 1/2
Beans		
Baked with pork	1/3 cup	3
Lima, green, canned	3/4 cup	5
String	3 1/2 cups	14
Beef		
Consommé	10 cups	80
Corned	1 slice	1
Loin (lean)	1 slice	1 1/2
Rib (lean)	1 slice	1 1/3
Roast	1 slice	2
Sirloin steak (lean)	1 small slice	2
Tongue	2 slices	1 1/2
Beer	1/2 can	6
Biscuits, baking powder	1 (2-in. diameter)	1
Bran, wheat	1 cup	2
Bread	1 1/2 slices	1
Broccoli	3 stalks	10
Butter	2 small squares	1/2
Cabbage, fresh, cooked	2 1/2 cups	12
Cake		
Angel	1 slice (2 in.)	1 1/3
Fruit	1 small slice	1
Sponge	1 slice (2 in.)	1
Candy bar, chocolate	1 piece	2/3
Cantaloupe	1/2 melon (5-in. diameter)	15
Carrots, fresh, cooked	2 cups	10
Cauliflower, raw	3 cups	12
Celery, raw, diced	6 cups	18
Cheese		
American	Small cube	1
Cheddar	1-in. cube	1
Cottage	4 tbs	3 1/2
Sandwich, American	1/3 sandwich	4
Soufflé	1/2 cup	2
Chicken		
Broiled	1 slice	2
Roast	1 slice	2
Club sandwich	1/4 sandwich	—
Cookies		
Plain	1 medium (3-in. diameter)	1
Lady fingers	3	1
Oatmeal raisin	1	1 1/2
Corn		
Canned	1/2 cup (creamed)	4
Flakes	1 1/4 cups	1
Corned beef sandwich	1/3 sandwich	—
Crackers		
Cheese or oyster	20	1
Normal-sized	3	1
Saltines	7	1

(*continued*)

TABLE 14-5. 100-kilocalorie Portions (*Continued*)

Food (oz)	Portion	Weight/volume
Cream, heavy	2 tbs	—
Cream cheese	2 tbs	1
Cucumbers	3 whole (large)	24
Doughnuts	1/2	1
Eggs		
Raw	1 1/3	2
Boiled	1 1/3	2
Whites only	7	7 1/2
Yolk only	2	1
Flounder	1 slice	3
Frankfurter	1	1 1/2
French dressing	1 1/2 tbs	3/4
Fruit salad	1 cup	8
Grapefruit	1/2 fruit (4-in. diameter)	
Fresh	1 cup	8
Juice, canned		8
Grapes	1 large bunch (40)	5
Griddle cake	1 (4-in. diameter)	2
Haddock, cooked	2/3 fillet	5
Ham, fresh, lean	1 slice	1
Hamburger, lean	Very small patty	2
Hash, corned beef	1/4 cup	1 1/2
Ice cream	1/3 cup	2
Jam, marmalade, jellies	1 1/2 tbs	1 1/2
Lettuce	2 heads	20
Luncheon meat	1 slice	1 1/4
Macaroni, elbow, cooked	1/2 cup	2 1/2
Manhattan cocktail	1/2 glass	1 1/2
Mayonnaise	1 tbs	1/2
Milk		
Skim	1 1/4 cups	10
Whole	2/3 cup	5
Muffins	1	2
Nonfat solids	3 1/2 tbs	—
Noodles		
Soup	1 cup	8
Uncooked	1/4 cup	1
Oatmeal, cooked	3/4 cup	5
Oil, cooking or salad	4/5 tbs	1/2
Olives		
Green	16 (extra large)	—
Ripe	12	—
Onions	2 medium (2 1/2-in. diameter)	7
Oranges		
Fresh	1 large	7
Juice, fresh	1 cup	8
Marmalade	1 tbs	1
Oysters	8–12 medium	5
Peanuts, roasted	20	1/2
Peanut butter	1 tbs	1/2
Pears		
Fresh	1 large (3-in. diameter)	6
Canned	2 1/2 halves	5
Peas		
Canned	3/4 cup	3 1/2
Dried, split	2 tbs	1
Green, fresh	3/4 cup	4
Soup	1/2 cup	4

(*continued*)

TABLE 14-5. 100-kilocalorie Portions (*Continued*)

Food (oz)	Portion	Weight/volume
Peppers, green	5	12
Pickles		
Dill	6 large (1 3/4 × 4 in.)	—
Sweet	3 small (3/4 × 2 3/4 in.)	—
Pineapple		
Canned or fresh	2 slices	6
Juice	3/4 cup	6
Pizza (tomato and cheese pie)	3-in section (14-in. pie)	1 1/2
Plums, canned or fresh	4 fruits	6 1/2
Pork		
Chops, broiled	1/2 lean chop	2
Tenderloin, broiled	1/2 slice	2 1/2
Potato		
Boiled or baked	1 medium	3
Chips	8 large	1/2
Mashed, white	1/2 cup	3 1/2
Salad	1/4 cup	2
Soup	1/2 cup	4
Pretzels	2 large or 8 small	1
Prune		
Dried or fresh	4 medium	1 1/2
Juice	1/2 cup	4
Whip	1/2 cup	2 1/2
Raisins	2 tbs	1
Red wine (dry)	1 1/3 glasses	4
Rice, boiled	3/4 cup	4
Rice Krispies	3/4 cup	1
Rye bread	1 slice	1 1/2
Salami	2/3 slice	3/4
Salmon		
Fresh or canned	1/2 cup	2 1/2
Smoked	1/2 small slice	2
Shrimp	15 medium	3
Soft drinks, carbonated	1 cup	8
Spaghetti, cooked	3/4 cup	4
Spinach, cooked	2 cups	12
Split pea soup	3/4 cup	6
Squash		
Summer, boiled	3 cups	21
Winter, boiled	1 1/3 cups	9
Strawberries, fresh, no sugar	2 cups	9
Sugar		
Cubes	4 lumps	—
Granular	6 1/2 tbs	—
Powdered	2 1/2 tbs	—
Syrup, maple or corn	1 1/2 tbs	1
Tomatoes		
Fresh	3	16
Canned	2 1/6 cups	—
Juice	2 cups	16
Soup	1 cup	8
Triscuit	5 wafers	1 2/3
Turkey	1 slice	2
Veal		
Breast	1/2 slice	2
Cutlet	1/2	1 1/2
Steak	1/3	1 1/2

(*continued*)

TABLE 14-5. 100-kilocalorie Portions (*Continued*)

Food (oz)	Portion	Weight/volume
Vegetable soup	1 cup	8
Waffles	1	1 1/2
Watermelon	1 medium slice	12
Wheat bread	1 1/3 slices	1
Whitefish	1/3 portion	2
White wine (dry)	1 1/2 glasses	5
Yogurt	2/3 cup	6

TABLE 14-6. Calorie Intake Calculator

Present weight (lb)	Present daily intake (total number of calories to maintain present body weight)[a]	Daily calorie intake to lose 1 lb/week (500 kcal less per day than present daily intake)	Daily calorie intake to lose 2 lb/week (1,000 kcal less per day than present daily intake)
295	4,425	3,925	3,425
290	4,350	3,850	3,350
285	4,275	3,775	3,275
280	4,200	3,700	3,200
275	4,125	3,625	3,125
270	4,050	3,550	3,050
265	3,975	3,475	2,975
260	3,900	3,400	2,900
255	3,825	3,325	2,825
250	3,750	3,250	2,750
245	3,675	3,175	2,675
240	3,600	3,100	2,600
235	3,525	3,025	2,525
230	3,450	2,950	2,450
225	3,375	2,875	2,375
220	3,300	2,800	2,300
215	3,225	2,725	2,225
210	3,150	2,650	2,150
205	3,075	2,575	2,075
200	3,000	2,500	2,000
195	2,925	2,425	1,925
190	2,850	2,350	1,850
185	2,775	2,275	1,775
180	2,700	2,200	1,700
175	2,625	2,125	1,625
170	2,550	2,050	1,550
165	2,475	1,975	1,475
160	2,400	1,900	1,400
155	2,325	1,825	1,325
150	2,250	1,750	1,250
145	2,175	1,675	1,175
140	2,100	1,600	1,100
135	2,050	1,525	1,025
130	1,950	1,450	950
125	1,875	1,375	875

[a] Daily calorie intake to maintain present weight equals weight times 15.

TABLE 14-7. Nutritionally Sound Commercial Weight-Loss Programs

Health Management Resources (143,147)
59 Temple Place
Boston, MA 02111
www.hmrprogram.com

Jenny Craig International (143,144)
5770 Fleet St.
Carlsbad, CA 92008
www.jennycraig.com

Medifast
1145 Cronhill Dr.
Owings Mills, MD 21117
www.medifast1.com

NutriSystem, Inc.
200 Welsh Road
Horsham, PA 19044
www.nutrisystem.com

OPTIFAST (143)
Novartis Medical Nutrition
1600 Utica Ave. South
Minneapolis, MN 55416
www.optifast.com

Overeaters Anonymous
World Service Office
6075 Zenith Ct. NE
P.O. Box 44020
Rio Rancho, NM 87174-4020
www.oa.org

Take Off Pounds Sensibly (TOPS) Club (143)
4575 South 5th St.
P.O. Box 070360
Milwaukee, WI 53207-0360
www.tops.org

Weight Watchers International (143,145)
11 Madison Avenue
New York, NY 10010
www.weightwatchers.com

participants (142), although high attrition rates and the regaining of lost weight are common in *any* weight loss program, irrespective of cost. Nonetheless, commercial programs can facilitate weight loss (142–146) and it is clear that structured weight loss programs achieve better results than unstructured, self-help approaches (142,144,145).

Most commercial weight loss programs offer diets that are nutritionally balanced, and they encourage eating habits that can be maintained after the desired amount of weight has been lost. One major appeal of the balanced diet with a moderate caloric deficit is that it forms a basis for dietary habits that can be continued indefinitely and help to maintain weight at a desirable level. Nonetheless, while a balanced diet approach using a modest caloric deficit is perfectly reasonable, success rates are often low and documented maximum weight loss has only amounted to about 5%, or less, on average, although values as high as 27% have been reported (142). Since weight loss with modest caloric restriction is slow, averaging about 1 pound per week, many people fail to lose weight with a conservative approach because they do not comply with the diet for a sufficiently long period of time. The rate of weight loss is not actually slow, if one considers the caloric deficit necessary to lose 1 pound, but it appears slow compared with the dieter's expectations and with the claims of the commercial diet programs. If the dieter's expectations are realistic, the likelihood of discouragement will be lessened. Another factor contributing to poor compliance is the palatability of the food. On a balanced diet with a modest caloric deficit, a subject consumes many of the foods that were eaten before the diet was started, only in smaller portions. The foods are palatable and familiar, and the likelihood that the dieter will eat more than the diet allows is high. Thus, the issue of palatability is a two-edged sword. If the food is too palatable, the dieter is tempted to eat too much; if the food is not palatable enough, the dieter will lose enthusiasm and abandon the diet.

Advice on choosing a commercial weight-loss program can be found online from:

The National Institutes of Health, http://win.niddk.nih.gov/publications/choosing.htm; the Federal Trade Commission, www.ftc.gov/bcp/conline/pubs/health/wgtloss.pdf and www.ftc.gove/bcp/online/pubs/health/evidence.pdf; and the International Food Information Council, www.ific.org

Do Not Attempt Very-Low-Calorie Diets without Trained Professional Help. VLCDs are a proven, effective means to achieve significant weight loss in extremely obese individuals (139,145,146). However, because of the specialized nutritional needs required by individuals using these diets and because of the potential complications associated with the use of such diets, VLCDs should only be prescribed by trained professionals. Similarly, individuals who consider using VLCDs must due so only under structured supervision by trained health care professionals experienced in the use of such diets.

Other Dietary Approaches. Because of the low success rate associated with the use of a balanced diet that has a modest caloric deficit, a wide variety of other dietary approaches have been developed in an attempt to achieve better weight loss. Almost every type of dietary manipulation conceivable has been proposed as a weight loss program. Most of these approaches are based on misinformed concepts of nutrition, and a few of them are dangerous. The most popular permutations manipulate the macronutrient sources of calories (high-carbohydrate, low-fat; high-protein, low-carbohydrate; high-fat, low-carbohydrate) (Figure 14-8). The American Heart Association has identified the features of a fad diet: (a) magic or miracle foods that burn fat, (b) bizarre quantities of only one food or type of food, (c) rigid menus, (d) specific food combinations, (e) promises of rapid weight loss, (f) no recommendations for increasing physical activity, and (g) no warnings for persons with medical conditions.

Perhaps the most prevalent adjunct dietary approach today is the use of low glycemic index (GI) and glycemic load (GL) diets. These diets focus primarily on the proposed "quality" of ingested carbohydrates, rather than manipulating the absolute quantity of the ingested carbohydrates. The glycemic index is a method of classifying foods based on their potential for increasing blood sugar after ingestion (147,148). Foods with a high glycemic index produce a greater rise in blood sugar than those with a low glycemic index. The glycemic load of a food is the amount of carbohydrate consumed as the particular food multipled by the glycemic index of that food (147,148). The glycemic load of a diet is the sum of the glycemic loads of the individual foods consumed in the diet (147,148). When used for the treatment of obesity, the rationale is that a postprandial reduction in glycemia (accompanied by a corresponding reduction in pancreatic insulin response) decreases carbohydrate oxidation and fat storage and increases the oxidation of fat. Further, based on the theory that an excessive increase in blood sugar and insulin level after a meal leads to relative hypoglycemia later in the postprandial period and, consequently, an increased sensation of hunger, the use of low GI/GL diets is said to promote satiety and suppress hunger (148,149). Nonetheless, others have seriously questioned both the theory and practice of the GI/GL (150–152), and a recent randomized trial comparing the effects of a low-glycemic load and a higher-glycemic load diet on weight loss in young adults was unable to show a difference in body weight or body fat between the diet groups (153). Similarly, although not necessarily equivalent to low GI/GL diets, low-carbohydrate diets generally deliver a low GL because total carbohydrate intake is low. A recent systematic review of low-carbohydrate diets was unable to show clear evidence of improved efficacy due to the low carbohydrate content (154).

Figure 14-8 shows the macronutrient compositional differences among some popular and fad diets according to macronutrient distribution. When the distribution of calories becomes highly skewed in favor of a single macronutrient, the diet tends to become monotonous and unpalatable. As a result, the dieter's caloric intake decreases and weight is lost. Another dietary approach to weight loss is a nutritionally unbalanced diet that focuses on the consumption of large amounts of a single food (e.g., the "grapefruit" diet). These diets are also unpalatable and monotonous and so lead to short-term weight loss. A third approach is to limit food intake to a single product sold by the promoters of the diet. These products are usually liquids, which may be nutritionally balanced or unbalanced. Weight loss with these regimens may be based in part on the fact that monotony leads to a diminished consumption of energy. Nonetheless, there is no question that adherence to various popular "fad" diets can result in weight loss (155,156). The mechanisms for the effects of such diets, however, are not

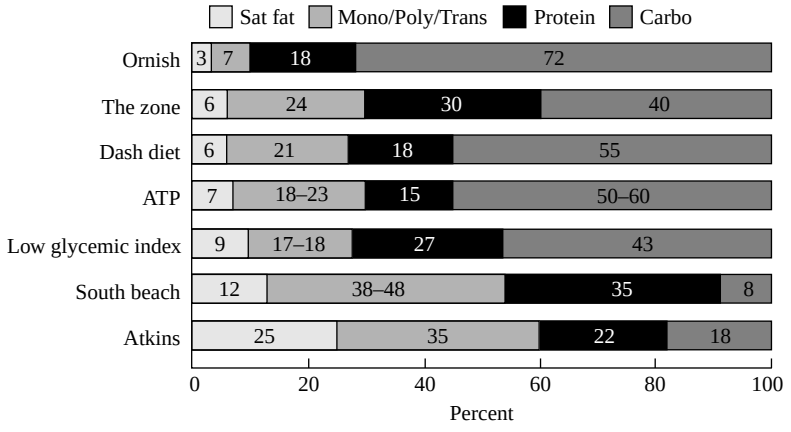


FIGURE 14-8. Macronutrient composition of various popular weight reduction diets. (From Wadden TA, Butryn ML, Wilson C. Lifestyle modification for the management of obesity. *Gastroenterology* 2007;132:2226, with permission.)

completely understood and one plausible explanation may be, simply, that certain individuals may be able to comply better and longer with the hypocaloric regimens of one type of diet than of another. In any case, even following successful weight loss following a "fad" diet, individuals invariably regain a substantial fraction of the weight lost as time progresses.

Unfortunately, many fad diets do not promote long-term lifestyle changes. Most are based on a gimmick (e.g., eating just one food or eating different foods on an unusual schedule), and many dieters find the gimmicks useful, at least in the short term. Fad diets often produce short-term weight loss because they focus an individual's behavior on his or her food intake and offer a means to try to control the food environment—common behavioral modification practices discussed above (134). However, the same "strangeness" that makes unbalanced regimens successful for short periods of time makes them unsuccessful as programs to maintain weight loss. They do not modify the dieter's eating habits or bring about other lifestyle changes that are necessary to maintain the desired reduced weight after it has been reached.

Thus, low-carbohydrate diets are associated with rapid weight loss early in the diet period. In part, this is due to the fact that the dietary regimen eliminates carbohydrates, normally the principal fractional contributor to daily energy intake. Also, at first, the body breaks down glycogen and protein to glucose to maintain the blood glucose level. The water associated with both glycogen and protein is lost from the body when they are broken down. Diuresis contributes to the large weight loss seen early in the course of low-calorie, low-carbohydrate diets. These diets also cause ketosis, which may induce anorexia and hence enhance compliance.

A detailed consumer-oriented summary and rating of diet plans and diet books can be found at www.consumerreports.org/cro/health-fitness/

Physical Activity

Energy economy is a balance between intake and expenditure. Increasing the expenditure of energy through physical activity is a cornerstone of maintaining a healthful weight and an important adjunct in losing weight. Weight loss programs that include increasing physical activity as a healthy lifestyle enhancement are invariably more successful than those that focus on dietary modification alone (133,157,158). The health benefits of regular physical activity of all kinds are extensive and extend beyond those

afforded to persons who want to lose weight. Unfortunately, though, when it comes to the arithmetic of energy expenditure, the number of calories burned during exercise is not as great as some might hope. A 70-kg man jogging a mile in 9 minutes expends only 126 additional calories (Table 14-8) [see Table 5-6 for the physical activity level (PAL) equivalents of common activities]. However, recent studies suggest that exercise may influence energy balance through more mechanisms than the direct expenditure of calories, although it must be understood that exercise enhances weight maintenance much more than it increases weight loss. Exercise has a small and probably clinically insignificant effect on preserving lean body mass. Exercise may also affect appetite; engaging in exercise shortly before a meal reduces food intake. Increased physical activity, including traditional exercise activities if possible, is thus an important adjunct to dietary therapy in the management of obesity. If incorporated into a healthful lifestyle and sustained over the long term, a combination of increased exercise and decreased caloric intake will surely promote negative energy balance more effectively than either modality alone and can also contribute to weight maintenance when hypocaloric diets are discontinued (157,158).

Behavior Modification

In persons of normal weight, eating is prompted by hunger. However, in many obese persons, eating is triggered by factors such as environment and mood rather than hunger. Some eat because they are angry or depressed, and some eat because "it is time to eat,"

TABLE 14-8. Energy Expenditure Resulting from Exercise

Activity	kcal/min/kg	kcal per half-hour	
		Reference female (5 ft 5 in., 128 lb)	Reference male (5 ft 9 in., 154 lb)
Badminton	0.097	170	205
Basketball	0.138	240	290
Canoeing	0.044	75	90
Cycling			
5.5 mph	0.064	110	135
9.4 mph	0.100	175	210
Dancing, ballroom	0.051	90	90
Field hockey	0.134	235	280
Golf	0.085	150	180
Gymnastics	0.066	115	140
Horseback riding	0.110	190	230
Jogging (9 min/mile)	0.193	335	405
Judo, karate	0.195	340	410
Running (6 min/mile)	0.252	460	535
Skiing			
Cross-country	0.143	250	300
Downhill	0.098	190	230
Squash	0.212	370	445
Swimming, slow crawl	0.128	225	270
Tennis	0.109	190	230
Volleyball	0.050	90	105
Walking (normal pace, 15 min/mile)	0.080	140	165

Adapted from Katch F, McArdle W. *Nutrition, Weight Control and Exercise.* Boston: Houghton-Mifflin, 1983.

irrespective of their own hunger or satiety signals. Many people will eat when presented with especially attractive food, even if they are not hungry. Such eating habits have led some therapists to use behavior modification as the cornerstone of obesity management. The goal of behavior modification is to make changes in the daily patterns of eating and achieve permanent alterations in lifestyle behavior that will be continued far beyond the period of weight reduction. Through behavior modification techniques, obese persons gain insights into why they start eating, how they choose what to eat, and why they stop eating. Patients then learn a method for controlling their eating behavior. Some sample techniques for altering the environment to reduce stimuli to eating are applicable to most people.

1. Eat in only one place.
2. Eat only while sitting down at a table.
3. Do not eat while watching television.
4. Eat slowly and pause between bites.
5. Make food inconspicuous when not eating.

As discussed earlier (134), most obese people who are trying to lose weight benefit from initial self-monitoring—that is, keeping a record of eating behavior: where and when they eat, what mood they are in, what they choose to eat and how much, and activities during eating. A review of this material provides insight into the events that trigger eating and how they can be modified. The self-monitoring period is followed by a period of goal setting in regard to caloric intake and physical activity and the introduction of behavioral modification strategies, including stimulus control, problem solving, cognitive restructuring, and relapse prevention (134). When practiced appropriately, behavioral modification has proved more effective than other weight loss regimens or has enhanced their effects.

Drug Therapy

The use of drugs to treat obesity depends on many factors, such as the patient's willingness to attempt lifestyle changes and ability to maintain a modest reduction in weight without drugs. Although most obese persons are not candidates for drug therapy (mostly because of a lack of willingness to make them part of a total treatment approach), candidacy for drug therapy is primarily based on the goal of improving health in individuals whose BMI is greater than 30 kg/m^2 or whose BMI is greater than 27 kg per m^2 if a comorbid condition such as hypertension, diabetes, hyperlipidemia, or the metabolic syndrome is present (159–161). Only three drugs are currently approved for the long-term treatment of overweight and obesity in the United States.

Sibutramine

This drug belongs to a class of compounds that selectively inhibit the reuptake of serotonin and norepinephrine at nerve endings. The net effect is to reduce appetite and food intake. Sibutramine has been well studied in clinical trials and is reasonably safe (159–161). Several meta-analyses have been published establishing the superiority of sibutramine treatment over that offered by nondrug interventions (159). Two-thirds of subjects taking sibutramine lose 5% of their original weight and another third lose $\geq$10% of their entry weight. Additionally, sibutramine is useful in maintaining weight loss for periods as long as two years. Lifestyle changes implemented through behavioral modification further enhance the effects of sibutramine treatment (159). Because sibutramine use is associated with a significant increase in both systolic and diastolic blood pressure, it should be used cautiously in combination with other drugs that increase blood pressure. Because of its effect on blood pressure, sibutramine is contraindicated in persons with cardiovascular disease and stroke, even though patients taking sibutramine reduce triglycerides and LDL cholesterol and show an increase in HDL cholesterol because of their reduction in body weight (159).

Orlistat

This drug inhibits lipase activity within the gastrointestinal tract and, as a consequence, leads to the increased fecal loss of fat with the net result of a decreased absorption of dietary energy from fat. It has been estimated that only about two-thirds of dietary fat intake is absorbed when a person taking orlistat is consuming a typical American diet. Meta-analyses demonstrate that subjects taking orlistat for 2 years lose three to four more kilograms of weight than subjects taking a placebo, and subjects taking orlistat for longer periods regain a small amount of weight but maintain a significant weight loss for up to 4 years (159). Since orlistat is not absorbed, it has no systemic side effects, but causes localized gastrointestinal symptoms related to fat malabsorption. These tend to subside over time, as subjects become more familiar with controlling the limits of their dietary fat intakes. One concern, however, is the possibility that some subjects taking orlistat will not meet their fat soluble vitamin requirements because of decreased absorption of these vitamins accompanying the decreased absorption of dietary fat. For this reason, many health care professionals recommend that subjects consuming orlistat also take a multivitamin supplement at bedtime.

Rimonabant

This drug is a selective cannabinoid-1 receptor blocker whose net effects are diminished appetite in the CNS and increased lipolysis and adiponectin release in the adipocyte. Three published randomized, controlled trials have demonstrated significantly increased weight loss in those individuals taking the drug compared with the placebo, differences that were maintained for up to 2 years of therapy (159).

Surgical Management

Surgical approaches to weight reduction have been popularized because they are highly effective at producing weight loss in morbidly obese individuals whose BMIs exceed 40 kg per m^2, if they have no comorbidities, or whose BMIs are greater than 35 kg per m_2 in the presence of comorbidities. As a rule, other nonsurgical interventions have had less success in producing significant weight loss in these individuals while bariatric surgery can produce weight losses in the range of 50% to 75% of initial weight (162–166), decrements rarely achieved by medical management alone, with notable exceptions (139). Surgery should be used only in patients with documented failure on medical weight loss programs. Liposuction, a less invasive alternative to bariatric surgical procedures, is only capable of removing limited quantities of fat, and the procedure is more cosmetically than medically beneficial for anyone with significant obesity. In fact, liposuction does not significantly improve insulin resistance or the other metabolic abnormalities associated with obesity (167).

References

1. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation on Obesity.* Geneva: World Health Organization, 1998. http://www.who.int/bmi/index.jsp?introPage=intro_3.html
2. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA*. 2006;295:1549.
3. Ogden CL, Yanovski SZ, Carroll MD, et al. The epidemiology of obesity. *Gastroenterology*. 2007;132:2087.
4. Troiano RP, Frongillo EA Jr, Sobal J, et al. The relationship between body weight and mortality: a quantitative analysis of combined information from existing studies. *Int J Obes*. 1996;20:63.
5. Allison DB, Zhu SK, Plankey M, et al. Differential associations of body mass index and adiposity with all-cause mortality among men in the first and second National Health and Nutrition Examination Surveys (NHANES I and NHANES II) follow-up studies. *Int J Obes*. 2002;26:410.
6. Calle EE, Thun MJ, Petrelli JM. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med*. 1999;341:1097.
7. Flegal KM. Epidemiologic aspects of overweight and obesity in the United States. *Physiol Behav*. 2005;86:599.
8. Flegal KM. Excess deaths associated with obesity: Cause and effect. *Int J Obes*. 2006;30:1171.
9. Flegal KM, Graubard BI, Williamson DF, et al. Excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2005;293:1861.

10. Fontaine KR, Redden DT, Wang C, et al. Years of life lost due to obesity. *JAMA*. 2003;289:187.
11. Gregg EW, Cheng YJ, Cadwell BL, et al. Secular trends in cardiovascular disease risk factors according to body mass index in US adults. *JAMA*. 2005;293:1868.
12. Gu D, He J, Duan X, et al. Body weight and mortality among men and women in China. *JAMA*. 2006;295:776.
13. Hu FB, Willett WC, Li T, et al. Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med*. 2004;351:2694.
14. Jee SH, Sull JW, Park J, et al. Body-mass index and mortality in Korean men and women. *N Engl J Med*. 2006;355:779.
15. McGee DL, Diverse Populations Collaboration. Body mass index and mortality: A meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol*. 2005;15:87.
16. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *N Engl J Med*. 1995;333:677.
17. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: A systemic review of cohort studies. *Lancet*. 2006;368:666.
18. Schulte H, Cullen P, Assmann G. Obesity, mortality and cardiovascular disease in the Münster Heart Study (PROCAM). *Atherosclerosis*. 1999;144:199.
19. Song Y-M, Ha M, Sung J. Body mass index and mortality in middle-aged Korean women. *Ann Epidemiol*. 2007;17:556.
20. Thomas F, Bean K, Pannier B, et al. Cardiovascular mortality in overweight subjects: The key role of associated risk factors. *Hypertension*. 2005;46:654.
21. Yusuf S, Hawken S, Ôunpuu S, et al. Obesity and the risk of myocardial infarction in 27000 participants from 52 countries: A case-control study. *Lancet*. 2005;366:1640.
22. Zhu S, Heo M, Plankey M, et al. Associations of body mass index and anthropometric indicators of fat mass and fat free mass with all-cause mortality among women in the First and Second National Health and Nutrition Examination Surveys Follow-up Studies. *Ann Epidemiol*. 2003;13:286.
23. Kruger DJ, Nesse RM. Sexual selection and the male:female mortality ratio. *Evol Psychol*. 2004;2:66.
24. Jha P, Peto R, Zatonski W, et al. Social inequalities in male mortality, and in male mortality from smoking: Indirect estimation from national death rates in England and Wales, Poland, and North America. *Lancet*. 2006;368:367.
25. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med*. 2007;356:2388-2398.
26. Heo M, Allison DB, Faith MS, et al. Obesity and quality of life: Mediating effects of pain and comorbidities. *Obes Res*. 2003;11:209.
27. McAdams MA, Van Dam RM, Hu FB. Comparison of self-reported and measured BMI as correlates of disease markers in U.S. adults. *Obesity*. 2007;15:188.
28. Nyholm M, Gullberg B, Merlo J, et al. The validity of obesity based on self-reported weight and height: Implications for population studies. *Obesity*. 2007;15:197.
29. Curtin F, Morabia A, Pichard C, et. al. Body mass index compared to dual-energy X-ray absorptiometry: evidence for a spectrum bias. *J Clin Epidemiol*. 1997;50:837.
30. Stevens J, Cai J, Pamuk ER, et al. The effect of age on the association between body mass-index and mortality. *N Engl J Med*. 1998;338:1.
31. Corrada MM, Kawas CH, Mozaffar F. Association of body mass index and weight change with all-cause mortality in the elderly. *Am J Epidemiol*. 2006;163:938.
32. Price GM, Uauy R, Breeze E, et al. Weight, shape, and mortality risk in older persons: Elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. *Am J Clin Nutr*. 2006;84:449.
33. Visscher TLS, Seidell JC, Molarius A, et al. A comparison of body mass index, waist–hip ratio and waist circumference as predictors of all-cause mortality among the elderly: The Rotterdam Study. *Int J Obes*. 2001;25:1730.
34. Zamboni M, Mazzali G, Zoico E, et al. Health consequences of obesity in the elderly: A review of four unresolved questions. *Int J Obes*. 2005;29:1011.
35. Han TS, van Leer EM, Seidell JC, et al. Waist circumference action levels in the identification of cardiovascular risk factors: prevalence study in a random sample. *Br Med J*. 1995;311:1401.
36. Lemieux S, Prud'homme D, Bouchard C, et. al. A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. *Am J Clin Nutr*. 1996;64:685.
37. Rexrode KM, Carey VJ, Hennekens CH, et al. Abdominal adiposity and coronary heart disease in women. *JAMA*. 1998:280;1843.
38. Pouliot MC, Despres JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indices of abdominal visceral adipose tissue accumulation and reduced cardiovascular risk in men and women. *Am J Cardiol*. 1994;73:460.
39. Klein S, Allison DB, Heymsfield SB, et al. Waist circumference and cardiometabolic risk: A consensus statement from Shaping America's Health: Association for Weight Management and Obesity Prevention; NAASO, The Obesity Society; the American Society for Nutrition; and the American Diabetes Association. *Am J Clin Nutr*. 2007;85:1197.

40. Després J-P, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444:881.
41. Klein S, Burke LE, Bray GA, et al. Clinical implications of obesity with specific focus on cardiovascular disease: A statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2004;110:2952.
42. Rimm EB, Stampfer MJ, Giovannucci E, et al. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older U.S. men. *Am J Epidemiol*. 1995;141:1117.
43. Flegal KM. Waist circumference of healthy men and women in the United States. *Int J Obes*. 2007; 31:1134.
44. Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr*. 1999;69:373.
45. LaMonte MJ, Blair SN. Physical activity, cardiorespiratory fitness, and adiposity: contributions to disease risk. *Curr Opin Clin Nutr Metab Care*. 2006;9:540.
46. Thompson PD, Franklin BA, Balady GJ., et. al. Exercise and acute cardiovascular events, placing risks into perspective. A scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology in collaboration with the American College of Sports Medicine. *Circulation*. 2007;115:2358.
47. Sui X, LaMonte MJ, Blair SN. Cardiorespiratory fitness and risk of nonfatal cardiovascular disease in women and men with hypertension. *Am J Hypertens*. 2007;20:608.
48. International Diabetes Institute, World Health Organization. *The Asia-Pacific Perspective: Redefining Obesity and Its Treatment*. Geneva: World Health Organization, 2000:1. Available on line at *http://www.idi.org.au/obesity_report.htm*. Accessed May 5, 2007.
49. Shiwaku K, Anuurad E, Enkhmaa B, et. al. Overweight Japanese with body mass indexes of 23.0–24.9 have higher risks for obesity-associated disorders: a comparison of Japanese and Mongolians. *Int J Obes*. 2004;28:152.
50. Chang C-J, Wu C-H, Chang C-S, et al. Low body mass index but high percent body fat in Taiwanese subjects: implications of obesity cutoffs. *Int J Obes*. 2003;27:253.
51. National Center for Health Statistics, National Health and Nutrition Examination Survey. Clinical growth charts. Available at www.cdc.gov/nchs/about/major/nhanes/growthcharts/clinical_charts.htm. Accessed May 1, 2007.
52. Department of Health and Human Services. Centers for Disease Control and Prevention. National Center for Health Statistics. 2000 CDC Growth Charts for the United States: Methods and Development. *Vital and Health Statistics*. 2002; Series 11, Number 246 [DHHS Publication No. (PHS) 2002-1696]. Available at www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf. Accessed May 1, 2007.
53. Society of Actuaries and Association of Life Insurance Medical Directors of America. *Build Study, 1979*. Chicago: Society of Actuaries, 1980.
54. Maes HHM, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. *Behav Genet*. 1997;27:325.
55. Hewett JK. The genetics of obesity: what have genetic studies told us about the environment? *Behav Genet*. 1997;27:353.
56. Allison DB, Faith MS. A proposed heuristic for communicating heritability estimates to the general public, with obesity as an example. *Behav Genet*. 1997;27:441.
57. Allison DB, Heshka S, Neale MC, et al. A genetic analysis of relative weight among 4,020 twin pairs, with an emphasis on sex effects. *Health Psychol*. 1994;4:362.
58. Allison DB, Kaprio J, Korkeila M, et al. The heritability of body mass index among an international sample of monozygotic twins reared apart. *Int J Obes Res Relat Metab Disord*. 1996;6:501.
59. Faith MS, Pietrobelli A, Nunez, et. al. Evidence for independent genetic influences on fat mass and body mass index in a pediatric twin sample. *Pediatrics*. 1999;104:61.
60. Rankinen T, Zuberi A, Chagnon YC, et. al. The human obesity gene map: the 2005 update. *Obesity*. 2006;14:529.
61. Chung WK, Leibel RL. Molecular physiology of syndromic obesities in humans. *Trends Endocrinol Metab*. 2005;16,267.
62. Clément K. Genetics of human obesity. *C R Biol*. 2006;329:608–622.
63. Farooqi IS, O'Rahilly S. Genetics of obesity in humans. *Endocrine Rev*. 2006;27:710.
64. Farooqi IS, O'Rahilly S. Monogenic obesity in humans. *Annu Rev Med*. 2005;56:443.
65. Mutch DM, Clément K. Genetics of human obesity. *Best Pract Res Clin Endocrinol Metabol*. 2006;20:647.
66. Mutch DM, Clément K. Unraveling the genetics of human obesity. *PLoS Genet*. 2006;2:e188.
67. Bell CG, Walley AJ, Froguel P. The genetics of human obesity. *Nature Rev Genet*. 2005;6:221.
68. Challis BG, Luan J, Keogh J, et al. Genetic variation in the corticotrophin-releasing factor receptors: identification of single-nucleotide polymorphisms and association studies with obesity in UK Caucasians. *Int J Obes Relat Metab Disord*. 2004;28:442.
69. Gibson WT, Pissios P, Trombly DJ, et al. Melanin-concentrating hormone receptor mutations and human obesity: functional analysis. *Obes Res*. 2004;12:743.
70. Farooqi IS, Wangensteen T, Collins S, et al. Clinical and molecular genetic spectrum of congenital deficiency of the leptin receptor. *New Engl J Med*. 2007;356:237.

71. Lee YS, Poh LK, Loke KY. A novel melanocortin 3 receptor gene (MC3R) mutation associated with severe obesity. *J Clin Endocrinol Metab*. 2002;87:1423.
72. Rached M, Buronfosse A, Begeot M, et al. Inactivation and intracellular retention of the human I183N mutated melanocortin 3 receptor associated with obesity. *Biochim Biophys Acta*. 2004;1689:229.
73. Tao YX, Segaloff DL. Functional characterization of melanocortin-3 receptor variants identify a loss-of-function mutation involving an amino acid critical for G protein-coupled receptor activation. *J Clin Endocrinol Metab*. 2004;89:3936.
74. Dubern B, Clément K, Pelloux V, et al. Mutational analysis of melanocortin-4 receptor, agouti-related protein, and α-melanocyte-stimulating hormone genes in severely obese children. *J Pediatr*. 2001; 139:204.
75. Farooqi IS, Keogh JM, Yeo GSH, et al. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N Engl J Med*. 2003;348:1085.
76. Hinney A, Hohmann S, Geller F, et al. Melanocortin-4 receptor gene: Case-control study and transmission disequilibrium test confirm that functionally relevant mutations are compatible with a major gene effect for extreme obesity. *J Clin Endocrinol Metab*. 2003;88:4258.
77. Larsen LH, Echwald SM, Sørensen TIA, et al. Prevalence of mutations and functional analyses of melanocortin 4 receptor variants identified among 750 men with juvenile-onset obesity. *J Clin Endocrinol Metab*. 2005;90:219.
78. Lubrano-Berthelier C, Dubern B, Lacorte J-M, et al. Melanocortin 4 receptor mutations in a large cohort of severely obese adults: Prevalence, functional classification, genotype-phenotype relationship, and lack of association with binge-eating. *J Clin Endocrinol Metab*. 2006;91:1811.
79. MacKenzie RG. Obesity-associated mutations in the human melanocortin-4 receptor gene. *Peptides*. 2006;27:395.
80. Vaisse C, Clement K, Durand E, et al. Melanocortin-4 receptor mutations are a frequent and heterogeneous cause of morbid obesity. *J Clin Invest*. 2000;106:253.
81. Xiang Z, Litherland SA, Sorensen NB, et al. Pharmacological characterization of 40 human melanocortin-4 receptor polymorphisms with the endogenous proopiomelanocortin-derived agonists and the agouti-related protein (AGRP) antagonist. *Biochemisty*. 2006;45:7277–7288.
82. Cone RD. Haploinsufficiency of the melanocortin-4 receptor: part of a thrifty genotype? *J Clin Invest*. 2000;106:185.
83. Farooqi, IS, Yeo GSH, Keogh JM. Dominant and recessive inheritance of morbid obesity associated with melanocortin-4-receptor deficiency. *J Clin Invest*. 2000;106:271.
84. Kublaoui BM, Zinn AR. *MC4R* Mutations – Weight before screening! *J Clin Endocrinol Metab*. 2006; 91:1671.
85. Yeo GS, Connie Hung CC, Rochford J, et. al. A de novo mutation affecting human TrkB associated with severe obesity and developmental delay. *Nat Neurosci*. 2004;7:1187.
86. Challis BG, Pritchard LE, Creemers JW, et al. A missense mutation disrupting a dibasic prohormone processing site in pro-opiomelanocortin (POMC) increases susceptibility to early-onset obesity through a novel molecular mechanism. *Hum Mol Genet*. 2002;11:1997.
87. Krude H, Biebermann H, Luck W, et al. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by *POMC* mutations in humans. *Nature Genet*. 1998;19:155.
88. Krude H, Biebermann H, Schnabel D, et al. Obesity due to proopiomelanocortin deficiency: Three new cases and treatment trials with thyroid hormone and ACTH4-10. *J Clin Endocrinol Metab*. 2003;88:4633.
89. Jackson RS, Creemers JW, Farooqi IS, et al. Small-intestinal dysfunction accompanies the complex endocrinopathy of human proprotein convertase 1 deficiency. *J Clin Invest*. 2003;112:1550.
90. Jackson RS, Creemers JW, Ohagi S, et al. Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. *Nat Genet*. 1997;16:303.
91. Faivre L, Cormier-Daire V, Lapierre JM, et al. Deletion of the SIM1 gene (6q16.2) in a patient with a Prader-Willi-like phenotype. *J Med Genet*. 2002;39:594. Erratum in *J Med Genet*. 2004;41:320.
92. Holder JL Jr, Butte NF, Zinn AR. Profound obesity associated with a balanced translocation that disrupts the SIM1 gene. *Hum Mol Gene*. 2000;9:101.
93. Heo M, Leibel RL, Boyer BB, et al. Pooling analysis of genetic data: The association of leptin receptor (*LEPR*) polymorphisms with variables related to human adiposity. *Genetics*. 2001;159:1163.
94. Heo M, Leibel RL, Fontaine KR, et al. A meta-analytic investigation of linkage and association of common leptin receptor (*LEPR*) polymorphisms with body mass index and waist circumference. *Int J Obes*. 2002;26:640.
95. Paracchini V, Pedotti P, Taioli E. Human genome epidemiology (HuGE) review: Genetics of leptin and obesity: A HuGE review. *Am J Epidemiol*. 2005;162:101.
96. TM Frayling. Genome-wide association studies provide new insights into type 2 diabetes aetiology. Nat Rev Genet. 2007;8:152.
97. Fujisawa T, Ikegami H, Kawaguchi Y, et al. Meta-analysis of the association of $Trp^{64}Arg$ polymorphism of β_3-adrenergic receptor gene with body mass index. *J Clin Endocrinol Metab*. 1998;83:2441.
98. Kurokawa N, Nakai K, Kameo S, et al. Association of BMI with the β3-adrenergic receptor gene polymorphism in Japanese: Meta-analysis. *Obesity Res*. 2001;9:741.

99. Faith MS, Fontaine KR, Baskin ML, et al. Toward the reduction of population obesity: Macrolevel environmental approaches to the problems of food, eating, and obesity. *Psych Bull*. 2007;133:205.
100. Keith SW, Redden DT, Katzmarzyk PT, et al. Putative contributors to the secular increase in obesity: Exploring the roads less traveled. *Int J Obes*. 2006;30:1585.
101. Hill JO, Peters JC, Wyatt HR. The role of public policy in treating the epidemic of global obesity. *Clin Pharmacol Ther*. 2007;81:772.
102. Schwartz MW, Woods SC, Porte D Jr, et al. Central nervous system control of food intake. *Nature*. 2000;404:661.
103. Friedman JM. The function of leptin in nutrition, weight, and physiology. *Nutr Rev*. 2002;60:S1.
104. Friedman JM. Modern science versus the stigma of obesity. *Nature Med*. 2004;10:563.
105. Montez JM, Soukas A, Asilmaz E, et al. Acute leptin deficiency, leptin resistance, and the physiologic response to leptin withdrawal. *Proc Natl Acad Sci USA*. 2005;102:2537.
106. Korner J, Leibel RL. To eat or not to eat – How the gut talks to the brain. *N Engl J Med*. 2003;349:926.
107. Adan RAH, Tiesjema B, Hillebrand JJG, et al. The MC4 receptor and control of appetite. *Brit J Pharmacol*. 2006;149:815.
108. Bloom S. Hormonal regulation of appetite. *Obesity Rev*. 2007;8(Suppl. 1):63.
109. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: A review. *Obesity Rev*. 2007;8:21.
110. Murphy KG, Bloom SR. Gut hormones and the regulation of energy homeostasis. *Nature*. 2006;444:854.
111. Murphy KG, Dhillo WS, Bloom SR. Gut peptides in the regulation of food intake and energy homeostasis. *Endocrine Rev*. 2006;27:719.
112. Rosen ED, Spiegelman BM. Adipocytes as regulators of energy balance and glucose homeostasis. *Nature*. 2006;444:847.
113. Cummings DE, Overduin J. Gastrointestinal regulation of food intake. *J Clin Invest*. 2007;117:13.
114. Wren AM, Bloom SR. Gut hormones and appetite control. *Gastroenterology*. 2007;132:2116.
115. Bray GA. The epidemic of obesity and changes in food intake: the Fluoride Hypothesis. *Physiol Behav*. 2004;82:115.
116. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444:860.
117. Van Gaal LF, Mertens IL, DeBlock CE. Mechanisms linking obesity with cardiovascular disease. *Nature*. 2006;444:875.
118. Bäckhed F, Manchester JK, Semenkovich CF, et al. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci USA*. 2007;104:979.
119. Bajzer M, Seeley RJ. Obesity and gut flora. *Nature*. 2006;444:21.
120. Turnbaugh PJ, Ley RE, Mahowald MA, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006;444:1027.
121. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*. 2006;444:1022.
122. Faith MS, Keller KL, Johnson SL, et al. Familial aggregation of energy intake in children. *Am J Clin Nutr*. 2004;79:844.
123. Prentice A. Are defects in energy expenditure involved in the causation of obesity? *Obes Rev*. 2007;8(suppl.1):89.
124. Travulsi J, Schoeller DA. Evaluation of dietary assessment instruments against doubly labeled water, a biomarker of habitual energy intake. *Am J Physiol Endocrinol Metab*. 2001;281:E891.
125. Bucholz AV, Schoeller DA. Is a calorie a calorie? *Am J Clin Nutr*. 2004;79 (suppl):899S.
126. Leibel RL, Hirsch J, Appel BE, et al. Energy intake required to maintain body weight is not affected by wide variation in diet composition. *Am J Clin Nutr*. 1992;55:350.
127. Jebb SA. Dietary determinants of obesity. *Obes Rev*. 2007;8 (Suppl 1):93.
128. Bray G, Popkin BM. Dietary fat intake does affect obesity! *Am J Clin Nutr*. 1998;68:1157.
129. Willett WC. Dietary fat and obesity: An unconvincing relation. *Am J Clin Nutr*. 1998;68:1149.
130. Pérusse L, Bouchard C. Gene-diet interactions in obesity. *Am J Clin Nutr*. 2000;72(Suppl):1285S.
131. Chaston TB, Dixon JB, O'Brien PE. Changes in fat-free mass during significant weight loss: a systematic review. *Int J Obes*. 2007;31:743.
132. National Heart, Lung and Blood Institute (NHLBI) and the North American Association for the Study of Obesity (NAASO). The practical guide: Identification, evaluation, and treatment of overweight and obesity in adults. Bethesda, MD: National Institutes of Health, 2000. Available at http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_c.pdf
133. Wadden TA, Butryn ML, Wilson C. Lifestyle modification for the management of obesity. *Gastroenterology*. 2007;132:2226.
134. Poston WSC, Foreyt JP. Successful management of the obese patient. *Am Fam Physician*. 2000;61:3615.
135. Ayyad C, Anderson T. Long-term efficacy of dietary treatment of obesity: A systematic review of studies published between 1931 and 1999. *Obesity Rev*. 2000;1:113.
136. Anderson JW, Konz EC, Frederich RC, et al. Long-term weight-loss maintenance: A meta-analysis of U.S. studies. *Am J Clin Nutr*. 2001;74:579.

137. Curioni CC, Lourenço PM. Long-term weight loss after diet and exercise: a systematic review. *Int J Obes.* 2005;29:1168.
138. Norris SL, Zhang X, Avenell A, et al. Long-term effectiveness of lifestyle and behavioral weight loss interventions in adults with Type 2 diabetes: A meta-analysis. *Am J Med.* 2004;117:762.
139. Anderson JW, Conley SB, Nicholas AS. One hundred-pound weight losses with an intensive behavioral program: changes in risk factors in 118 patients with long-term follow-up. *Am J Clin Nutr.* 2007;86:301.
140. Ledikwe JH, Rolls BJ, Smiciklas-Wright H, et al. Reductions in dietary energy density are associated with weight loss in overweight and obese participants in the PREMIER trial. *Am J Clin Nutr.* 2007; 85:1212.
141. Ello-Martin JA, Roe LS, Ledikwe H, et al. Dietary energy density in the treatment of obesity: a year-long trial comparing 2 weight-loss diets. *Am J Clin Nutr.* 2007;85:1465.
142. Tsai AD, Wadden TA. Systematic review: An evaluation of major commercial weight loss programs in the United States. *Ann Intern Med.* 2005;142:56.
143. Rock CL, Pakiz B, Flatt SW, et al. Randomized trial of a multifaceted commercial weight loss program. *Obesity.* 2007;15:939.
144. Heshka A, Greenway F, Anderson JW, et al. Self-help weight loss versus a structured commercial program after 26 weeks: A randomized controlled study. *Am J Med.* 2000;109:282.
145. Anderson JW, Luan J, Høie LH. Structured weight-loss programs: meta-analysis of weight loss at 24 weeks and assessment of effects of intervention intensity. *Adv Ther.* 2004;21:61.
146. Anderson JW, Vichitbandara S, Qian W, et al. Long-term weight maintenance after an intensive weight-loss program. *J Am Coll Nutr.* 1999:18:620.
147. Aston LM. Glycaemic index and metabolic disease risk. *Proc Nutr Soc.* 2006;65:125.
148. McMillan-Price J, Brand-Miller J. Low-glycaemic index diets and body weight regulation. *Int J Obes.* 2006;30:540.
149. Ludwig DS. Clinical update: the low-glycemic-index diet. *Lancet.* 2007;369:890.
150. Flint A, Møller BK, Raben A, et al. Glycemic and insulinemic responses as determinants of appetite in humans. *Am J Clin Nutr.* 2006;84:1365.
151. Sloth B, Astrup A. Low glycemic index diets and body weight. *Int J Obes.* 2006;30:S47.
152. Pi-Sunyer FX. Glycemic index and disease. *Am J Clin Nutr.* 2002;76:290S.
153. Ebbeling CB, Leidig MM, Feldman HA, et al. Effects of a low-glycemic load vs low-fat diet in obese young adults: A randomized trial. *JAMA.* 2007;297:2092.
154. Bravata DM, Sanders L, Huang J, et al. Efficacy and safety of low-carbohydrate diets: A systematic review. *JAMA.* 2003;289:1837.
155. Gardner CD, Kiazand A, Alhassan S, et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women. The A to Z weight loss study: A randomized trial. *JAMA.* 2007;297:969.
156. Foster GD, Wyatt JR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Eng J Med.* 2003;348:2082.
157. Fogelholm M, Kukkonen-Harjula K. Does physical activity prevent weight gain–a systematic review. *Obesity Rev.* 2000;1:95.
158. Catenacci VA, Wyatt HR. The role of physical activity in producing and maintaining weight loss. *Nat Clin Pract Endocrinol Metab.* 2007;3:518.
159. Bray GA, Ryan DH. Drug treatment of the overweight patient. *Gastroenterology.* 2007;132;2239.
160. Bray GA. A concise review of the therapeutics of obesity. *Nutrition.* 2000;16:953.
161. Bray GA, Tartaglia LA. Medicinal strategies in the treatment of obesity. *Nature.* 2000;404:672.
162. Elder KE, Wolfe BM. Bariatric surgery: A review of procedures and outcomes. *Gastroenterology.* 2007;132:2253.
163. Leslie D, Kellog TA, Ikramuddin S. Bariatric surgery primer for the internist: Keys to surgical consultation. *Med Clin N Am.* 2007;91:353.
164. Bennett JM, Mehta S, Rhodes M. Surgery for morbid obesity. *Postgrad Med J.* 207;83:8.
165. DeMaria EJ. Bariatric surgery for morbid obesity. *N Engl J Med.* 2007;356:21.
166. O'Brien PE, McPhail T, Chaston TB, et al. Systematic review of medium-term weight loss after bariatric surgery. *Obes Surg.* 2006;16:1032.
167. Klein S, Fontana L, Young VL, et al. Absence of an effect of liposuction on insulin action and risk of factors for coronary heart disease. *N Engl J Med.* 2004;350:25.

15 NUTRITIONAL CONSIDERATIONS IN CHRONIC WASTING DISEASES (CANCER, AIDS)

GENERAL CONSIDERATIONS

There are two roles for nutrition in the management of chronic diseases; first, to prevent the disease, and second, to manage it once it is established. The first approach tries to take advantage of epidemiologic dietary associations, especially when the etiology is complex or unknown. These studies lead to prospective intervention studies, but these may not be equivalent to the diet itself or studied in patients who manifest nutritional deficiencies that may have influenced the original epidemiologic association. The second approach is usually focused on stimulating food intake of a balanced diet and reversing any micronutrient deficiencies that develop on the basis of an inadequate intake of food.

There are multiple problems in trying to develop a reasonable evidence base for studies of diet. It is unusual for randomized studies of diet to be accomplished, and when they are, it is not usual for only a single component to be altered. Meta-analyses are often used to "settle" the issue, but in many cases they are not suitable to do so, either because the entry criteria do not allow inclusion of all the "relevant" papers, or because meta-analyses were designed in part to demonstrate areas of uncertainty, not to finalize clinical decisions. These problems are highlighted by two examples. In the first two, Cochrane systematic reviews on nutrition in cardiovascular disease reached largely negative conclusions that have not been endorsed or adopted by expert committees (1). This result may have been complicated by bias on the part of the expert committees, but nonetheless, the results of the meta-analyses have not yet been accepted.

In the second example, large prospective studies as part of the Women's Health Initiative have led to disappointment about nutritional intervention for all patients with breast cancer (2), colon cancer (3), and osteoporosis (4). Dietary modification did significantly reduce the risk of invasive breast cancer when the tumor was positive for estrogen receptor and negative for progesterone receptor. Although calcium and vitamin D supplementation did achieve a modest improvement in bone mineral density but without a change in fracture rates, this result was obtained in patients allowed to take at least the DRI for those nutrients. It seems quite possible that patients who were deficient in either nutrient in their diet and/or body stores might have shown a change in fracture rates. Nonetheless, these are examples of well-designed and large studies that demonstrate how difficult it is to document a benefit of "standard" dietary programs across an unselected population.

The above discussion might suggest that providing a defined diet or dietary supplements may not be useful. The value of providing only dietary advice as opposed to advice plus oral nutritional supplements has been reviewed (5). Sixteen trials in patients with illness-related malnutrition were examined, showing that provision of oral supplements leads to more energy intake and more weight gain. Once again, however, this systematic review was not designed to provide definitive answers, but forms the background to large interventional trials.

CANCER

Dietary Guidelines to Minimize Cancer Risk

Much epidemiologic evidence is available to suggest that environmental and dietary factors play a role in the development of carcinomas in a variety of organs (6–8). Individual dietary

components have been examined as part of an effort to compile recommendations for reducing the risk for cancer (Table 15-1). All reports suggest increasing one's intake of fruits, vegetables, and grains and cereals; decreasing one's intake of fatty meats, fats and oils, saturated fats, and refined sugars; and avoiding excessive salt. All reports also suggest maintaining a healthful body weight, engaging in physical activity, and limiting one's intake of alcohol to less than two drinks a day for men, or one for women.

The National Research Council of the National Academy of Sciences concluded that the human diet contains anticarcinogens and protective factors, most of which have not been identified. It also contains carcinogens. The precise role of diet in reducing cancer risk is poorly defined, but 30% of cancers may be affected. The recommendations for a prudent diet are included in the reports of the Council (6,8). The recommendations are not novel, and their effectiveness has never been prospectively demonstrated (2,3). There were trends suggesting protection in the study with the low-fat diet for breast cancer if the patients had been followed up for longer than 6 years (2). However, the existing recommendations are sensible guidelines for sound nutrition, and their use can certainly be encouraged (see below and the sections on folate and vitamins C, A, and E in Chapter 6).

Although altering many aspects of the diet at the same time would make the most sense for cancer prevention, such an intervention is not as practical as changing a single component or adding a specific supplement. However, there are some suggestions that such a global approach may be useful. In the Lyon Diet Heart Study, prospective use of a Mediterranean-type diet (more bread and cereals, more fresh fruit and vegetables, more legumes and fish, less beef and pork, no butter and cream, and replacement with an experimental canola oil margarine) was associated with a reduced cancer death rate in comparison with the step 1 American Heart Association prudent diet (9). Nearly 600 patients with colonic adenomas (part of the European Cancer Prevention [ECP] Intervention Study of calcium and fiber supplementation) completed a dietary questionnaire that identified three patterns: Mediterranean, sweets and snacks, and high fat and proteins (10). In women, the Mediterranean pattern diet had high consumption of olive oil, vegetables, fruits, fish, and lean meat, and had a reduced adenoma incidence. A review of over 12,000 cases of cancer in Northern Italy between 1983 and 1998 showed a lower relative risk of developing cancers in the digestive tract, breast, urinary tract, and female genital tract (11). However, there is still not enough epidemiologic evidence that change of the entire diet will be protective for cancers (12). Thus, large prospective trials are needed, especially in Mediterranean countries where delivering such a diet would be practical. The issue of the length of such a trial is important, as data on the regular use of multivitamins were protective in the Cancer Prevention Study II Nutrition Cohort of 145,260 men and women, but the use had to have occurred more than 10 years before the study began (13). If the lag time to see an effect on cancer prevention is greater than a decade, the existing studies may not be providing us with a complete data set on which to alter the general recommendations in Table 15-1.

American Cancer Society 2001 Recommendations

The American Cancer Society (ACS) Nutrition and Physical Activity Guidelines Advisory Committee updated the ACS guidelines in 2001 (14) (Table 15-2). These recommendations are more focused on cancer than the general recommendations for healthy populations, especially regarding food preparation and preservation, but the general restrictions regarding the composition of the diet are very similar.

Additional information for patients regarding diets and cancer can be obtained from the American Cancer Society, 90 Park Avenue, New York, New York 10016 (www.cancer.org), and from the American Institute for Cancer Research, Washington, DC 20069.

1. **Reduce intake of dietary fat (saturated and unsaturated) from 40% to 30% of total calories.** The evidence for this recommendation is twofold. First, an increased intake of fat is correlated with an increased incidence of cancer of the breast, colon, and prostate. However, a low-cholesterol diet is not the same thing as a low-fat diet because the total

TABLE 15-1. Recommendations to Modify Dietary Components Associated with Reducing the Risk of Cancer (1989–2005)[a]

Report	Veg/fruit (servings/day)	Starch/grains (servings/day)	Meat (servings/day)	Fiber (g/day)	CHO (% energy)	Fats/oils (% energy)	Sat/unsat (% energy)	Refined sugar	Salt (g/day)
U.S. NAS '89	≥5	≥6	Lean	yes	>55	<30	<10	ind	<6
WHO '90	>400 g	ind	ns	16–24	50–75	15–30	0–10	0–10	<6
U.S. DHHS '91	≥5	≥6	nc	ind	ind	<30	<10	nc	mod
CCS '92	yes	yes	nc	ind	ns	<30	ns	nc	mod
SO '93	3+	ind	↓	>16	<40	<35	<11	<10	4
ESO '94	5	6	nc	ind	ind	<30	<10	ns	6
U.S. ACS '96	5	3+	Lean	ns	nc	↓	↓	nc	ns
U.S. HR '96	>5	ind	<1/week	ns	↑ complex	no	↓ animal	↓	mod
WCRF '97	5	7	<3 oz/day	38/25 g for M/F	45–65	15–30	Limit animal fat	Limit intake	<6 g
U.S. ACS '01	5	Whole grains	Lean	ns	nc	30	Limit animal fat	nc	ns
WHO/FAO '03	>400g	Whole grain esp	ns	>25 g	55–75	15–30	<10 S, <1 trans, 6–10 PUFA	<10	5–6 iodized
USDA/DHHS '05	>5, all five groups	3 whole grain	Lean meat	Fiber-rich foods	ind	25–30	<10 SFA, limit trans fat	Limit sugar and sweeteners	<2.3 (1 tsp)

ACS, American Cancer Society; CCS, Canadian Cancer Survey; DHHS, Department of Health and Human Services; ESO, European States Organization; HR, Harvard Report on Cancer Prevention; ind, restriction/increase indicated but not quantified; NAS, National Academy of Science; nc, not asked; ns, not stated; SO, Scotland; USDA/DHHS, US Dept of Agriculture/Dept of Health and Human Services: *Dietary Guidelines for Americans 2005,* Government Printing Office, Washington DC; WCRF, World Cancer Research Fund/American Institute for Cancer Research: Food, *Nutrition and the Prevention of Cancer,* Washington DC; WHO/FAO, World Health Organization: Diet, Nutrition and the Prevention of Chronic Diseases, Report of a Joint FAO/WHO Expert Consultation, WHO Technical report Series 916.

[a]The U.S. reports offer recommendations for individuals. The European reports offer percentages of population limits. Adapted from National Research Council, Commission on Life Sciences, Food and Nutrition Board, Committee on Diet and Health. *Diet and Health Implications for Reducing Chronic Disease Risk.* Washington, DC: National Academies Press, 1989, and from Kolonel L, Global Health & Environment Monitor, CECHE (Center for Communications, Health & the Environment) 2006;14:1 (www.ceche.org).

TABLE 15-2. American Cancer Society (ACS) Guidelines on Nutrition and Physical Activity for Cancer Prevention: Recommendations for Individual Choice

Eat a variety of healthful foods, with an emphasis on plant sources

Eat five or more servings of a variety of vegetables and fruits/day (e.g., 1 serving = 1 medium apple, banana, or orange; 1/2 cup of chopped, cooked, or canned fruit or vegetables; 3/4 cup of 100% fruit or vegetable juice; 1 cup of raw, leafy vegetables).
Choose whole grains in preference to processed (refined) grains and sugars (e.g., 1 serving = 1 slice of bread; 1 ounce of ready-to-eat cereal; 1/2 cup of cooked cereal, rice, or pasta).
Limit consumption of red meats to 1 serving, especially those high in fat and processed (e.g., 1 serving = 2–3 ounces of cooked, lean meat, poultry, or fish).
Choose foods that help maintain a healthful weight, avoiding calorie-dense foods and limiting portion size.

Adopt a physically active lifestyle

Adults should engage in at least moderate activity for 30–45 min or more on 5 or more days/week.
Suggested ways to reduce sedentary behavior include: using stairs rather than an elevator; walking or biking to your destination, if possible; exercising at lunch with your co-workers or family; taking a 10-min exercise break at work or home; dancing; planning active vacations; joining a sports team; using a stationary bicycle or exercise machine at home; planning your exercise routine.

Maintain a healthful weight throughout life

Balance caloric intake with physical activity.
Lose weight if currently overweight or obese.

If you drink alcoholic beverages, limit consumption

Adapted from Jacobs EJ, Connell CJ, Chao A, et al. Multivitamin use and colorectal cancer incidence in a US cohort: does timing matter? *Am J Epidemiol*. 2003;158:621.

intake of fat is not usually decreased unless a low-cholesterol diet is combined with a weight-reducing diet. Second, in animal studies, caloric restriction appears to decrease cancer risk. In humans, obesity is connected with cancer of the breast, endometrium, colon, and prostate. However, case–control and cohort studies have not provided conclusive evidence for an association between total dietary fat and breast, colorectal, or prostate cancer, but this may be related to the difficulty of measuring dietary fat and the genetic variability of populations. The low-fat intervention trial in the Women's Health Initiative (WHI) lowered fat intake from ~40% to 20% of total energy and increased vegetable and fruit consumption to ~5 servings per day, but found a lower hazard ratio among women who ingested a high-fat diet at baseline and adhered to the study diet (2). In the colorectal cancer study of the WHI, the fat intake was decreased by only ~10%, and no protection was noted. Nonetheless, current recommendations have not been altered, as decreasing fat and calorie intake still makes sense for other reasons (14). To carry out the recommendation for a reduced intake of fat, the guidelines for a low-fat diet should be followed.

- Bake, broil, or boil foods instead of frying them.
- Trim excess fat off meat or buy low-fat meats.
- Use less cooking oil, butter, margarine, salad dressing, and cream.
- Use fat substitutes when possible (e.g., nondairy creamer).

2. **Increase intake of fruits and vegetables (the antioxidant hypothesis).** The best epidemiologic evidence at present involves foods containing β-carotenes, vitamin A, and vitamin C (15–17) (Table 15-3). Most of the evidence to support a relationship between diet and cancer (or other chronic disease) prevention comes from consumption of foods, not dietary supplements. There is a substantial body of evidence that a diet rich in fruits and vegetables is important in disease prevention, yet a causal link between these factors has never been established (17). Among the antioxidants, the epidemiologic evidence for β-carotene has been the most complete. A review of carotenoid intake and lung cancer risk in North America and Europe showed that

TABLE 15-3. Epidemiologic Evidence for Associations between Diet, Lifestyle, and Cancer Prevention

Level of evidence	Decreases risk	Increases risk
Convincing	Physical activity (colorectal, breast)	Overweight/obesity (esophagus, colorectal, breast (postmenopausal), endometrium, kidney Alcohol (oral cavity, pharynx, larynx, esophagus, liver, breast Aflatoxin (liver) Salted fish, Chinese or Japanese style (nasopharynx) Tobacco (lung, oropharynx, esophagus) Sedentary life style (colorectal, breast, endometrium)
Possible	Fruits and vegetables (oral cavity, lung, esophagus, stomach, colorectum) Selenium (prostate, colorectum) Folate containing multivitamins (colorectum)	Preserved meat and red meat (colorectum) Salt preserved foods and salt itself (stomach) Very thermally hot foods and drinks (oral cavity, pharynx, esophagus) High-dose antioxidants in susceptible high-risk patients (lung, digestive system)
Insufficient	Soy components, ω-3 fatty acids, carotenoids, vitamins B_2, B_6, folate, C, D, E, calcium, zinc, nonnutrient plant components (e.g., flavonoids, isoflavones, allium compounds)	Animal fats, heterocyclic amines, polycyclic aromatic hydrocarbons, nitrosamines Sugar (stomach, colorectal)

Adapted from Williams MT, Hord NG. The role of dietary factors in cancer prevention: beyond fruits and vegetables. *Nutr Clin Pract*. 2005;20:451.

β-carotene intake was not associated with lung cancer, and only β-cryptoxanthin intake was inversely related to lung cancer (18). However, in the Polyp Prevention Trial, baseline dietary intake of α-carotene and vitamin A was inversely related to colorectal polyp recurrence in nonsmokers and nondrinkers (19). This result might be related to healthy lifestyle factors other than the diet. It is also possible that cruciferous vegetables contain other, undefined inhibitors of carcinogens. Most of the data in humans are from case–control and cohort studies showing an inverse correlation between cancer rates and dietary intake or serum vitamin levels, nearly all of them within the normal range.

Intervention trials with these vitamins have not demonstrated a protective effect to date, and in fact β-carotene increases risk of lung cancer in intervention studies (see Table 15-4) (20). Some of the data suggest prevention, but in general the data are negative, especially when specific interventions are attempted (see Chapter 6 for information on vitamins and Chapter 12 for a discussion of fiber). Some cohort studies continue to suggest a role for vitamin intake, but most do not (21–24). Even when premalignant endpoints are examined, such as colorectal polyps, the data for the role of increased fiber, prospectively provided, are negative (23). The relative risk of pooled data shows a value near unity for all interventions, but the 95% confidence intervals are very large. For esophageal cancer, where the pooled risk with β-carotene supplementation is 0.15 and apparently protective, the 95% CI were 0.01 to 3.72 (20). The addition of the antioxidants vitamin E, β-carotene, and vitamin C has

TABLE 15-4. Randomized, Controlled Nutrition Intervention Trials for Prevention of Neoplasia

Study	Patient group	Sample size	Intervention	Result
DeCosse 1989	Familial adenomatous polyposis	58	Wheat bran, vitamin C, vitamin E	No reduction in polyp number
McKeowyn-Eyssen 1994	Prior colorectal adenoma	201	Low fat + fiber 22.5 g/day	No effect
MacLennan 1995	Prior colorectal adenoma	424	Low fat, wheat bran 25 g/day, β-carotene	No overall effect
Alberts 2000	Prior colorectal adenoma	1,429	Wheat bran fiber 13.5 g/day	12% ↓, not significant
Schatzkin 2000	Prior colorectal adenoma	2,079	Low fat, fiber 18 g/day, 5–8 extra fruit and vegetable servings	No effect
Faivre 1997	Prior colorectal adenoma	655	Fiber 3.8 g/day vs calcium	Significant 67% ↓ with fiber, 34% ↓ with calcium, not significant
Beresford 2006, Prentice 2006	Women's Health Initiative	48,835	Fat intake ↓ by ~10%, ↑ fruit, veg, grain	No effect on invasive colorectal or breast cancer
Wactawski-Wende J 2006	Women's Health Initiative, post-menopausal	36,282	Calcium 1,000 mg + 400 IU vitamin D/day	No effect on colorectal cancer
ATBC 1994	Male smokers in Finland	29,133	β-carotene 20 mg + vitamin E 50 mg/day	↑ risk of lung cancer
Albanes 1996	Male and female smokers in the U.S. (CARET study)	32,568	β-carotene 30 mg or retinyl palmitate 25,000 IU	↑ risk of lung cancer
Hennekens 1996	Physicians' Health Trial, only 11% smokers	22,071	β-carotene 50 mg qod	No effect
Lee 1999	Women's Health Study, only 13% smokers	39,876	β-carotene 50 mg qod	No effect
Duffield-Lillico 2002	Nutritional Prevention of Cancer Trial in Eastern USA	1,312	Selenium 200 μg/day	↓risk for prostrate cancer, no effect on colorectal or lung cancer, ↑ in skin cancer

Data are derived in part from Forman MR, Hursting SD, Umar A, Barrett JC. Nutrition and cancer prevention: a multidisciplinary perspective on human trials. *Annu Rev Nutr.* 2004;24:223.

been extensively studied in prevention of prostate cancer as part of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial (25). There is not strong evidence for an effect of high-dose supplementation in 1,338 cases of prostate cancer among 29,361 men, although vitamin E supplements in smokers and β-carotene supplements in those with low dietary intake were associated with reduced risk of disease. The effect of supplementation with selenium (200 μg per day) has been studied over a decade in the Nutritional Prevention of Cancer Trial. No effect was found on the incidence of cancers of the lung, colon and rectum, and skin, but there was a protective effect on prostate cancer in males with a lower baseline plasma selenium concentration (26).

Because tumor production appears to be closely linked to oxidative and inflammatory processes, and it takes a long time to develop, antioxidant-rich foods or supplements might still be useful. There are several results of studies that suggest a possible role for antioxidants, although most results are negative. Trials of antioxidant supplements are hampered by the lack of a valid measurement of antioxidant status, preventing identification of a susceptible population to select for supplementation, and of the supplement most likely to be efficacious. Those patients at risk for cancer might benefit from a balanced diet or a multivitamin/multimineral preparation. The current recommendation to consume five servings of fruits and vegetables containing 200 to 280 mg per day of vitamin C (among other vitamins) is still felt to be sensible, awaiting further data (16). At least one large study (7,377 cancer cases in the European Prospective Investigation into Cancer and Nutrition [EPIC]) showed no association between cancer risk and intake of fruits and vegetables (27). If recommending, dietary sources of natural antioxidants are liver (vitamin A); dark green and yellow vegetables, including spinach, carrots, and tomatoes (β-carotenes); cruciferous vegetables, such as broccoli, brussels sprouts, cabbage, and cauliflower (vitamins A and C); and citrus fruits, berries, green peppers, peaches, melons, tomatoes, and green and leafy vegetables (vitamin C).

3. **Drink alcoholic beverages only in moderation.** The carcinogenic effect of alcohol is associated with a large intake, especially when combined with cigarette smoking. Intake should be limited to no more than two drinks per day for men and one for women. One drink is equal to 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof distilled liquor.

Other Unresolved Issues in Cancer Prevention

Calcium and Vitamin D

The epidemiologic data suggesting an association are reasonable. These two components are intimately associated, and separating them may prove difficult. Addition of calcium and vitamin D supplements did not alter the risk for colorectal cancer (28). In the Poly Prevention Trial no association was found between adenoma recurrence and dietary calcium or vitamin D intake (29). Studies suggest that intake of vitamin D above the usual recommended dietary intake of 200 to 400 IU may be necessary to decrease the risk of colorectal (and other) cancer (30). Also, vitamin D status at baseline may influence the course of the disease. This is a recurrent theme in cancer chemoprevention, that is, identification of a group most likely to respond to nutrient intervention.

Meat Consumption

There is a positive relationship between meat consumption and the risk of colorectal cancer (31). An even larger study in 478,040 adults in the European EPIC study showed similar findings, but when controlled for covariates, showed significance only for processed meats and not red meat (32). Yet another study showed no relationship after following 45,496 women for a decade (33). It seems safe to conclude that there is some relationship between meat intake and colorectal cancer, but the data are not strong enough to recommend a change in diet, or if so, what change. Some experts recommend a conservative compromise, a modest meat intake as part of an overall dietary strategy, replacing meat protein (especially processed and well done meats) with that from fish, nuts, poultry, and legumes (34). It is still unclear, however, what the relationship is between high consumption of fish and marine fatty acids and the risk of cancer (35).

Polyphenols

Polyphenols contain more than one phenol ring and include flavonoids. In tea catechins comprise the majority of the polyphenols. Green tea is steamed or pan-fried, preserving the catechins, whereas black tea is dried first and then fermented, converting the catechins to other polyphenols with different properties. A cup of black tea contains 24 to 40 mg of catechins (166 to 193 mg of polyphenols), but a cup of green tea has up to 200 mg of catechins. Mean polyphenol intake in the United States is 1.1 g per day (100 to 2000 mg range) (36). The literature is full of publication bias with no large trials (37,38); larger and better studies are needed. The amount of green tea needed for benefit, if any, is not known.

Ingestion of 6 to 10 cups has been suggested (39), but other dietary differences between Western and Japanese or Chinese diets are so great that no conclusions can be made.

Folate

Mandatory folate fortification to prevent neural tube defects has produced increased serum folate levels, but the data are still mixed on whether folate supplements help or worsen cancers (40). Variant genotypes of the folate metabolizing enzyme, methylenetetrahydrofolate reductase (MTHFR), that decrease metabolism would be expected to increase the cancer risk, if folate were protective, but the opposite result was found (41). It is not even clear what the relationship is between folate status and antifolate chemotherapy-related toxicities (42). Clearly, more studies will be needed to resolve the issue of folate status and cancer prevention or treatment.

Diagnosis of Nutritional Abnormalities in Cancer Patients

Nonspecific Findings

A number of findings in patients with advanced cancer are related to nutrition but are often difficult to treat with specific nutritional intervention. The most prevalent of these are weight loss and a decreased intake of food (43). Abnormal carbohydrate metabolism is characterized by glucose intolerance and insulin resistance. Body fat tends to become more depleted relative to protein loss, and lipolysis is increased. Protein turnover in the entire body increases as the disease progresses, with a reduced fractional synthetic rate in muscle. The protein kinetics in cancer patients with weight loss resemble those in persons with trauma and infection; patients with these clinical conditions cannot easily be brought into positive nitrogen balance, even with total parenteral nutrition (TPN). When sepsis develops, serum levels of tumor necrosis factor (TNF) increase, but high levels, such as are seen in childhood leukemias, have not been reproducibly found in patients with solid tumors (44).

There are multiple factors that produce unintentional weight loss in cancer patients. These include obstruction of the gastrointestinal tract, malabsorption due to hormones (e.g., VIP) or nutritional deficiency (e.g., vitamin D), and anorexia. Anorxia can be related to altered taste, depression, or altered metabolism of substances that affect appetite, especially hormones (e.g., ghrelin, leptin) or neuropeptides (e.g., neuropeptide Y) (43). The hormones synthesized by some tumors cause clinical syndromes that appear to be nutritionally based (e.g., weight loss, bone disease) but are not. These include carcinoid syndrome, Zollinger–Ellison syndrome, hypercalcemia, and oncogenic osteomalacia secondary to renal phosphate wasting and decreased levels of plasma dihydroxyvitamin D, parathyroid hormone, and calcium. These syndromes must be identified and the manifestations of increased hormone production treated with available (non-nutritional) methods.

Cachexia

Anorexia frequently accompanies the cachexia of cancer. Proposed mediators of cachexia have included hypothalamic serotonin, leptin, proinflammatory cytokines (TNF-α, IL-1, IL-6, IFN-γ), prostaglandins, and tumor-specific products (45). Many of these circulating catabolic factors can be produced by either the host or tumor itself. However, none of these has been documented to be causative in the anorexia of cancer (44). Starvation is characterized by an excessive loss of nutrients, but cachexia is associated with the acute-phase responses that are part of underlying inflammatory or malignant conditions. Thus, feeding does not reverse the macronutrient deficiency. Body compartment analysis in cachexia, in contrast to starvation, shows increases in resting energy expenditure, protein degradation, and serum insulin and cortisol levels (46). These changes lead to increases in urinary nitrogen loss, skeletal protein breakdown, and lipolysis and to glucose intolerance. Despite aggressive caloric replacement, lean body mass decreases in critically ill patients with underlying infection or tumor (46).

Nutritional Management of Patients with Malignancy

The first thing that must be done is to identify weight loss early enough so that intervention might have a chance to be effective (47). However, providing dietary advice alone is

not sufficient, and the data suggest that dietary supplements are needed as part of the program to maintain good nutrition (48). Many studies have shown that a loss of body weight or lean body mass is associated with an increase in mortality. However, no data indicate that wasting is the cause of death or that nutritional support reverses wasting. It is just as likely that wasting is a measure of disease severity. The use of nutritional support does not improve the condition of patients with cancer (49,50) or AIDS (51). A conference examining the current evidence concluded that the routine use of short-term enteral or parenteral feeding does not decrease complications or mortality in patients with cancer, and that it does not reverse wasting syndrome in patients with HIV infection if decreased food intake alone is not the cause of wasting (51). However, these conclusions are not meant as guidelines for individual patients. The use of nutritional support can be considered for patients with documented or probable deficiencies who require nutrition if other treatments are to proceed. However, no clear indication for the use of nutritional support as primary therapy can be found in the literature.

Many attempts have been made to alter anorexia and cachexia pharmacologically with steroids, antiserotoninergics (cyproheptadine), and hydrazine sulfate, but these have not been successful. The ideal agent should have sustained effects on the appetite, lead to repletion of body cell mass, and have few adverse effects on the host or on tumor therapy. None of the available agents comes close to this ideal profile. The progestational agents megestrol acetate and dihydroxyprogesterone acetate inconstantly improve appetite (44) (see later discussion of their use in AIDS) and increase weight, but the weight gain represents increases in fat, not fat-free tissue. Both these agents produce side effects, including venous thrombosis and peripheral edema, the latter finding supporting the observation that the weight gain does not represent an increase in lean tissue mass. Growth hormone has not yet been shown to be useful in managing cachexia. However, anabolic steroids (e.g., 20 mg of oxandrolone per day in conjunction with a high intake of protein and physical therapy) do increase fat-free mass (46,52). Although inhibition of proinflammatory cytokines has not been shown to increase weight, such treatment may decrease protein breakdown and be clinically useful. For example, the use of thalidomide in HIV-infected patients being treated for tuberculosis can promote weight gain (46), and 200 mg per day produced weight gain in patients with advanced pancreatic cancer, but no change in survival (53). Thus, nutrition may not be a critical variable in advanced cancer, but improved nutrition may contribute to quality of life. Preliminary studies of a combination of a progestational agent and nonsteroidal antiinflammatory drugs have reported some success, but no recommendation can be made from such early data. The administration of 6 g of eicosapentaenoic acid per day or 2 g of fish oil per day appeared to stabilize the weight of patients with cancer cachexia when added to a protein- and energy-dense diet (54).

Nutritional intervention is sometimes appropriate when a specific cancer causes a clinical syndrome or problem that can be reversed. Most often, calories or fluid is provided when oral intake becomes limited, either by the cancer itself or by the side effects of medication. In such situations, nutritional intervention may resolve the immediate problem, but in most instances, the effect on the eventual outcome is small. The metabolic alterations caused by the tumor usually blunt or prevent the effects of nutritional intervention. Thus, nutritional intervention must be undertaken with a full understanding on the part of both patient and physician of the limited goals of such therapy. Table 15-5 outlines some of the more common nutritionally related problems that develop in cancer patients.

A frustrating situation is created when decreased food intake, vomiting, weight loss, and chronic fluid loss develop in a patient undergoing chemotherapy. With a malnourished patient, there is often little choice but to intervene, provided the intervention does not create a distasteful situation (e.g., gastrostomy) that will continue after the course of chemotherapy is over. A meta-analysis of 12 randomized studies of normally nourished patients receiving chemotherapy showed no benefit of TPN (55). Even though enteral feeding causes fewer complications than TPN does, it is unlikely that enteral nutrition would produce a different long-term result. In severely malnourished patients who are undergoing major surgery, analysis of the available data suggests a very modest improvement in survival (~10%) when TPN is given perioperatively (51).

TABLE 15-5. Nutritional Consequences of Cancer and Its Treatment

Problem	Pathophysiology	Nutritional intervention
Weight loss	Decreased intake	Table foods, calorie supplements
Nausea	Multifactorial	Encourage oral intake, antiemetics limited except at chemotherapy
Enterocutaneous fistula	Fluid/electrolyte loss	Replacement, orally if possible
Protein-losing enteropathy	Lymphatic blockage	Low-fat diet
Anemia	Blood loss (iron), ↓ intake (folate)	Iron, folate supplements, orally if possible
Abdominal radiation	Diarrhea, malabsorption	Opiates as needed
Oral/mediastinal radiation	Ulcers, dysphagia, stricture	Full liquid diets, avoid TPN or gastrostomy, if possible
Vagotomy	Steatorrhea	Limit fat intake
Gastrectomy	Loss of reservoir, intrinsic factor, dumping syndrome	Small meals, antidumping diet, vitamin B_{12} supplement
Ileal resection	↓ Bile salt pool, bile salt/fatty acid diarrhea	Low fat intake, Ca/Mg supplements, ? cholestyramine
Ileostomy/colostomy	↓ Salt, fluid absorption	Replace orally, if possible
Pancreatectomy	↓ Pancreatic enzymes	Limit fat intake
Corticosteroids	Salt retention	Limit salt intake
Chemotherapy	Nausea, diarrhea, anorexia	None, use serotonin-receptor antagonists
Surgery	↑ Catabolism in severely malnourished patients	Limited benefit (up to 10% ↑ survival) of TPN given perioperatively

TPN, total parenteral nutrition.

Nutritional Management of Treatment-Induced Mucositis

The mucosa of the mouth and gastrointestinal tract turns over relatively rapidly, and is at risk for being damaged by radiation or chemotherapy used to treat cancers, when no specific tumor target can be identified. Mucositis is a troublesome complication, because the symptoms are those of pain and inability to eat. Many treatments have been tried with the view to replace nutrients that will help to preserve mucosal cell mass, or help it to regenerate. Glutamine has been used in large doses (1 to 2 g per m^2 intravenously, or 8 to 30 g per day orally) as it has been suggested that glutamine supply may be limited in acute stress. A review of the literature from 1980 to 2003 revealed some instances where glutamine improved either mouth pain or diarrhea, but not in all studies (56). Some double-blind randomized studies showed a protective effect after radiation on the symptoms of mucositis by α-tocopherol 400 mg (57) and of zinc sulfate 50 mg as elemental zinc tid (58). However, most studies are small (<50 patients). Placebo controlled larger studies are needed to know if any of these nutritional supplements will be of value in managing treatment-related mucositis.

HIV INFECTION

Weight Loss

AIDS and its complications remain a national concern and a major priority in health care management. Patients infected with HIV are frequently malnourished, and the causes of protein–energy malnutrition in patients with AIDS are multiple. Wasting is usually defined according to weight loss as mild (<5%), moderate (6% to 10%), or severe (>10%). However, weight loss can represent loss of lean tissue or loss of fat stores, and the severity

of malnutrition can be underestimated in severely ill patients if they have large fat stores. At all stages of the HIV-mediated wasting syndrome, women lose more body fat than men, but lean mass is also lost (59). Measurements of body composition can be used to detect fat stores (e.g., triceps skin folds), but these are not usually helpful for routine clinical management. The recommended method for detecting weight loss and wasting is to monitor weight every 6 months if only HIV-positive, and every 3 months for patients with documented weight loss (59). Wasting is diagnosed when patients have weight <90% of ideal body weight, or a BMI <18.5, along with weight loss >10% from the premorbid maximal weight, or >5% from weight in the previous 6 months. Generalized malnutrition may explain some of the immune dysfunction, as more protein is lost during acute periods of weight loss than could be predicted from starvation alone (60).

Etiology of Nutritional Deficiency in Patients with HIV Infection

A person's nutritional status represents a balance of caloric and nutrient intake, absorption or malabsorption, and energy expenditure, which are altered by hormonal and metabolic factors. Weight loss is the most frequent finding associated with HIV infection. A weight loss of 10% is generally considered to have a significant impact on a patient's functional status. Weight loss may be caused by inadequate oral intake, intestinal malabsorption, altered metabolism, or a combination of these factors (61). Major factors that predict wasting in HIV-positive patients are heavy alcohol use, cocaine or crack use, and protease inhibitor treatment (62).

Causes of Decreased Intake of Nutrients

Anorexia. A loss of appetite may be caused by myriad reasons, including systemic infection and fever, depression, and side effects of medication. Alterations in taste sensation resulting from medications or oral infections may decrease salivation and appetite. Ulcerative gastritis or duodenitis also may cause anorexia. Nausea, vomiting, anorexia, abdominal discomfort, or diarrhea may compound the loss of appetite. These symptoms may be secondary to drugs or to the underlying medical process. The intake of food may be decreased by a complete loss of appetite, early satiety, or fear of pain or diarrhea. An early recognition of these concerns is important in preventing malnourishment in these patients.

Oral and Esophageal Pain and Dysphagia. Oral pain and discomfort can be secondary to oral candidiasis, oral herpes, cytomegalovirus (CMV) infection, aphthous ulcers, oral hairy leukoplakia, or oropharyngeal bulky tumors of Kaposi's sarcoma or non-Hodgkin lymphoma. HIV-associated gingivitis and HIV-associated periodontitis can be rapidly destructive and may resist therapy. Esophageal odynophagia and dysphagia may be caused by ulceration from CMV, herpes simplex virus (HSV), or candidal infection. Pharyngeal or esophageal lesions of Kaposi's sarcoma may cause dysphagia through obstruction.

Nausea and Vomiting. Nausea and vomiting may be secondary to gastrointestinal (GI) or central nervous system (CNS) malignancies or infections. Symptoms also may be exacerbated by any of the commonly used therapeutic agents.

Neurologic Causes of Decreased Nutritional Intake. HIV-associated dementia, CNS pathogens, weakness, debilitation, and depression also may contribute to a decreased oral intake. CNS disease processes include CMV infection, HIV encephalitis, cryptococcal meningitis, primary lymphomas, and progressive multifocal leukoencephalopathy.

Cytokines. Cytokines such as TNF may cause anorexia by decreasing GI motility. Interleukin-1 and α- and γ-interferons have been shown to contribute to anorexia. TNF and α- and γ-interferons have been reported to induce nausea and vomiting during therapeutic trials, although their precise role in causing anorexia in clinical disease is not known.

Causes of Diarrhea and Malabsorption

With improved diagnostic capabilities and a greater awareness of the spectrum of diarrheal pathogens in AIDS, an increasing number of causes of chronic diarrhea are being identified.

Infections of the GI Tract. Parasitic causes include *Cryptosporidium parvum, Giardia lamblia, Isospora belli,* and *Enterocytozoon bieneusi* (microsporidia). Viral causes include CMV and HSV. Bacterial agents include *Campylobacter* and *Mycobacterium avium-intracellulare*. Cryptosporidiosis and microsporidiosis are associated with decreased jejunal disaccharidase activity and D-xylose absorption. The pattern of injury is similar to that in tropical and nontropical sprue, with rapid turnover and functional immaturity of villus enterocytes.

Bacterial Overgrowth. Bacterial overgrowth has been reported and may be related in part to the high frequency of gastric achlorhydria seen in HIV infection, especially with enteropathogenic strains of *Escherichia coli.*

Malabsorption. Malabsorption may be present, even in the absence of diarrhea. Lactase deficiency is common and causes lactose intolerance. Abnormal findings on D-xylose absorption studies, Schilling tests, or [^{14}C]glycocholate absorption studies suggest small-bowel dysfunction. Fat malabsorption secondary to small-bowel disease or pancreatic insufficiency may lead to caloric and fat-soluble vitamin depletion. Vitamin B_{12} deficiency occurs in at least 15% of patients with HIV infection. An abnormal Schilling test result in some patients despite the coadministration of intrinsic factor and pancreatic enzymes suggests small-bowel disease as the cause of malabsorption (63).

Kaposi's Sarcoma. In approximately 40% of HIV-infected patients with Kaposi's sarcoma, GI lesions are detected on endoscopy. Kaposi's sarcoma in the GI tract is rarely symptomatic, but when involvement is extensive, it may contribute to malabsorption and diarrhea.

Altered Metabolism

Concurrent Infection. Hypermetabolism was considered a significant contributor to the wasting syndrome in the past. However, when caloric intake and resting energy expenditure were examined in HIV-infected patients with weight loss at various stages of disease, only the patients with secondary infections lost weight (64). In patients without infection, only those with a decreased intake lost weight, and only in those patients was total energy expenditure decreased (65). Thus, it now appears that weight loss in HIV-infected patients is caused by decreased food intake, not hypermetabolism. A similar observation has been made in cancer patients (45). Although the metabolic rate can be extremely high (e.g., because of fever), food intake is invariably diminished in such patients.

These observations translate into practical considerations. When the provision of calories was increased (by TPN) in patients with AIDS wasting, the increased caloric intake led to weight gain (66). When weight loss was secondary to malabsorption or GI disease, the administration of TPN increased body cell mass (67). However, patients with AIDS wasting who had infection but not malabsorption continued to lose weight on TPN therapy (67).

Protease Inhibitors. Antiretroviral therapy stabilizes weight and lessens the severity of malnutrition (62,68). However, body cell mass is decreased even in patients on protease inhibitors; some patients do not respond optimally, and some gain weight on treatment even though their lean body mass does not increase (69). Residual nutrition-related abnormalities in HIV-infected patients treated with protease inhibitors include subcutaneous and visceral accumulation of fat, hypertriglyceridemia and hypercholesterolemia, and peripheral insulin resistance (70). These effects were initially considered to be caused by protease inhibitors, but clearly they can occur in patients not taking protease inhibitors (71). In the HAART era we now see lean tissue wasting (lipodystrophy) that may not be reflected in

weight change *per se*. Fat accumulates in the abdomen, dorsocervical, and breast areas, with loss of fat in limbs and the face. The optimal management of these patients requires the same working knowledge and skillful management of nutrition that is required in the management of others, plus a knowledge of the numerous symptoms, complications, and infections associated with progressive HIV infection.

Effects of Malnutrition

Protein–Calorie Malnutrition

In AIDS patients, body cell mass depletion is increased out of proportion to total weight loss. Body cell mass, measured by total body potassium, is more depleted than body fat mass in immunodeficient patients (72). A linear relationship can be found between the degree of body mass depletion and time to death. The loss of body cell mass correlates with time to death when the body cell mass is depleted by about 50% and the body weight is decreased by about 33%. The time to death does not correlate with body fat depletion. Thus, it has been surmised that the time to death in AIDS patients with wasting may be more closely related to the degree of body cell mass depletion than to its underlying cause (73).

Nutrition and the Immune System

Both malnourishment and overnourishment affect immune status. Nutritional deficiencies, seen most commonly in some Third World countries, are linked with decreased immune function and increased rates of infection. However, no solid scientific data are available to prove that malnutrition *per se* predisposes HIV-infected patients to AIDS. Body cell mass correlates better than immune function (assessed by CD4+ lymphocyte count) with physical performance (74).

Individual Micronutrients

Vitamin B_6. Pyridoxine deficiency may result from decreased food intake or from treatment with pyridoxine antagonists such as isoniazid or hydralazine. Symptoms of peripheral neuropathy, seborrheic dermatitis, and oral lesions, including glossitis, angularis stomatitis, and cheilosis, may be present.

Vitamin B_{12}. Deficiency is present in 16% to 33% of patients with AIDS. Vitamin B_{12} deficiency may be secondary to malabsorption resulting from ileal dysfunction, bacterial overgrowth with bacterial binding of vitamin B_{12}, or intrinsic factor deficiency (71). Symptoms include anorexia, loss of taste, glossitis, diarrhea, hair loss, impotence, and anemia, which may result in weakness, fatigue, and dyspnea. Neurologic symptoms include paresthesias, loss of sensory and motor function, irritability, and memory disturbances. Many of these patients do not have megaloblastic changes; however, when deficiency is suspected, it should be documented with elevated serum methylmalonic acid and homocysteine levels (see Chapter 7). If the diagnosis remains in doubt, treatment should not be withheld.

Folate. Folate levels are low in one-third of patients. Absorption may be decreased by inhibition of the dihydrofolate reductase enzyme by drugs, including methotrexate, trimethoprim, pyrimethamine, and triamterene. Supplements should be administered when a deficient state is suspected or when these drugs are used. It is essential to include vitamin B_{12} replacement when deficiencies of both vitamins are expected.

Vitamin D. Excess amounts of vitamin D have been shown to decrease T-cell function. It is important to monitor for additional regimens that patients may be taking, including megadoses of certain vitamins and minerals.

Iron. Deficiency favors *Candida* and *Salmonella* infections. The prevalence of iron deficiency is higher in adults with recurrent HSV infections than in matched controls. However, current data do not indicate that correction of this deficiency protects against infection. Deficiency results in depletion of storage iron, a decrease in circulating iron, and

a hypochromic, microcytic anemia. Iron-containing substrates such as muscle myoglobin and mitochondrial cytochromes are also affected, which may account for symptoms of weakness.

Zinc. Deficiency is secondary to decreased absorption and increased losses in chronic diarrhea. Zinc deficiency itself may cause diarrhea in addition to poor wound healing, dysgeusia, skin rashes, and apathy.

Selenium. Selenium deficiency is common in HIV-infected patients and may play a role in the pathogenesis of cardiomyopathy. It also is an independent factor associated with decreased survival (75).

Evaluation of Malnutrition in Patients with AIDS

The assessment and evaluation of the nutritional status of patients with AIDS follow the general nutritional principles discussed in detail in Chapter 5. Evaluation for individual micronutrient deficiencies is covered in Chapters 6 and 7.

Anthropometric Parameters

Anthropometric parameters provide the most reliable overall assessment of nutritional status. These include weight and height. A body mass index below 20 and an involuntary weight loss of more than 10% are most often seen in late stages of disease. Other measurements of body composition, such as bioimpedance analysis, and dual X-ray absorptiometry, can sometimes be helpful in earlier disease but are more useful for clinical studies (69).

Further Investigations

Intercurrent Disease. If the history does not suggest a significantly decreased intake of food, a careful search for oral pathology, infection, or CNS disease should be undertaken.

Laboratory Tests. Serum albumin is the most readily available and commonly performed test. A serum protein such as retinol-binding protein is a more reliable index of short-term changes in nutritional status, given the short half-life in comparison with that of albumin. Both measurements may be affected by extracellular fluid status. Anemia with abnormal red blood cell indices may indicate low levels of folate, vitamin B_{12}, or iron.

Protein–Calorie Malnutrition. Parameters such as a low lymphocyte count or a diminished delayed-type hypersensitivity reaction, which are used in patients without AIDS, may not be valid in patients with immunodeficiency resulting from HIV infection.

Treatment for Specific Complications of HIV Infection Contributing to Malnutrition

Table 15-6 outlines the nutrition-related treatment recommendations for HIV-infected patients. No standard of nutritional management in AIDS is universally accepted. The American Dietetic Association and the Dietitians of Canada have endorsed a position statement that supports the following: maintaining optimal weight and preventing rapid weight loss, reducing or discontinuing smoking and alcohol consumption, reducing or balancing intake of foods and beverages rich in calcium and vitamin D and protein, supplementing with calcium when needed, minimizing side effects of HAART, and use of regular weight-bearing or resistance exercises (60). In general, patients who are not malnourished do not require nutritional supplements. However, they do need an adequate intake of macronutrients and micronutrients from a balanced diet of table foods. The use of nutritional supplements in HIV-infected patients has produced small and variable effects, although the studies were small and were done around the time HAART was introduced (76). Most are safe to give, but no claims can be made for efficacy. Many websites are available to obtain information on nutrition in AIDS (Table 15-7).

TABLE 15-6. Nutrition-Related Treatment Recommendations for AIDS Patients

Clinical evaluation	Resulting action
Normal weight, food intake, body composition (if used)	Ensure that intake of protein, fat, and carbohydrate is adequate, including ≥1 g protein/kg body weight
Normal weight, food intake	Provide adequate amounts (about two or three times the DRI or RDA) for each nutrient
Weight loss, decreased food intake	Give appetite-stimulating drugs
Decreased stores of micronutrients	Treat with larger doses of appropriate nutrients
Laboratory evidence of hypogonadism	Give testosterone (parenteral) in men
Severe weight loss failing other treatments	Growth hormone (0.1 mg/kg/day) can be tried

DRI, dietary reference intake; RDA, recommended dietary allowance.
From Corcoran C, Grinspoon S. Treatments for wasting in patients with the acquired immunodeficiency syndrome. *N Engl J Med.* 1999;340:1740.

Dietary Recommendations

1. Optimal oral and dental hygiene is essential to prevent infections, oral discomfort, and changes in taste.
2. Patients who are at risk for aspiration because of oropharyngeal dysfunction should be evaluated by a speech pathologist or ear, nose, and throat specialist.
3. Meals and the administration of medication should be timed to avoid anticipatory vomiting. Drugs that induce nausea or vomiting should be administered long before meals.
4. Foods should be thoroughly cooked and stored with adequate refrigeration. Leftover foods should be completely reheated. Bacterial food contamination can be fatal in the immunocompromised patient. Raw or undercooked shellfish and seafood, meat, poultry, and unpasteurized milk products (e.g., steak tartare and sushi) should be avoided because they may lead to enteric infections with *Salmonella, Campylobacter, Listeria,* and *Escherichia coli.* Separate cutting boards should be used for uncooked meats, fruits, and vegetables. Neutropenic diets, in which uncooked fruits and vegetables are avoided, are advisable for patients whose white blood cell counts are low.
5. Avoidance of significant alcohol consumption is advisable. Ethanol abuse decreases function in multiple components of the immune system and further compromises nutrient absorption, utilization, storage, and secretion (77).
6. Patients with diarrhea or fat malabsorption should limit intake of fatty foods.

TABLE 15-7. Websites with Nutrition Information for AIDS Patients

Organization	Material offered	URL
American Dietetic Association	A Guide to Nutrition (2003)	www.eatright.org
Assoc. of Nutrition Services Providers (ANSA)	Materials for AIDS meal providers	www.aidsnutrition.org
Canadian AIDS Treatment Information Exchange (CATIE)	Fact sheets, treatment information	www.catie.ca
Gay Men's Health Crisis (GMHC)	Client education	www.gmhc.org
Health Resources and Services Administrations, HIV/AIDS bureau	Client education and nutrition manual	www.aids-etc.org
HIV/AIDS Dietetic Practice Group	Dietetics professionals' resources	www.hivaidspg.org
Medscape Infectious Disease forum	Conference reviews, articles	www.medscape.com

7. For anorectic patients, meals should be served in an appetizing fashion in a well-lit environment free from distractions. Frequent small meals served on small plates are often best tolerated. Providing nutrient-dense foods may help in these situations. Variety in the temperatures of food is welcomed by some. Offering favorite foods in a pleasant atmosphere in the presence of family members or companions may help.
8. Foods served at cool temperatures may be more soothing. Foods with strong aromas and spices should be avoided.
9. Fluid intake during meals, which causes early satiety, should be avoided. The remainder of the fluid requirement should be ingested between meals.
10. For patients with dysgeusia, serving liquids at meal time and altering the texture and temperatures of foods may stimulate sensory feedback. Serving foods with small amounts of liquids may aid chewing and swallowing. Sour candy may stimulate salivation in patients with dry mouth.
11. Enteral nutritional supplementation is best given at times other than meal times, such as just before bedtime, to allow for optimal appetite during meals. Iso-osmolar formulas with an increased fat content may be better tolerated by patients with sepsis who are glucose intolerant. Patients with malabsorption may benefit from low-fat diets or diets containing medium-chain triglycerides. The use of these supplemental diets may be limited because of their potentially adverse effects of hyperosmolarity and diarrhea. The intake of carbohydrate and fat in both table foods and enteral supplements should be adjusted to reduce symptoms of diarrhea.

Appetite Stimulants and Anabolic Agents

These should be reserved for patients with weight loss and decreased food intake (Table 15-8).

Megestrol Acetate. The progestational agent megestrol acetate may increase appetite and promote weight gain in AIDS patients without any clear underlying cause of weight loss. Similar benefits have been seen in some cancer patients. In two trials in which 800 mg of megestrol acetate was given daily for 12 weeks to AIDS patients with anorexia and cachexia, a weight gain of 3 to 4 kg was reported (78,79). The optimal dosing of megestrol acetate remains to be determined. No significant side effects were observed during the course of therapy. Long-term effects on weight gain, repletion of body cell mass, and quality of life are not yet known. Consistent with its glucocorticoid action, the drug can exacerbate diabetes (80) and cause adrenal insufficiency on withdrawal. Fat deposition may be the major component of weight gain.

TABLE 15-8. Anabolic Treatments for Patients with AIDS Wasting

Treatment	Usual dose	Demonstrated result
Appetite-stimulating drugs		
Megestrol acetate	800 mg/day	Improved appetite, weight gain (mostly fat)
Dronabinol	5 mg/day	
Testosterone and analogues		
Testosterone, IM	300 mg q 3week	↑ lean body mass
Testosterone, transdermal	5 mg/day	"
Oxandrolone, oral	20 mg/day	Weight gain, ↑ lean body mass
Nandrolone, IM	100 mg q 2week	
Recombinant human growth hormone	6 mg/day	Weight gain, ↑ lean body mass (short-term)
Exercise training	Individualized	↑ Lean body mass
Cytokine modulators		
Thalidomide	200–400 mg/day	Weight gain

From Corcoran C, Grinspoon S. Treatments for wasting in patients with the acquired immunodeficiency syndrome. *N Engl J Med.* 1999;340:1740.

Dronabinol (Δ-9-tetrahydrocannabinol). The active agent in marijuana has been shown to enhance appetite, but weight gain is very slight (81). The body composition of this weight gain has yet to be evaluated. Side effects include drowsiness, anxiety, poor coordination, and confusion.

Anabolic Steroids. These have been useful only in men, producing a modest increase in lean body mass and a weight gain of about 1 kg over control during 12 to 14 weeks (69). Both oxandrolone (20 to 80 mg per day) and oxymetholone (10 to 150 mg per day) are active orally and are 5 to 10 times more active than testosterone, with fewer side effects (82).

Growth Hormone. Patients with weight loss may have some resistance to endogenous growth hormone, perhaps related to malnutrition or underlying HIV infection. In an uncontrolled 3-month study, an increase in weight of 3 kg was achieved by giving 5 mg subcutaneously every other day. Other studies showed an improved exercise capacity and a confirmed modest weight gain in comparison with controls (19). However, the recombinant drug is very expensive, and side effects include edema, arthralgias/myalgias, and decreased glucose tolerance.

Thalidomide. The use of thalidomide in treating cancers and inflammatory conditions is well documented (83). The drug acts via an active metabolite by interfering with TNF-α or interleukin 1β-induced activation of IκK, with subsequent suppression of NFκB. In randomized, placebo-controlled trials of patients with painful oral ulcers, over half responded to doses of 100–200 mg per day. Several trials in HIV+/AIDS patients showed improved weight gain over short periods (83). Usual doses range from 100 to 1,200 mg per day. Adverse effects include sedation, peripheral neuropathy, and teratogenicity, but rash, dizziness, constipation, tremor, mood changes, and headache are also common. Thalidomide has been used largely in combination with other drugs for malignant disease, but is effective as monotherapy in inflammatory disorders, particularly of the skin and gut.

Accompanying disorders

The causes of weight loss must be evaluated. Treatment of any underlying infection is imperative when feasible. Evaluation of diarrhea should begin with stool studies for culture and toxins of *Salmonella, Campylobacter, Shigella,* and *Clostridium difficile*. These patients may have accompanying fever and abdominal pain, and the diarrhea is often bloody. Bacteremia is common, and parenteral antibiotics should be administered empirically to severely ill patients pending the results of stool culture. The stool should also be examined for ova and parasites. Duodenal aspiration may be useful to identify *Cryptosporidium, Giardia lamblia,* and *Entamoeba histolytica* and may be better tolerated than endoscopy by some patients. However, endoscopy with biopsy is useful to diagnose *M. avium-intracellulare* infection, microsporidiosis, and CMV infection. It is important to keep in mind that multiple pathogenic processes may exist concurrently in these immunocompromised hosts.

Gastrointestinal Kaposi's sarcoma can be diagnosed histologically by endoscopic biopsy. When these lesions are symptomatic or interfere with nutrition, they can be treated with chemotherapy and radiation.

AIDS and other chronic, incurable diseases frequently precipitate anxiety, fear, and depression. These symptoms alone can contribute significantly to a decline in adequate nutritional intake. Appropriate measures should be taken to address these primary problems, both for nutritional purposes and to optimize the quality of the patient's remaining life.

NUTRITIONAL SUPPORT IN PATIENTS WITH CATABOLIC CONDITIONS (CHRONIC MEDICAL DISEASES OR SURGERY)

Although weight loss may not have occurred following acute surgical procedures, the net catabolic state is similar to those that produce weight loss. When the patient at baseline has lost weight and is malnourished, as is often the case with surgical patients and

chronic medically ill patients, the need for nutritional support seems quite logical. Perioperative nutritional support is most often provided for patients with cancer and appears to be of benefit if the patient is malnourished at baseline (51,84). The definition of malnutrition versus catabolic state in the face of chronic illness can be difficult, however (see Chapter 5), as malnutrition implies a response to exogenous nutrients. Perhaps the reason why more studies have not been positive is that it takes ~7 days or more of preoperative positive nitrogen balance to reduce infectious complications when patients are malnourished, and most patients do not receive such a prolonged preoperative treatment (85). Studies do not show a benefit when supplements are provided postoperatively. For patients with distal bowel surgery it is now clear that oral feeding is possible and desirable because the gut recovers within a few days in most patients (86). When oral nutrition was compared with enteral or parenteral supplements in cancer patients (with weight loss) during postoperative recovery, no difference was seen in outcome, except that the supplemented groups had more complications (87). Thus, oral nutrition is probably preferred postoperatively.

When nutrition support was given to patients with chronic obstructive pulmonary disease, weight was not affected by dietary supplementation (88). However, only six studies were found that were randomized and controlled, and it is not clear whether weight loss in this condition could be prevented by calorie supplementation (57). Patients with severe Crohn disease generally benefited (fewer complications or less bowel resected) from preoperative nutrition, either parenteral or oral, but the few published studies have used historical controls for comparison (89,90). Prospective randomized trials are needed. Protein energy malnutrition (PEM) is common in patients with end-stage liver disease (ESLD), despite the difficulty in diagnosing PEM with certainty in these patients. The use of branched-chain amino acid formulas has provided no evidence that they are superior to standard amino acid formulations for improving nitrogen balance or encephalopathy (91).

Alzheimer disease (AD) is associated with disordered eating behavior, weight loss, and increased risk of infection. The European program to prevent weight loss includes monthly weight, periodic use of the Mini Nutritional Assessment (see Chapter 5), a balanced diet, physical exercise, and practical diet suggestions (92). If only one or two meals are eaten each day, provision of adequate protein and micronutrients must be included. The REAL French group study on AD has shown in 523 patients that patients living at home are at risk for undernutrition, and that these patients have more rapid progression of disease, but paradoxically respond best to acetylcholinesterase inhibitors (93). Other data suggest that supplementation with micronutrients that improve mitochondrial metabolism might prove useful, although the data are too incomplete to support a definite recommendation (94). An epidemiologic study in the United States concluded that dietary supplementation of vitamin E plus vitamin C (but not vitamin E alone) reduced the incidence of AD by ~50% in an elderly population (95). Higher intake of vitamin E (both α- and γ-tocopherol) was associated with a lower incidence of AD in 1,041 elderly patients (96). γ-Tocopherol has anti-inflammatory activity not found in α-tocopherol, the form found in dietary supplements of vitamin E (see Chapter 6). High doses of vitamin E (2,000 IU/day) did not improve cognition but delayed progression of the disease (97). However, another double-blind study showed no effect of the same dose on mild cognitive impairment, felt to be a prodrome of AD (98). Acetyl L-carnitine (ALCAR) facilitates the transfer of fatty acids into mitochondria. A meta-analysis of 15 double-blind trials suggested that ALCAR was helpful for symptoms of mild AD in doses of 1.5 to 3.0 g perday (99).

IMMUNONUTRITION

Immune modulation has been proposed to benefit patients under intense stress. The rationale is that key nutrients, normally not essential, are made conditionally essential when the rate of consumption or need is increased. The nutrients suggested for such a role include glutamine (a nutrient for immune cells and gut barrier protector), arginine (an NO

precursor), nucleotides (improve T lymphocyte function), sulfur-containing amino acids (enhance antioxidation via glutathione production), and n-3 fatty acids (anti-inflammatory, suppress cytokine production) (100). However, there are no definitive data in humans to confirm the conditionally essential role for these nutrients, most especially for glutamine (101) or arginine (102) where the most data have been gathered. Nonetheless, commercial products have been developed and used, particularly in patients who are critically ill. The data using these products have shown mixed results, but also suggest that harm can be produced by their use.

The most commonly used products in the past were Immun-Aid and Impact, but Immun-Aid is no longer available (Table 15-9). A meta-analysis of the use of such products in 22 studies revealed that they were associated with fewer infections but no change in mortality (103). Results were markedly heterogeneous, and surgical patients had lower infection rates than critically ill patients, contrary to the hypothesis that more stress produces conditional deficiencies. Most of the studies were small, few were blinded, few had any follow-up data, and all were compared to "standard" nutrition support that varied between studies. But standard nutrition support may be harmful in itself, as n-6 fatty acids are proinflammatory (104). Standard lipid emulsions contain only 4% to 11% of the lipid as n-3 linolenic acid. To deliver enough nutrients to improve immune function (at least theoretically), a large volume (>800 mL) is needed, and the studies often do not provide such volume (105). In addition, sepsis in the patients was often severe, and nutrition was not delivered early. Three studies using Immun-Aid showed increased mortality (106–108), and another study (Ross) was stopped because of increased mortality in the treated group (102). Despite these concerns, the data suggesting that arginine-rich products might decrease infection rates in critically ill patients have led to cautious recommendations for their use (109,110). They have been found useful in surgical patients during the preoperative period (111). Not all experts agree that these products should be used (103,105,112). It seems prudent to use immune-modulating products sparingly on an individual basis, until more data are available.

One other means to modify immune function in the critically ill patient is to maintain normal blood sugar levels, as this is associated with a decreased rate of infection (113). It seems useful to avoid overfeeding during parenteral nutrition, providing only 9 to 18 kcal per kg as glucose (114).

TABLE 15-9. Oral Immune-Modulating Products

Product	Source	kcal/mL	arg (g/L)	gln (g/L)	Nucleotide (g/L)	n-3 FA (g/L)	n-6 FA (g/L)
AlitraQ	Ross	1.0	3.0	14.2	0	0.02	6.6
Crucial	Nestle	1.5	12	0	0	3.6	7.7
Immun-Aid[a]	Braun	1.0	14	9	1.0	1.1	2.4
Impact	Novartis	1.0	12.5	0	1.2	1.7	2.5
Impact Glutamine	Novartis	1.3	16.3	15	1.6	1.7	3.9
Impact 1.5	Novartis	1.5	18.7	0	1.8	2.6	3.8
Impact Recover	Novartis	1.0	16.9	21.1	1.6	1.8	4.6
IntensiCal	Mead Johnson	1.3	6.5	0	0	NA	NA
Optimental	Ross	1.0	5.5	0	0	4.8	4.2
Oxepa	Ross	1.5	0	0	0	10.2	18.8
Perative	Ross	1.3	6.5	0	0	1.2	6.8

Arg = arginine, gln = glutamine, FA = fatty acid.
[a] No longer available in the United States.

There are no data available regarding the use of these products in any situation but that of acute medical or surgical stress. However, some patients are immunosuppressed chronically and might benefit from measures to prevent stress to their immune systems. It is standard procedure following hematopoietic stem cell transplantation to use a diet low in microbial content (115). The most commonly restricted foods are fresh fruits and fruit juices, fresh vegetables, and raw eggs. Also restricted are raw and undercooked meat, unpasteurized milk or cheeses, aged or blue cheeses, unroasted nuts or nuts in the shell, uncooked raw grains, raw honey, all miso products, sun tea, and herbal preparations and nutrient supplements. Guidelines for safe food handling practices can be found at www.foodsafety.gov, www.fda.gov, www.fsis.usda.gov, and www.cdc.gov.

References

1. Truswell AS. Some problems with Cochrane reviews of diet and chronic disease. *Eur J Clin Nutr*. 2005;2001 Suppl 1:S150.
2. Prentice RL, Caan B, Chlebowski RT, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295:629.
3. Beresford SAA, Johnson KC, Ritenbaugh C, et al. Low-fat dietary pattern and risk of colorectal cancer. The Women's Health Initiative randomized controlled dietary modification trial. *JAMA*. 2006;295:643.
4. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Eng J Med*. 2006;354:669.
5. Baldwin C, Parsons T, Logan S. Dietary advice for illness-related malnutrition in adults. *Cochrane Database Syst Rev*. 2001:CD002008.
6. Chief Medical Officers' Committee on Medical Aspects of Food. *Nutritional aspects of the development of cancer.* London: Stationery Office, 1998 (Department of Heath report on health and social subjects No. 48).
7. Forman MR, Hursting SD, Umar A, et al. Nutrition and cancer prevention: a multidisciplinary perspective on human trials. *Annu Rev Nutr*. 2004;24:223.
8. National Research Council, Commission on Life Sciences, Food and Nutrition Board, Committee on Diet and Health. *Diet and Health Implications for Reducing Chronic Disease Risk*. Washington DC: National Academies Press, 1989.
9. de Logeril M, Salen P, Martin J-L, et al. Mediterranean dietary pattern in a randomized trial. *Arch Intern Med*. 1998;158:1181.
10. Cottet V, Bonithon-Kopp C, Kronborg O, et al. Dietary patterns and the risk of colorectal adenoma recurrence in a European intervention trial. *Eur J Cancer Prev*. 2005;14:21.
11. La Vecchia C. Mediterranean diet and cancer. *Public Health Nutr*. 2004;7:965.
12. Martinez-Gonzalez MA, Estruch R. Mediterranean diet, antioxidants and cancer: the need for randomized trials. *Eur J Cancer Prev*. 2004;13:327.
13. Jacobs EJ, Connell CJ, Chao A, et al. Multivitamin use and colorectal cancer incidence in a US cohort: does timing matter? *Am J Epidemiol*. 2003;158:621.
14. Byers T, Nestle M, McTiernan A, et al. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*. 2002;52:92.
15. Williams MT, Hord NG. The role of dietary factors in cancer prevention: beyond fruits and vegetables. *Nutr Clin Pract*. 2005;20:451.
16. Lee KW, Lee HJ, Surh YJ, et al. Vitamin C and cancer chemoprevention: reappraisal. *Am J Clin Nutr*. 2003;78:1074.
17. Stanner SA, Hughes J, Kelly CNM, et al. A review of the epidemiological evidence for the 'antioxidant hypothesis'. *Public Health Nutr*. 2003;7:407.
18. Mannisto S, Smith-Warner SA, Spiegelman D, et al. Dietary carotenoids and risk of lung cancer in a pooled analysis of seven cohort studies. *Cancer Epidemiol Biomarkers Prev*. 2004;13:40.
19. Steck-Scott S, Forman MR, Sowell A, et al. Carotenoids, vitamin A and risk of adenomatous polyp recurrence in the polyp prevention trial. *Int J Cancer*. 2004;112:295.
20. Bjelakovic G, Nikolava D, Simonetti RG, et al. Antioxidant supplements for prevention of gastrointestinal cancers: A systematic review and meta-analysis. *Lancet*. 2004;364:1219.
21. Zhang S, Hunter DJ, Hankinson SE, et al. A prospective study of folate intake and the risk of breast cancer. *JAMA*. 1999;281:1632.
22. Cummings JH, Bingham SA. Diet and the prevention of cancer. *BMJ*. 1998;317:1636.
23. Janne PA, Mayer RJ. Chemoprevention of colorectal cancer. *N Engl J Med*. 2000;342:1960.
24. Biasco G, Paganelli GM. European trials on dietary supplementation for cancer prevention. *Ann N Y Acad Sci*. 1999;889:152.
25. Kirsh VA, Hayes RB, Mayne ST, et al. Supplemental and dietary vitamin E, β-carotene, and vitamin C intakes and prostate cancer risk. *J Natl Cancer Inst*. 2006;98:245.
26. Duffield-Lillico AJ, Reid ME, Turnbull BW, et al. Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: A summary report of the Nutritional Prevention of Cancer Trial. *Cancer Epidemiol Biomarkers Prev*. 2002;11:630.

27. van Gils CH, Peeters PHM, Bueno-de-Mesquita HB, et al. Consumption of vegetables and fruits and risk of breast cancer. *JAMA*. 2005;203:183.
28. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med*. 2006;354:684.
29. Hartman TJ, Albert PS, Snyder K, et al. The association of calcium and vitamin D with risk of colorectal adenomas. *J Nutr*. 2005;135:252.
30. Giovannucci E. The epidemiology of vitamin D and colorectal cancer: Recent findings. *Curr Opin Gastroenterol*. 2006;22:24.
31. Chao A, Thun MJ, Connell CJ, et al. Meat consumption and risk of colorectal cancer. *JAMA*. 2005;293:172.
32. Norat T, Bingham S, Ferrari P, et al. Meat, fish, and colorectal cancer risk: The European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst*. 2005;97:906.
33. Flood A, Velie EM, Sinha R, et al. Meat, fat, and their subtypes as risk factors for colorectal cancer in a prospective cohort of women. *Am J Epidemiol*. 2003;158:59.
34. Willett WC. Diet and cancer: An evolving picture. *JAMA*. 2005;293:233.
35. Terry PD, Rohan TE, Wolk A. Intakes of fish and marine fatty acids and the risks of cancers of the breast and prostate and of other hormone-related cancers: a review of the epidemiologic evidence. *Am J Clin Nutr*. 2003;77:532.
36. Hakim IA, Hartz V, Harris RB, et al. Reproducibility and relative validity of a questionnaire to assess intake of black tea polyphenols in epidemiological studies. *Cancer epidemiol biomarkers prev* 1002;10:667.
37. Arab L, Il'yasova D. The epidemiology of tea consumption and colorectal cancer incidence. *J Nutr*. 2003;133:3310S.
38. Rietveld A, Wiseman S. Antioxidant effects of tea: Evidence from human clinical trials. *J Nutr*. 2003;133:3285S.
39. Weisburger JH, Chung FL. Mechanisms of chronic disease causation by nutritional factors and tobacco products and their prevention by tea polyphenols. *Food Chem Toxicol*. 2002;40;1145–1154.
40. Kim Y-I. Will mandatory folic acid fortification prevent or promote cancer? *Am J Clin Nutr*. 2004;80:1123.
41. Little J, Sharp L, Duthie S, Narayanan S. Colon cancer and genetic variation in folate metabolism: The clinical bottom line. *J Nutr*. 2003;133:4758S.
42. Robien K. Folate during antifolate chemotherapy: what we know . . . and don't know. *Nutr Clin Pract*. 2005;20:411–422.
43. Mattox TW. Treatment of unintentional weight loss in patients with cancer. *Nutr Clin Pract*. 2005;20:400.
44. Barber MD. The pathophysiology and treatment of cancer cachexia. *Nutr Clin Pract*. 2002;17:203.
45. Esper DH, Harb WA. The cancer cachexia syndrome: a review of metabolic and clinical manifestations. *Nutr Clin Pract*. 2005;20:369.
46. Kotler DP. Cachexia. *Ann Intern Med*. 2000;133:622.
47. Capra S, Bauer J, Davidson W, Ash S. Nutritional therapy for cancer-induced weight loss. *Nutr Clin Pract*. 2002;17:210.
48. Baldwin C, Parsons T, Logan S. Dietary advice for illness-related malnutrition. *Cochrane Database Syst Rev*. 2001;CD002008.
49. Klein S, Koretz RL. Nutrition support in patients with cancer: What do the data really show? *Nutr Clin Pract*. 1994;9:91.
50. McGeer AJ, Detsky AS, O'Rourke KO. Parenteral nutrition in cancer patients undergoing chemotherapy: a meta-analysis. *Nutrition*. 1990;6:233.
51. Klein S, Kinney J, Jeejeebhoy K, et al. Nutrition support in clinical practice: review of published data and recommendations for future research directions. *JPEN J Parenter Enteral Nutr*. 1997;21:133.
52. Orr R, Singh MF. The anabolic androgenic steroid oxandrolone in the treatment of wasting and catabolic disorders. *Drugs*. 2004;64:72
53. Gordon JN, Trebble TM, Ellis RD, et al. Thalidomide in the treatment of cancer cachexia: A randomized placebo controlled trial. *Gut*. 2005;54:540.
54. Fearon KC, von Meyenfeldt MF, Moses AG, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: A randomized double blind trial. *Gut*. 2003;52:1479.
55. American College of Physicians. Position paper. Parenteral nutrition in patients receiving cancer chemotherapy. *Ann Intern Med*. 1989;110:734.
56. Savarese DMF, Savy G, Vahdat L, et al. Prevention of chemotherapy and radiation toxicity with glutamine. *Cancer Treatment Rev*. 2003;29:501.
57. Ferreira PR, Fleck JF, Diehl A, et al. Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucositis: A double-blind randomized trial. *Head Neck*. 2004;26:313.
58. Ertekin MV, Koc M, Karslioglu I, et al. Zinc sulfate in the prevention of radiation-induced oropharyngeal mucositis: a prospective, placebo-controlled, randomized study. *Int J Radiat Oncol Biol Phys*. 2004;58:167.
59. Grinspoon S, Mulligan K. Weight loss and wasting in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 2003;36(Suppl 2):S69.
60. Fields-Gardner C, Fergusson P; American Dietetic Association; Dietitians of Canada. Position of the American Dietetic Association and the Dietitians of Canada: Nutrition intervention in the care of persons with human immunodeficiency infection. *J Am Diet Assoc*. 2004;104:1425.

61. Mangili A, Murman DH, Zampini AM, Wanke CA. Nutrition and HIV infection: review of weight loss and wasting in the era of highly active antiretroviral therapy from the Nutrition for Healthy Living cohort. *Clin Infect Dis.* 2006;42:836.
62. Campa A, Yang Z, Lai S, et al. HIV-related wasting in HIV-infected drug users in the era of highly active antiretroviral therapy. *Clin Infect Dis.* 2005;41:1179.
63. Harriman GR, Smith PD, Horne MK. Vitamin B_{12} malabsorption in patients with acquired immunodeficiency syndrome. *Arch Intern Med.* 1989;149:2039.
64. Grunfeld C, Pang M, Shimizu L, et al. Resting energy expenditure, caloric intake, and short-term weight change in human immunodeficiency virus infection and AIDS. *Am J Clin Nutr.* 1992;55:455.
65. Macallan DC, Noble C, Baldwin C, et al. Energy expenditure and wasting in human immunodeficiency virus infection. *N Engl J Med.* 1995;333:83.
66. Melchior J, Chastang C, Gelas P, et al. Efficacy of 2-month total parenteral nutrition in AIDS patients: a controlled randomized prospective trial. *AIDS.* 1996;10:379.
67. Suttmann U, Ockenga O, Selberg O, et al. Incidence and prognostic value of malnutrition and wasting in human immunodeficiency virus-infected outpatients. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995;8:239.
88. Flexner C. HIV-protease inhibitors. *N Engl J Med.* 1998;338:1281.
69. Corcoran C, Grinspoon S. Treatments for wasting in patients with the acquired immunodeficiency syndrome. *N Engl J Med.* 1999;340:1740.
70. Kotler DP. Nutrition and wasting in HIV infection. In: *HIV Clinical Management* (vol 8). Available at: www.medscape.com/home/topics/internalmedicine/internal medicine.html. Accessed November 4, 1999.
71. Lo JC, Mulligan K, Tai VW, et al. Buffalo hump in men with HIV-1 infection. *Lancet.* 1998;351:867.
72. Kotler DP, Wang J, Pierson RN. Body composition studies in patients with the acquired immunodeficiency syndrome. *Am J Clin Nutr.* 1985;42:1255.
73. Kotler DP, Tierney AR, Wang J, et al. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. *Am J Clin Nutr.* 1989;50:444.
74. Ott M, Fischer H, Polat H, et al. Bioelectrical impedance analysis as a predictor of survival in patients with human immunodeficiency virus infection. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995;9:20.
75. Baum MK, Shor-Posner G, Lai S, et al. High risk of HIV-related mortality is associated with selenium deficiency. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;15:370.
76. Keithley JK, Swanson B. Oral nutritional supplements in human immunodeficiency virus disease: a review of the evidence. *Nutr Clin Pract.* 2001;16:98.
77. Watzl B, Watson RR. Role of alcohol abuse in nutritional immunosuppression. *J Nutr.* 1992;122:733.
78. Von Roenn JH, Armstrong D, Kotler DP, et al. Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med.* 1994;121:393.
79. Oster MH, Enders SR, Samuels SJ, et al. Megestrol acetate in patients with AIDS and cachexia. *Ann Intern Med.* 1994;121:400.
80. Henry K, Rathgaber S, Sullivan C, et al. Diabetes mellitus induced by megestrol acetate in a patient with AIDS and cachexia. *Ann Intern Med.* 1992;116:53.
81. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage.* 1995;10:89.
82. Gervasio J. Anabolic agents: Adjuncts to nutrition support. *Nutr Clin Pract.* 2004;19:263.
83. Franks ME, Macpherson GR, Figg WD. Thalidomide. *Lancet.* 2004;363:1802.
84. Van Way CW IIII. Perioperative nutritional support as an adjunct to surgical therapy for cancer. *Nutr Clin Pract.* 2002;17:214.
85. Howard L, Ashley C. Nutrition in the perioperative patient. *Annu Rev Nutr.* 2003;23:263.
86. Naslund E, Hellstrum PM, Kral JG. The gut and food intake: an update for surgeons. *J Gastrointest Surg.* 2001;5:556.
87. Hyltander A, Bosaeus I, Svedlund J, et al. Supportive nutrition on recovery of metabolism, nutritional state, health-related quality of life, and exercise capacity after major surgery: A randomized study. *Clin Gastroenterol Hepatol.* 2005;3:466.
88. Schols AMWJ. Nutritional and metabolic modulation in chronic obstructive pulmonary disease management. *Eur Respir J.* 2003;22(Suppl 46):81S.
89. Lashner BA, Evans AA, Hanauer SB. Perioperative total parenteral nutrition for bowel resection in Crohn's disease. *Dig Dis Sci.* 1989;34:741.
90. Rombeau JL, Barot LR, Williamson CE, et al. Preoperative total parenteral nutrition and surgical outcome in patients with inflammatory bowel disease. *Am J Surg.* 1982;143:139.
91. Patton KM, Arand-Michel J. Nutritional aspects in liver disease and liver transplantation. *Clin Nutr Pract.* 2002;17:332.
92. Riviere S, Gillette-Guyonnet S, Nourhashemi F, et al. Nutrition and Alzheimer's disease. *Nutr Rev.* 1999;57:363.
93. Vellas B, Lauque S, Gillette-Guyonnet S, et al. Impact of nutritional status on the evolution of Alzheimer's disease and on response to acetylcholinesterase inhibitor treatment. *J Nutr Health Aging.* 2005;9:75.
94. Kidd PM. Neurodegeneration from mitochondrial insufficiency: nutrients, stem cells, growth factors, and prospects for brain rebuilding using integrative management. *Altern Med Rev.* 2005;10:268.
95. Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: The Cache County Study. *Arch Neurol.* 2004;61:82.

96. Morris MC, Evans DA, Tangney CC, et al. Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. *Am J Clin Nutr*. 2005;81:508.
97. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study . *N Engl J Med*. 1997;336:1216.
98. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*. 2005;352:2379.
99. Montgomery SA, Thal LJ, Amrein R. Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *Int Clin Psychopharmacol*. 2003;18:61.
100. Grimble RF. Immunonutrition. *Curr Opin Gastroenterol*. 2005;21L216.
101. Alpers DH. Glutamine: Do the data support the cause for glutamine supplementation in humans? *Gastroenterology*. 2006;130:S106.
102. Zaloga GP, Siddiqui R, Terry Cet al. Arginine: Mediator or modulator of sepsis? *Nutr Clin Pract*. 2004;19:201.
103. Heyland DK, Novak F, Drover JW, et al. Should immunonutrition become routine in critically ill patients? *JAMA*. 2001;286:944.
104. Griffiths RD. Specialized nutrition support in critically ill patients. *Curr Opin Crit Care*. 2003;9:249.
105. McCowen KC, Bistrian BR. Immunonutrition: problematic or problem solving? *Am J Clin Nutr*. 2003;77:764.
106. Galban C, Montejo JC, Masejo A, et al. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care patients. *Crit Care Med*. 2000;28:643.
107. Bower RH, Cerra FB, Bershadsky B, et al. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: Results of a multicenter, prospective, randomized clinical trial. *Crit Care Med*. 1995;23:436.
108. Atkinson S, Siefert E, Bihari D. A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. Guys Hospital Intensive Care Group. *Crit Care Med*. 1998;26:164.
109. Montejo JC, Zarazaga A, Lopez-Martinez J, et al. Immunonutrition in the intensive care unit. A systematic review and consensus statement. *Clin Nutr*. 2003;22:221.
110. Martindale MD, Miles J. Is immunonutrition ready for prime time? Two points of view. *Nutr Clin Pract*. 2003;18:489.
111. Sacks GS, Genton L, Kudsk KA. Controversy of immunonutrition for surgical critical-illness patients. *Curr Opin Crit Care*. 2003;9:300.
112. Koretz RL. Immunonutrition: Fact, fantasy, and future. *Curr Gastroenterol Reports*. 2002;4:322.
113. Van der Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345:1359.
114. Krishnan JA, Parce PB, Martinez A, et al. Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. *Chest*. 2003;124:297.
115. Lipkin AC, Lenssen P, and Dickson BJ. Nutrition issues in hematopoietic stem cell transplantation: State of the art. *Nutr Clin Pract*. 2005;20:423.

FACTS AND FORMULAS COMMONLY USED IN NUTRITIONAL THERAPEUTICS

A

Caloric Value of Macronutrients

1 g dietary fat = 9 kcal
1 g carbohydrate = 4 kcal
1 g protein = 4 kcal
1 g ethanol = 7 kcal
1 g medium-chain triglycerides = ~8 kcal
1 g IV dextrose monohydrate = 3.4 kcal
1 mL 10% fat emulsion = 1.1 kcal

Caloric Value of Alcohol-Containing Beverage

$$0.8 \times \frac{\text{Proof of Beverage}}{2} \times \text{Volume of Beverage (dL)} = \text{Weight of Alcohol (g)} \times 7 = \text{kcal}$$

Estimation of Nitrogen Content in Dietary Protein

$$\text{Nitrogen (g)} = \frac{\text{Protein (g)}}{6.25}$$

Estimation of Basal (Resting) Energy Needs (kcal/day)

Harris–Benedict Method for Calculating Basal Metabolic Rate

$$BMR \text{ (women)} = 665 + (9.6 \times W) + (1.8 \times H) - (4.7 \times A)$$

$$BMR \text{ (men)} = 66 + (13.7 \times W) + (5 \times H) - (6.8 \times A)$$

where W = weight (kg)
H = height (cm)
A = age (y)

World Health Organization/Food and Agriculture Organization of the United Nations Equations for Estimating Resting Energy Expenditure

Age (y)	Male	Female
0–3	$(60.9 \times W^a) - 54$	$(61.0 \times W) - 51$
3–10	$(22.7 \times W) - 495$	$(22.5 \times W) + 499$
10–18	$(17.5 \times W) + 651$	$(12.2 \times W) + 746$
18–30	$(15.3 \times W) + 679$	$(14.7 \times W) + 996$
30–60	$(11.6 \times W) + 879$	$(8.7 \times W) + 829$
> 60	$(13.5 \times W) + 987$	$(10.5 \times W) + 596$

[a] Weight in kilograms.

Estimate of Energy Requirements for Patients Based on Body Mass Index[a]

BMI (kg/m^2)	Energy requirements (kcal/kg/day)	
	Critically ill patients (RMR)	Other patients (RMR + TEF + TEA)
<15	35–40	35–40 + 20%
15–19	30–35	30–35 + 20%
20–29	20–25	20–25 + 20%
≥30	15–20[b]	15–20

RMR, resting metabolic rate; TEF, thermal energy of food; TEA, thermal energy of activity.
[a] Use the Harris–Benedict or World Health Organization equation to estimate the requirement for patients whose estimate by this method is less than 1,200 kcal/day.
[b] Do not exceed 2,000 kcal/day.

Estimation of Recommended Daily Protein Intake

Clinical condition	Protein requirements (g/kg IBW/day)[a]
Normal	0.75
Metabolic "stress/illness/injury"	
Mild/moderate	1.0–1.25
Moderate/severe	1.25–1.5
Severe with extra losses (e.g., skin, urine)	1.5–[a]
Renal failure, acute (undialyzed)	0.8–1.0
Hemodialysis	1.2–1.4
Peritoneal dialysis	1.3–1.5
Hepatic encephalopathy	0.4–0.6

IBW, ideal body weight.
[a] Upper limit determined from measured losses.

Estimation of Ideal Body Weight for Adults

Woman with medium frame: 120 lb for first 5 ft of height + 3 lb/in.
Man with medium frame: 130 lb for first 5 ft of height + 3 lb/in.
Small frame: Subtract 10 lb from above.
Large frame: Add 10 lb to above.

Approximate Calorie Equivalent of 1 lb of Body Weight

1 lb = 3,400 kcal

Body Mass Index

$BMI = W\,(kg)/H^2\,(m)$, or $= W\,(lb)/H^2\,(in) \times 703$

Conversion Factors for Major Minerals

1 mEq Na = 1 mmol Na = 23 mg Na
1 g Na = 43 mEq Na = 43 mmol Na

1 mEq K = 1 mmol K = 39 mg K
1 g K = 26 mEq K = 26 mmol K
1 mEq Ca = 0.5 mmol Ca = 20 mg Ca
1 g Ca = 50 mEq Ca = 25 mmol Ca
1 mEq Mg = 0.5 mmol Mg = 12 mg Mg
1 g Mg = 82 mEq Mg = 41 mmol Mg
1 mmol P = 2 mEq HPO_3 = 31 mg P
1 mEq Cl = 1 mmol Cl = 35 mg Cl
1 g Cl = 29 mEq Cl = 29 mmol Cl

Major Mineral Content in Various Compounds and Solutions

1 g NaCl = 393 mg Na = 17 mEq Na
1 g $NaHCO_3$ = 273 mg Na = 12 mEq Na
1,000 mL saline solution = 9 g NaCl = 3.5 g Na = 154 mEq Na
1,000 mL lactated Ringer's solution = 3 g Na = 130 mEq Na
1 ampule (50 mL) 7.5% $NaHCO_3$ = 1 g Na = 44 mEq Na
1 g KCl = 524 mg K = 13 mEq K
1 g $CaCl_2$-$2H_2O$[a] = 273 mg Ca = 13.6 mEq Ca
1 g calcium gluconate[b] = 93 mg Ca = 4.6 mEq Ca
1g $MgSO_4$-$7H_2O$[a] = 99 mg Mg = 8.1 mEq Mg
1 g Mg gluconate-$2H_2O$[a] = 54 mg Mg = 4.4 mEq Mg
1 g $CaCO_3$ = 400 mg Ca = 20 mEq Ca
1 g $FeSO_4$-$7H_2O$[a] = 201 mg Fe
1 g Fe gluconate-$2H_2O$[a] = 116 mg Fe
1 mL Fe dextran = 50 mg Fe

Liquid Measure Equivalents: Volume

Apothecary	Metric	Household
1 fluid gram	4 milliliters (mL)	1 teaspoon (tsp)
1/2 fluid ounce (oz)	15 mL	1 tablespoon (tbs) (3 tsp)
1 oz	30 mL	2 tbs (1/8 cup)
4 oz	118 mL	8 tbs (1/2 cup)
8 oz	237 mL	16 tbs (1 cup)
16 oz	473 mL	1 pint (pt)
32 oz	947 mL	1 quart (qt) (2 pt)
128 oz	3,785 mL	1 gallon (gal) (4 qt)

[a] When weighed in hydrated forms, as indicated.
[b] Small amounts of calcium D-saccharate may be added for stabilization and contribute to the total calcium content.

B RECOMMENDED DIETARY ALLOWANCES

The National Academy of Sciences will release new data on macronutrients in late 2001. Please consult the NAS web site (www.nas.edu) for further information.

TABLE B-1. Dietary Reference Intakes: Recommended Intakes for Individuals

Life stage group	Calcium (mg/day)	Phosphorus (mg/day)	Magnesium (mg/day)	Vitamin D (μg/day)[a,b]	Fluoride (mg/day)	Thiamine (mg/day)
Infants						
0–6 months	210*[1]	100*	30*	5*	0.01*	0.2*
7–12 months	270*	275*	75*	5*	0.5*	0.3*
Children						
1–3 years	500*	**460**	**80**	5*	0.7*	0.5
4–8 years	800*	**500**	**130**	5*	1*	0.6
Males						
9–13 years	1,300*	**1,250**	**240**	5*	2*	**0.9**
14–18 years	1,300*	**1,250**	**410**	5*	3*	**1.2**
19–30 years	1,000*	**700**	**400**	5*	4*	**1.2**
31–50 years	1,000*	**700**	**420**	5*	4*	**1.2**
51–70 years	1,200*	**700**	**420**	10*	4*	**1.2**
>70 years	1,200*	**700**	**420**	15*	4*	**1.2**
Females						
9–13 years	1,300*	**1,250**	**240**	5*	2*	**0.9**
14–18 years	1,300*	**1,250**	**360**	5*	3*	**1.0**
19–30 years	1,000*	**700**	**310**	5*	3*	**1.1**
31–50 years	1,000*	**700**	**320**	5*	3*	**1.1**
51–70 years	1,200*	**700**	**320**	10*	3*	**1.1**
>70 years	1,200*	**700**	**320**	15*	3*	**1.1**
Pregnancy						
≤18 years	1,300*	**1,250**	**400**	5*	3*	**1.4**
19–30 years	1,000*	**700**	**350**	5*	3*	**1.4**
31–50 years	1,000*	**700**	**360**	5*	3*	**1.4**
Lactation						
≤18 years	1,300*	**1,250**	**360**	5*	3*	**1.4**
19–30 years	1,000*	**700**	**310**	5*	3*	**1.4**
31–50 years	1,000*	**700**	**320**	5*	3*	**1.4**

TABLE B-1. Dietary Reference Intakes: Recommended Intakes for Individuals (*Continued*)

Riboflavin (mg/day)	Niacin (mg/day)[c]	Vitamin B_6 (mg/day)	Folate (μg/day)[d]	Vitamin B_{12} (μg/day)	Pantothenic acid (mg/day)	Biotin (μg/day)
0.3*	2*	0.1*	65*	0.4*	1.7*	5*
0.4*	4*	0.3*	80*	0.05*	1.8*	6*
0.5	6	0.5	**150**	**0.9**	2*	8*
0.6	8	0.6	**200**	**1.2**	3*	12*
0.9	**12**	**1.0**	**300**	**1.8**	4*	20*
1.3	**16**	**1.3**	**400**	**2.4**	5*	25*
1.3	**16**	**1.3**	**400**	**2.4**	5*	30*
1.3	**16**	**1.3**	**400**	**2.4**	5*	30*
1.3	**16**	**1.7**	**400**	**2.4**[g]	5*	30*
1.3	**16**	**1.7**	**400**	**2.4**[g]	5*	30*
0.9	**12**	**1.0**	**300**	**1.8**	4*	20*
1.0	**14**	**1.2**	**400**[h]	**2.4**	5*	25*
1.1	**14**	**1.3**	**400**[h]	**2.4**	5*	30*
1.1	**14**	**1.3**	**400**[h]	**2.4**	5*	30*
1.1	**14**	**1.5**	**400**	**2.4**[h]	5*	30*
1.1	**14**	**1.5**	**400**	**2.4**	5*	30*
1.4	**18**	**1.9**	**600**[i]	**2.6**	6*	30*
1.4	**18**	**1.9**	**600**[i]	**2.6**	6*	30*
1.4	**18**	**1.9**	**600**[i]	**2.6**	6*	30*
1.6	**17**	**2.0**	**500**	**2.8**	7*	35*
1.6	**17**	**2.0**	**500**	**2.8**	7*	35*
1.6	**17**	**2.0**	**500**	**2.8**	7*	35*

(*continued*)

TABLE B-1. Dietary Reference Intakes: Recommended Intakes for Individuals (*Continued*)

Life stage group	Choline[e] (mg/day)	Vitamin C (mg/day)	Vitamin E[f] (mg/day)	Selenium (μg/day)	Vitamin A (μg/day)[j]	Vitamin K (μg/day)
Infants						
0–6 months	125*	40*	4*	15*	**400**	2.0
7–12 months	150*	50*	6*	20*	**500**	2.5
Children						
1–3 years	200*	**15**	**6**	**20**	**300**	30
4–8 years	250*	**25**	**7**	**30**	**400**	50
Males						
9–13 years	375*	**45**	**11**	**40**	**600**	60
14–18 years	550*	**75**	**15**	**55**	**900**	75
19–30 years	550*	**90**	**15**	**55**	**900**	120
31–50 years	550*	**90**	**15**	**55**	**900**	120
51–70 years	550*	**90**	**15**	**55**	**900**	120
>70 years	550*	**90**	**15**	**55**	**900**	120
Females						
9–13 years	375*	**45**	**11**	**40**	**600**	60
14–18 years	400*	**65**	**15**	**55**	**700**	75
19–30 years	425*	**75**	**15**	**55**	**700**	90
31–50 years	425*	**75**	**15**	**55**	**700**	90
51–70 years	425*	**75**	**15**	**55**	**700**	90
>70 years	425*	**75**	**15**	**55**	**700**	90
Pregnancy						
≤18 years	450*	**80**	**15**	**60**	**750**	75
19–30 years	450*	**85**	**15**	**60**	**770**	90
31–50 years	450*	**85**	**15**	**60**	**770**	90
Lactation						
≤18 years	550*	**115**	**19**	**70**	**1,200**	75
19–30 years	550*	**120**	**19**	**70**	**1,300**	90
31–50 years	550*	**120**	**19**	**70**	**1,300**	90

This table presents recommended dietary allowances (RDAs) in bold type and adequate intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97%–98%) individuals in a group. For healthy breast-fed infants, the AI is the mean intake. The AIs for other life-stage and gender groups are believed to cover the needs of all individuals in the group, but lack of data or uncertain data make it impossible to specify with confidence the percentage of individuals covered by these intakes.

[a] As cholecalciferol. 1 μg cholecalciferol = 40 IU vitamin D.

[b] In the absence of adequate exposure to light.

[c] As niacin equivalents (NE). 1 mg niacin = 60 mg tryptophan; 0–6 mo = preformed niacin (not NE).

[d] As dietary folate equivalents (DFE). 1 DFE = 1 μg food folate = 0.6 μg of folic acid from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach.

[e] Although AIs have been set for choline, few data have assessed whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages.

[f] As α-tocopherol. α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the *2R*-stereoisomeric forms of α-tocopherol (*RRR-*, *RSR-*, *RRS-*, and *RSS*-α-tocopherol) that

TABLE B-1. Dietary Reference Intakes: Recommended Intakes for Individuals (*Continued*)

Chromium (μg/day)	Copper (μg/day)	Iodine (μg/day)	Iron (mg/day)	Manganese (mg/day)	Molybdenum (μg/day)	Zinc (mg/day)
0.2	**200**	110	**0.27**	0.003	**2**	**2**
5.5	**200**	130	**11**	0.6	**3**	**3**
11	**340**	90	**7**	1.2	**17**	**3**
15	**440**	90	**10**	1.5	**22**	**5**
25	**700**	120	**8**	1.9	**34**	**8**
35	**890**	150	**11**	2.2	**43**	**11**
35	**900**	150	**8**	2.3	**45**	**11**
35	**900**	150	**8**	2.3	**45**	**11**
30	**900**	150	**8**	2.3	**45**	**11**
30	**900**	150	**8**	2.3	**45**	**11**
21	**700**	120	**8**	1.6	**34**	**8**
24	**890**	150	**15**	1.6	**43**	**9**
25	**900**	150	**18**	1.8	**45**	**8**
25	**900**	150	**18**	1.8	**45**	**8**
20	**900**	150	**8**	1.8	**45**	**8**
20	**900**	150	**8**	1.8	**45**	**8**
29	**1,000**	220	**27**	2	**50**	**13**
30	**1,000**	220	**27**	2	**50**	**11**
30	**1,000**	220	**27**	2	**50**	**11**
44	**1,300**	290	**10**	2.6	**50**	**14**
45	**1,300**	290	**9**	2.6	**50**	**12**
45	**1,300**	290	**9**	2.6	**50**	**12**

occur in fortified foods and supplements. It does not include the *2S*-stereoisomeric forms of α-tocopherol (*SRR-, SSR-, SRS-,* and *SSS*-α-tocopherol), also found in fortified foods and supplements.

[g] Because 10%–30% of older people may poorly absorb food-bound vitamin B_{12}, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with vitamin B_{12} or a supplement containing vitamin B_{12}.

[h] In view of evidence linking folate intake with neural-tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume 400 μg from supplements or fortified foods in addition to intake of food folate from a varied diet.

[i] It is assumed that women will continue consuming 400 μg from supplements or fortified food until their pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period—the critical time for formation of the neural tube.

[j] As retinol activity equivalents (RAE). 1 RAE = 1 μg all-*trans*-retinol, 12 μg β-carotene, 24 μg β-carotene, or 24 μg β-cryptoxanthin.

From the National Academy of Sciences. Reprinted courtesy of the National Academies Press, Washington, DC, 2000.

TABLE B-2. Dietary Reference Intakes (DRIs): Recommended Intakes for Individuals, Energy, Total Water, and Macronutrients

Life stage group	Energy (EER) (kcal/day)[a]	Total water[b] (L/day)	Carbohydrate (g/day)	Total fiber (g/day)	Linoleic acid (g/day)	Protein[c]	
						(g/day)	(g/kg/day)[d]
Infants							
0–6 months	570 (male)	0.7*	60*	ND	4.4*	9.1*	—
3 months	520 (female)						
7–12 months	743 (male)	0.8*	95*	ND	4.6*	**11.0**	1.0
Children							
1–3 years		1.3*	**130**	19*	7*	**13**	0.87
1–2 years	1,046 (male)						
24 months	992 (female)						
4–8 years		1.7*	**130**	25*	10*	**19**	0.76
3–8 years	1,742 (male)						
6 years	1,642 (female)						
Males							
9–13 years	2,279	2.4*	**130**	31*	12*	**34**	0.76
14–18 years	3,152 (14–17 years)	3.3*	**130**	38*	16*	**52**	0.73
18 years	3,067						
19–30 years	#	3.7*	**130**	38*	17*	**56**	0.66
31–50 years	#	3.7*	**130**	38*	17*	**56**	0.66
51–70 years	#	3.7*	**130**	30*	14*	**56**	0.66
>70 years	#	3.7*	**130**	30*	14*	**56**	0.66
Females							
9–13 years	2,071 (11 years)	2.1*	**130**	26*	10*	**34**	0.76
14–18 years	2,368 (16 years)	2.3*	**130**	26*	11*	**46**	0.71
19 years	2,403						
19–30 years	^	2.7*	**130**	25*	12*	**46**	0.66
31–50 years	^	2.7*	**130**	25*	12*	**46**	0.66
51–70 years	^	2.7*	**130**	21*	11*	**46**	0.66
>70 years	^	2.7*	**130**	21*	11*	**46**	0.66

Pregnancy							
14–18 years		3.0*	**175**	28*	13*	**71**	0.88
19–50 years	2,403 (1st)[e] 2,743 (2nd) 2,855 (3rd)	3.0*	**175**	28*	13*	**71**	0.88
Lactation							
14–18 years		3.8*	210	29*	13*	**71**	1.05
19–50 years	2,733 (6 months)[e] 2,803 (6–12 months)	3.8*	210	29*	13*	**71**	1.05

Recommended dietary allowances (RDAs) are shown in bold type and adequate intakes (AIs) are marked by an asterisk (*).
[a] Estimated energy requirement (EER) applies to moderately active residents of the United States and Canada, and is appropriate for individuals of the reference weight, height, and age (see Table 5-9).
[b] Total water includes all water in food, beverages, and drinking water.
[c] Protein (g/day) is based on the g protein/kg of body weight for the reference body weight for groups, as in the next column.
[d] These figures represent the estimated average requirements (EARs) for assessing adequacy of population intakes and as the basis for calculating recommended dietary allowances (RDAs) for individuals.
[e] These figures for EER apply to pregnant women age 19, either in each of the three trimesters of pregnancy, or in the first two 6-month periods of breast feeding.
For all males ages >19 years, subtract 10 kcal/day/year.
^ For all females ages >19 years, subtract 7 kcal /day/year.
Adapted from *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005); and *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005), National Academies Press, Washington, DC.

TABLE B-3. Dietary Reference Intakes: Tolerable Upper Intake Levels[a]

Life stage group	Calcium (g/day)	Phosphorus (g/day)	Magnesium (g/day)[b]	Vitamin D (μg/day)	Fluoride (mg/day)	Niacin (mg/day)[c]
Infants						
0–6 months	ND[e]	ND	ND	25	0.7	ND
7–12 months	ND	ND	ND	25	0.9	ND
Children						
1–3 years	2.5	3	65	50	1.3	10
4–8 years	2.5	3	110	50	2.2	15
Males, females						
9–13 years	2.5	4	350	50	10	20
14–18 years	2.5	4	350	50	10	30
19–70 years	2.5	4	350	50	10	35
>70 years	2.5	3	350	50	10	35
Pregnancy						
≤18 years	2.5	3.5	350	50	10	30
19–50 years	2.5	3.5	350	50	10	35
Lactation						
≤18 years	2.5	4	350	50	10	30
19–50 years	2.5	4	350	50	10	35

TABLE B-3. Dietary Reference Intakes: Tolerable Upper Intake Levels[a] (*Continued*)

Vitamin B_6 (mg/day)	Folate (μg/day)[c]	Choline (mg/day)	Vitamin C (mg/day)	Vitamin E (mg/day)[d]	Selenium (μg/day)	Vitamin A (μg/day)
ND	ND	ND	ND	ND	45	600
ND	ND	ND	ND	ND	60	600
30	300	1.0	400	200	90	600
40	400	1.0	650	300	150	900
60	600	2.0	1,200	600	280	1,700
80	800	3.0	1,800	800	400	2,800
100	1,000	3.5	2,000	1,000	400	3,000
100	1,000	3.5	2,000	1,000	400	3,000
80	800	3.0	1,800	800	400	2,800
100	1,000	3.5	2,000	1,000	400	3,000
80	800	3.0	1,800	800	400	2,800
100	1,000	3.5	2,000	1,000	400	3,000

(*continued*)

TABLE B-3. Dietary Reference Intakes: Tolerable Upper Intake Levels[a] (*Continued*)

Life stage group	Copper (μg/day)	Iodine (μg/day)	Iron (mg/day)	Manganese (mg/day)	Molybdenum (μg/day)	Zinc (mg/day)
Infants						
0–6 months			40			4
7–12 months			40			5
Children						
1–3 years	1,000	200	40	2	300	7
4–8 years	3,000	300	40	3	600	12
Males, females						
9–13 years	5,000	600	40	6	1,100	23
14–18 years	8,000	900	45	9	1,700	34
19–70 years	10,000	1,100	45	11	2,000	40
>70 years	10,000	1,100	45	11	2,000	40
Pregnancy						
≤18 years	8,000	900	45	9	1,700	34
19–50 years	10,000	1,100	45	11	2,000	40
Lactation						
≤18 years	8,000	900	45	9	1,700	34
19–50 years	10,000	1,100	45	11	2,000	40

ND, not determined because of lack of data for adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be food only to prevent high levels of intake.

[a] The tolerable upper intake level (UL) is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Because of a lack of suitable data, ULs could not be established for thiamine, riboflavin, vitamin B_{12}, pantothenic acid, or biotin. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b] The ULs for magnesium represent intake from a pharmacologic agent only and do not include intake from food and water.

[c] The ULs for niacin and folate apply to synthetic forms obtained from supplements, fortified foods, or a combination of these.

[d] As α-tocopherol; applies to any form of supplemental α-tocopherol.

From the National Academy of Sciences. Reprinted courtesy of the National Academies Press, Washington, DC, 2000 and 2001.

FOOD LABELING C

NEW REGULATIONS

Both the Food and Drug Administration (FDA) and the U.S. Department of Agriculture Food Safety and Inspection Service (FSIS) have established regulations for food labeling (*Code of Federal Regulations*; Title 21, Vol. 2, Parts 100 to 169, 4/1/99). The FDA rules comply with the provisions of the Nutrition Labeling and Education Act of 1990, and the FSIS rules are coordinated with the FDA rules. The FDA rules became effective May 8, 1994, and apply to most processed foods. Nutritional information is also available for fresh fruits and vegetables and raw fish at the point of purchase. The FSIS rules became effective July 6, 1994, and apply to meat and poultry products.

NUTRITION PANEL

The new food label has a revised nutrition panel that is now headed "Nutrition Facts." A new set of dietary components appears on the nutrition panel (Table C-1). These mandatory and voluntary components are the only ones allowed on the nutrition label and must be presented in the order given. "Voluntary" nutrients can be included if the manufacturer chooses; however, if a claim is made about them, or if a food is fortified or enriched with them, then they must be listed. This list of nutrients has been chosen because it reflects health concerns in the population. Nutrients are listed in the order of priority of current dietary recommendations. Thiamine, riboflavin, and niacin, which were required elements on the old nutrition label, are not required on the new nutrition label because they are no longer considered to be of public health significance; however, they can be listed voluntarily.

Data for each of the nutrients must be presented as grams (or milligrams) per serving and as percentage of daily value (Figure C-1). Daily values are a new way of presenting nutritional information. Percentage of daily value expresses the amount of a nutrient in a serving of a particular food as a percentage of the amount of the nutrient that would be consumed in a 2,000-calorie balanced diet. Daily values are based on two sets of new dietary standards, daily reference values (DRVs) and reference daily intakes (RDIs); however, only the term *daily value* appears on the label. DRVs have been established for fat, carbohydrate, protein, cholesterol, sodium, and potassium. DRVs for the energy-producing nutrients (fat, carbohydrates, and protein) are based on the number of calories consumed per day. The daily values that appear at the top of the nutrition label are based on a 2,000-calorie diet. Adjustments for other caloric intakes are included at the bottom of the label.

The DRVs for Macronutrients Are Calculated as Follows:

1. Fat is based on 30% of calories.
2. Saturated fat is based on 10% of calories.
3. Carbohydrates are based on 60% of calories.
4. Protein is based on 10% of calories.
5. Fiber is based on 11.5 g per 1,000 calories.

TABLE C-1. Mandatory and Voluntary Dietary Components of the Nutrition Panel

Total calories
Calories from fat
Calories from saturated fat
Total fat
Saturated fat
Polyunsaturated fat
Monounsaturated fat
Cholesterol
Sodium
Potassium
Total carbohydrate
Dietary fiber
Soluble fiber
Insoluble fiber
Sugars
Sugar alcohol (e.g., the sugar substitutes xylitol, mannitol, and sorbitol)
Other carbohydrates (difference between total carbohydrate and the sum of dietary fiber, sugars, and sugar alcohol if declared)
Protein
Vitamin A
Vitamin C
Calcium
Iron
Other essential vitamins and minerals

The DRVs for Some Nutrients Represent the Upper Limits of the Desirable Range based on Public Health Recommendations:

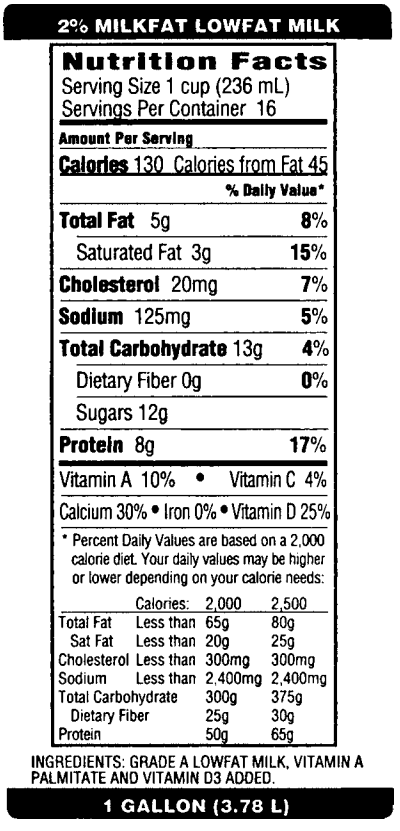
1. Total fat should be less than 65 g.
2. Saturated fat should be less than 20 g.
3. Cholesterol should be less than 300 mg.
4. Sodium should be less than 2,400 mg.

Reference Daily Intakes

The RDIs are reference values for vitamins and minerals; *RDI* replaces the term *U.S. recommended dietary allowance (RDA)*. The values for the RDIs are the same as those for the old U.S. RDAs. The required data for vitamin A, vitamin C, calcium, and iron are presented as a percentage of the RDI. Voluntary data for other vitamins and minerals are presented in the same way.

Daily values may be confusing for consumers because some of the data, such as those for vitamin A, vitamin C, iron, and calcium, are presented as a percentage of the smallest desirable daily intake, whereas other data, such as those for fat, cholesterol, and sodium, are presented as a percentage of the maximum recommended daily allowance. Thus, consumers may misinterpret the labels as indicating that at least 300 mg of cholesterol and at least 2,400 mg of sodium should be consumed, rather than no more than 300 mg of cholesterol and no more than 2,400 mg of sodium.

All the data in the new nutrition label are presented in relation to a defined serving size (which is presented in both household and metric measures); the same serving sizes must be used by all manufacturers. Under the old regulations, serving sizes were defined by the food manufacturer; under the new regulations, the serving sizes are defined by the FDA and represent amounts that people actually consume.



2% MILKFAT LOWFAT MILK

Nutrition Facts

Serving Size 1 cup (236 mL)
Servings Per Container 16

Amount Per Serving

Calories 130 Calories from Fat 45

% Daily Value*

Total Fat 5g	**8%**
Saturated Fat 3g	**15%**
Cholesterol 20mg	**7%**
Sodium 125mg	**5%**
Total Carbohydrate 13g	**4%**
Dietary Fiber 0g	**0%**
Sugars 12g	
Protein 8g	**17%**

Vitamin A 10% • Vitamin C 4%

Calcium 30% • Iron 0% • Vitamin D 25%

* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g
Protein		50g	65g

INGREDIENTS: GRADE A LOWFAT MILK, VITAMIN A PALMITATE AND VITAMIN D3 ADDED.

1 GALLON (3.78 L)

FIGURE C-1. Representative nutrition panel

NUTRIENT CONTENT DESCRIPTORS

The new regulations define terms that may be used to describe the level of a nutrient in a food.

Free

The term *free* means that a product does not contain the nutrient, or contains only a trivial or "physiologically inconsequential" amount. *Calorie-free* means less than 5 calories per serving. *Sugar-free* and *fat-free* both mean less than 0.5 g per serving.

Low

The general definition for *low* is that it is possible to consume a food low in a nutrient frequently during the course of a day without exceeding the dietary guidelines.

1. *Low in fat* means 3 g or less per serving.
2. *Low in saturated fat* means 1 g or less per serving.
3. *Low in sodium* means less than 140 mg per serving.
4. *Very low in sodium* means less than 35 mg per serving.
5. *Low in cholesterol* means less than 20 mg per serving.
6. *Low in calories* means 40 calories or less per serving.

Lean and Extralean

These terms are used to describe meats, poultry, and seafood. *Lean* means less than 10 g of fat, less than 4 g of saturated fat, and less than 95 mg of cholesterol per serving and per 100 g. *Extralean* means less than 5 g of fat, less than 2 g of saturated fat, and less than 95 mg of cholesterol per serving and per 100 g.

High

High means that a single serving of a food contains 20% or more of the daily value for a particular nutrient.

Good Source

The term *good source* means that one serving of a food contains 10% to 19% of the daily value for a particular nutrient.

Reduced

The term *reduced* means that a nutritionally altered product contains 25% less of a nutrient or 25% fewer calories than the regular (unaltered) product. A claim that a product is *reduced* cannot be made if the reference food already meets the requirements for a *low* claim.

Less

The term *less* means that a food contains 25% less of a nutrient or 25% fewer calories than the reference food. Pretzels with 25% less fat than potato chips can carry the *less* claim.

Light

The term *light* can mean that an altered product contains one-third fewer calories or half the fat of the reference item. If more than 50% of the calories in a food are derived from fat, then the fat must be reduced by 50% if the food is to qualify for a *light* claim. *Light* can also mean that the sodium content of a low-calorie, low-fat food has been reduced by 50%. A claim of *light in sodium* may be used on foods in which the sodium content has been reduced by 50%. The term *light* also can be applied to color and texture, in such terms as *light brown sugar*, as long as the meaning is clear.

More

The term *more* means that the quantity of a nutrient in a serving of food is at least 10% greater than the daily value of the reference food. The terms *enriched*, *fortified*, and *added* also can be used if the quantity of a nutrient is at least 10% greater than the daily value of the reference food, and in this case, the food must be altered.

Percentage Fat-free

To qualify for this claim, a product must meet the definition for *low in fat* or *fat-free*. In addition, the value for *percentage fat-free* must reflect the amount of fat in 100 g of the food. Thus, if a claim is to be made that a food is *95% fat-free*, 100 g of the food must contain no more than 5 g of fat.

Implied

Claims cannot be made when they wrongfully imply that a food contains or does not contain a meaningful level of a nutrient. Thus, one cannot claim that a food is "made with oat bran," implying that the food is a good source of fiber, unless the product contains enough oat bran to meet the definition for a *good source* of fiber.

Meals and Main Dishes

Claims for the amount of sodium or cholesterol in a meal or main dish must meet the same requirements as those for individual foods. Some other definitions are more

relaxed; *low-calorie*, when applied to a meal or main dish, means that the meal or main dish contains no more than 120 calories per 100 g.

Healthy

The term *healthy* can be used to describe a food that is low in fat and saturated fat and that contains no more than 480 mg of sodium and no more than 60 mg of cholesterol per serving.

Fresh

When the term *fresh* is used to suggest that a food is raw or unprocessed, it can be used only to refer to a food that has never been frozen or heated and that contains no preservatives (irradiation at low levels is allowed). The term *fresh frozen* can be used for foods that are quickly frozen while still fresh. Brief scalding before freezing (blanching) is allowed.

HEALTH CLAIMS

The FDA allows health claims for relationships between several nutrients and risk for a particular disease. The claims for the food product must meet the requirements for authorized health claims. They cannot state the degree of risk reduction and must use the word *may* or *might* in discussing the relationship between the nutrient and the disease. The claims also must phrase the relationship between the nutrient and the disease in a way that the consumer can understand. An example of an appropriate claim is the following: "While many factors affect heart disease, diets low in saturated fat and cholesterol may reduce the risk for heart disease." Claims for the following nutrient–disease relationships are allowed on food labels:

Calcium and Osteoporosis

A food must contain 20% or more of the daily value for calcium (200 mg) per serving, as much or more calcium than phosphorus, and a form of calcium that is readily absorbed. The claim must name the target groups most in need of an adequate calcium intake (teenagers and young, adult white and Asian women) and state the requirement for exercise and a healthy diet to prevent osteoporosis. A product that contains 40% or more of the daily value for calcium must state on the label that a total dietary intake of more than 200% of the daily value for calcium ($\geq$2,000 mg) is not known to be of additional benefit.

Fat and Cancer

To carry this claim, a food must meet the requirements for *low in fat* or, if the food is fish or a game meat, for *extralean*.

Saturated Fat and Cholesterol in Coronary Heart Disease

This claim may be used if the food meets the requirements for the descriptors *low in saturated fat*, *low in cholesterol*, and *low in fat*, or, if the food is fish or a game meat, for *extralean*. It may mention the link between a reduced risk for coronary heart disease and lower intakes of saturated fat and cholesterol to lower blood cholesterol levels.

Fiber-containing Grain Products, Fruits, and Vegetables and Cancer

To carry this claim, a food must be or contain a grain product, fruit, or vegetable, meet the requirements for the descriptor *low in fat*, and be a *good source* of dietary fiber without fortification.

Fruits, Vegetables, and Grain Products that Contain Fiber and Risk for Coronary Heart Disease

To carry this claim, a food must be or contain fruits, vegetables, or grain products. It also must meet the requirements for the descriptors *low in saturated fat*, *low in cholesterol*, and *low in fat* and contain, without fortification, at least 0.6 g of soluble fiber per serving.

Sodium and Hypertension

To carry this claim, a food must meet the requirements for the descriptor *low in sodium*.

Fruits and Vegetables in Cancer

This claim may be made for fruits and vegetables that meet the requirement for the descriptor *low in fat* and that, without fortification, are a *good source* of at least one of the following: dietary fiber, vitamin A, or vitamin C. This claim relates diets low in fat and rich in fruits and vegetables (and thus vitamins A and C and dietary fiber) to a reduced risk for cancer.

Folate and Neural Tube Defects

When pregnant women consume a diet containing a minimum of 400 μg of folate per day, the risk for neural tube defects in the fetus is reduced. Foods containing 400 μg of folate can make this claim.

Sugar Alcohols and Dental Caries

Between-meal consumption of foods high in sugars promotes tooth decay. Foods containing sugar alcohols, such as sorbitol, can claim an association with a reduced risk for tooth decay.

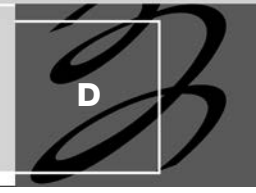
Soluble Fiber from Oats or Psyllium and Coronary Artery Disease

Foods that provide 3 g or more of B-glucan soluble fiber from whole oats per day or 7 g of soluble fiber from psyllium seed husk per day can claim an association with a reduced risk for coronary artery disease.

Soy Protein and Coronary Artery Disease

Foods containing at least 6.25 g of soy protein per serving can claim an association with a reduced risk for coronary artery disease.

DIETARY GUIDES FOR PATIENT USE



The diets outlined on the following pages are meant to be practical guides for patients. They should be given to patients along with explanations by the physician and individualized according to need. In some instances, the diet is sufficiently complex that referral to a dietitian will be needed. Those diets that require such expertise (e.g., diabetic, low-cholesterol, gluten-free diets, or diets with strict sodium restrictions) are not included here.

TABLE D-1. Patient's Guide to a Clear Liquid Diet

Food item	Foods allowed	Foods not allowed
Beverages		
Milk	None	All
Milk-free beverages	Carbonated beverages, coffee, iced tea, Kool-Aid, tea	Lemonade, orangeade
Available supplements	Citrotein, Polycose, Precision LR, Vivonex, Ensure	All other supplements
Soups	Broth, bouillon, consommé	All others
Animal protein sources		
Meat	None	All
Poultry	None	All
Fish	None	All
Nonmeat protein sources	None	All
Vegetables	None	All
Potato and substitutes	None	All
Breads and cereals	None	All
Fruits	Strained fruit juice	All others
Fats	None	All
Combination dishes	None	All
Snacks	None	All
Desserts and snacks	Flavored gelatin, hard sugar candy, honey, plain sugar	All others
Miscellaneous	None	Spices, condiments, seasonings

The unsupplemented clear liquid diet does not provide adequate calories, protein, vitamins, or minerals. It is not designed to be used for prolonged periods. Supplementation with commercial products (see below) can provide adequate nutrition.
Supplementation: One liter of clear liquid diet (fruit juices) plus three 8-oz servings of Ensure plus three 8-oz servings of Citrotein provide 1,760 cal with 58 g of protein and adequate vitamins and minerals.
Modified from *Barnes-Jewish Hospital Nutrition Guide.*

TABLE D-2. Dietary Preparation for Occult Blood Testing

1. Avoid these drugs: iron supplements, aspirin, nonsteroidal anti-inflammatory drugs, vitamin C supplements.
2. Avoid these foods for 72 hours before the test: rare red meat, broccoli, turnips, cantaloupe, cauliflower, red radishes, bean sprouts, cucumber, green beans, parsley, zucchini, lemon rind, mushrooms, and horseradish.
3. Chicken, turkey, and fish are low in peroxidase activity and may be eaten.

TABLE D-3. Patient's Guide to a Restricted-fat Diet

General guidelines
1. Meats should be baked or broiled, not fried.
2. The skin of chicken and turkey should be removed.
3. Avoid most desserts (cakes, cookies, pies, pastry, candy).
4. Avoid sauces and gravies.

Food item	Foods allowed	Foods not allowed
Beverages		
Milk	Skim milk and the following products if prepared with skim milk: buttermilk, instant breakfast	Chocolate milk, cocoa, eggnog, malted drinks, milkshakes, Ovaltine, 2% or whole milk
Milk-free beverages	Any	None
Available supplements	Casec, Citrotein, MCT oil, Polycose, Precision LR, Vivonex	Ensure, Portagen
Soups	Bouillon, consommé, fat-free broth, soups prepared with allowed foods	Cream soups
Animal protein sources		
Meat (any of the following foods or a combination of these foods must be limited to 7 oz/day)	Any whole or ground lean cuts of meat: beef, lamb, organ meats, pork, rabbit, squirrel, veal, venison	Creamed or fried meats, frankfurters, heavily marbled and fatty meats, luncheon meats, mutton, sausages, spare ribs
Poultry	Chicken, Cornish hen, turkey	Creamed or fried poultry, duck, goose
Fish	Fish, shellfish	Salted mackerel and the following fish if packed in oil: salmon, sardines, tuna; any creamed or fried fish
Nonmeat protein sources		
Any of these may be substituted for animal sources of protein	Boiled, poached, or scrambled egg; any cheese or yogurt	Fried eggs; canned pork and beans
Total protein must not exceed 7 oz/day	Dried beans, lentils, meat extenders, peas	Nuts, nut butter, peanut butter, soybeans
Vegetables	Canned, fresh, or frozen vegetables	Au gratin or creamed vegetables; avocado
Potato and substitutes	Any	Au gratin or creamed potato or pasta
Breads and cereals	All breads except those not allowed; any cereals prepared with skim milk; bread sticks, croutons, graham crackers, matzoh, melba toast, saltines, zwieback	Barley, biscuits, buns, cereals prepared with whole or 2% milk, cheesebread, cornbread dressing, crackers, dumplings, French toast, muffins, pancakes, rolls, waffles, except those allowed

(*continued*)

TABLE D-3. Patient's Guide to a Restricted-fat Diet (*Continued*)

Food item	Foods allowed	Foods not allowed
Fruits	Any canned, dried, fresh, or frozen fruit	None
Fats	None	All (margarine, butter, salad oil, mayonnaise)
Combination dishes	Any combination dish prepared with allowed foods	Any combination dish prepared with foods not allowed
Snacks	Unbuttered popcorn popped without oil	All other snacks
Desserts and sweets	Angel food cake, honey, plain flavored gelatin, plain sherbet or ices, sponge cake, sugars	Pies, other cakes and cookies, custard, Danish pastry, doughnuts, ice cream
Miscellaneous	Baking powder, baking soda, brewer's yeast	Gravy, olives

Modified from *Barnes-Jewish Hospital Nutrition Guide.*

TABLE D-4. Patient's Guide to a Minimal Lactose Diet

What is lactose?

Lactose is a sugar found in milk and milk products. When the body is unable to digest this sugar, it causes gas, bloating, and diarrhea. The best way to prevent this is by eliminating lactose-containing foods from the diet.

General instructions

1. Avoid milk and liquid milk products.
2. Read labels carefully. Products containing milk, milk products, milk solids, whey, curd, casein, lactose, galactose, skim milk powder, skim milk solids, or milk sugar contain lactose. Many patients can tolerate small doses of lactose and need not be so cautious with restricting their intake of prepared foods containing small amounts of lactose. Often, however, the amount of lactose is not stated on the label.
3. Milk or cream should not be used in cooking.
4. Small amounts of cheese and butter may be tolerated.
5. Commercially available fermented milk products (buttermilk, yogurt) are sweetened by adding cream or milk and are not low in lactose. Homemade yogurt is lower in lactose content, but considerable amounts of lactose remain. Nearly complete fermentation would produce an inedible product. However, natural yogurt is allowed in moderate amounts because the bacteria in the yogurt digest the lactose after it is eaten.

(*continued*)

TABLE D-4. Patient's Guide to a Minimal Lactose Diet (*Continued*)

Food item	Foods allowed	Foods not allowed
Meat, fish, poultry, cheese	Beef, veal, lamb, pork, fish, poultry, cold cuts (check labels for nonfat dry milk)	Creamed or breaded fish, meat, or poultry; sausage, frankfurters, and cold cuts containing nonfat dry milk; all cheese and cheese products
Eggs	Any prepared with allowed foods	Eggs prepared with milk products
Bread	Any bread or crackers that do not contain milk or milk products	All bread products, crackers, cereals containing milk or lactose
Cereals	Any that do not contain milk or milk products (e.g., oatmeal, puffed rice, shredded wheat, grapenuts, cornflakes, puffed wheat)	
Vegetables and vegetable juices	All vegetables and vegetable juices	Vegetables prepared with butter, margarine, milk, or cheese
Fruits and fruit juices	All except those listed to avoid	Canned or frozen fruits and fruit juices prepared with lactose
Beverages	Coffee, tea, carbonated beverages and cereal beverages, soy milk substitutes	All milk and milk drinks (skim, dried, evaporated, condensed), powdered soft drinks, whey, casein
Soups	Broth-based soups prepared with meat and vegetables only	All other soups
Fats	Bacon, lard, peanut butter, pure mayonnaise, vegetable oils, some cream substitutes (check labels), milk-free margarine	Butter, margarine, cream substitutes with added milk solids, salad dressings, sour cream
Desserts	Angel food cake; cakes made with vegetable oils; gelatin, puddings prepared with fruit juices, water, or allowed milk substitutes; fruit ices	Desserts prepared with milk and butter or margarine, commercial desserts and mixes, yogurt, sherbet
Potatoes or substitutes	White or sweet potato, hominy, macaroni, rice, spaghetti, noodles	Commercial potato products; any substitutes with milk, cheese, or butter

(*continued*)

TABLE D-4. Patient's Guide to a Minimal Lactose Diet (*Continued*)

Miscellaneous	Corn syrup, honey, nuts, nut butters, olives, pickles, pure seasonings and spices, pure sugar candies, some cream substitutes, sugar, popcorn made with allowed fats	Ascorbic acid and citric acid mixtures, butterscotch, caramels, chewing gum, chocolate candy, cordials, liqueurs, dried soups, frozen cultures, health and geriatric foods, molasses

Caution: This diet may be deficient in calcium; check with your physician to see if calcium supplements are required.
Enzyme replacement: Lactose-depleted milk can be prepared by hydrolysing the lactose with a yeast enzyme preparation (Lactaid, Sugarlo Company, Atlantic City, NJ 08404). When one packet containing lactase from the yeast *Kluveromyces lactis* is mixed with 1 quart of milk at 4ºC, lactose is 70% hydrolysed in 1 day and 90% hydrolysed in 2 or 3 days. Patients with limited tolerance can use this milk, which is sweeter than regular milk but well accepted in cooking or on cereal. Dairy products other than milk cannot be treated in this way.
Milk substitutes: A few chemically defined products are now available that simulate milk and use corn solids as the carbohydrate source. These products (e.g., Coffee Rich, Vita Rich) can be used as milk substitutes if the taste is acceptable, but their sugar content is high.
Modified from *Barnes-Jewish Hospital Nutrition Guide.*

TABLE D-5. Patient's Guide to a Low-oxalate Diet

Foods high in oxalate (>10 mg/serving). Avoid completely.
Beans in tomato sauce, beets, celery, chard, collards, dandelion greens, eggplant, escarole, leek, okra, parsley, green pepper, sweet potatoes, spinach, summer squash, blueberries, blackberries, black and red raspberries, strawberries, currants, Concord grapes, lemon and lime peel, rhubarb, draft beer or stout, Ovaltine, tea, chocolate, cocoa, nuts (especially peanuts and pecans), wheat germ, tomato soup, tofu, juices containing berries

Foods moderately high in oxalate (2–10 mg/serving). Limit to two 1/2-cup servings per day.
Sardines, asparagus, broccoli, carrots, corn, cucumber, canned peas, lettuce, lima beans, parsnips, tomato, turnips, apples, apricots, oranges, peaches, pears, pineapple, prunes, cornbread, sponge cake, chicken noodle soup (dried), pepper (>1 tsp/day), coffee (8 oz), orange or tomato juice (4 oz), cola beverage (12-oz limit/day), bottled beer (12-oz limit/day)

Foods low in oxalate (0–2 mg/serving). Eat as desired.
Avocado, brussels sprouts, cauliflower, cabbage, mushrooms, onions, peas (fresh), radishes, milk, yogurt, eggs, cheese, lean lamb, lean beef, lean pork, poultry, seafood, bananas, Bing cherries, grapefruit, green grapes, melons, nectarines, plums, rice, spaghetti, white bread, noodles, oatmeal, bacon, oils, salad dressing, jellies or preserves, apple juice, wine, lemonade or limeade (without peel)

TABLE D-6. Patient's Guide to a Higher-fiber Diet

A high-fiber diet contains 30 to 45 g of fiber per day. Dietary fiber can be increased by increasing the consumption of high-fiber foods or by supplementing the diet with commercial fiber supplements.

1. High-fiber foods

5 grams of total dietary fiber

Baked beans (1/4 cup)
Split peas (1/2 cup)
Butter beans, cooled (1/2 cup)
Blackberries (1/4 cup)
Grapes, white (12)
Raspberries (1/2 cup)
Bran wheat (1/4 cup)
All-Bran (1/3 cup)
Shredded wheat (2 biscuits)
Almonds (15)
Grapenuts (1 cup)
Prunes, stewed (1/2 cup)

4 grams of total dietary fiber

Peas, fresh or canned (1/2 cup)
Turnip greens (1/2 cup)
Broccoli (1 cup)
Apricots (5)
Apple (1 large)
Cranberries (1 cup)
Prunes, dried (3)
Pear (1 medium)
Figs, dried (2)

3 grams of total dietary fiber

Beets, boiled (1/2 cup)
Potato with skin, baked (one 2 1/2-in diameter)
Rye crackers (4)
Fruit pie (9-in diameter, 1/6 of pie)
Corn flakes (1 cup)

2. Commercial supplements

Product	Fiber source	Dose	Dietary fiber (g)
Bran, wheat	Wheat	1 tbsp	1.6
Citrucel	Methylcellulose	1 tbsp	2.0
Fiberall	Psyllium	1 tsp	3.4
FiberCon	Calcium polycarbophil	2 tablets	1.0
Hydrocil Instant	Psyllium	1 tsp	3.5
Konsyl	Psyllium	1 tsp	6.0
Maalox fiber therapy	Psyllium	1 tbsp	3.4
Metamucil			
Regular	Psyllium	1 tsp	3.4
Water	Psyllium	Water	3.0
Mylanta fiber supplement	Psyllium	1 tsp	3.4
Perdiem plain	Psyllium	1 tsp	4.0
Serutan toasted granules		1 tsp	2.5
Syllact	Psyllium	1 tsp	3.3

TABLE D-7. Patient's Guide to a Minimal-fiber Diet

This diet does not provide the minimal requirements for some nutrients and is not intended for long-term use. It can be used as a preoperative or postoperative diet for patients undergoing certain abdominal procedures or during some attacks of acute diverticulitis. It is not appropriate for the long-term management of diverticular disease or intestinal strictures.

Food item	Foods allowed	Foods not allowed
Beverages		
Milk	Any	None
Milk-free beverages	Any	None
Available supplements	Any	None
Soups	Any creamed or broth-based soups without vegetables	Soups with vegetables
Animal protein sources		
Meat	Any	None
Poultry	Any	None
Fish	Any	None
Nonmeat protein sources	Any cheese, yogurt made without fruit or seeds, any eggs, meat extenders, smooth peanut butter	Yogurt with seeds or fruit, chunky peanut butter, dried beans, lentils, nuts, peas, seeds
Vegetables	None	All vegetables
Potato and substitutes	Potato without skin	Kasha
Breads and cereals	Bagels, biscuits, bread crumbs, bread sticks without seeds, cornbread, croutons, enriched white or whole grain rolls made from finely milled flour, French toast, graham crackers, matzoh, pancakes, refined cereals, rusk, saltines, waffles	All-Bran, barley, bran flakes, cracked wheat bread and rolls, grapenut flakes, Pettijohns, shredded wheat, Wheat Chex
Fruits	Strained fruit juices	All fruits
Fats	Any fat	None
Combination dishes	Those made with cheese, fish, meat, pasta, or rice	Any made with fruits, vegetables, or other foods not allowed
Snacks	Corn chips, plain crackers without seeds or cracked grain, potato chips, pretzels	Any made from foods not allowed
Desserts and sweets	Any without seeds or fruit	Any made with cracked wheat, fruit, or seeds

Modified from *Barnes-Jewish Hospital Nutrition Guide.*

TABLE D-8. Patient's Guide to the Caffeine Content of Foods

Sensitivity to caffeine is usually proportional to the amount consumed. Some people who cannot tolerate a cup of percolated coffee (97 to 125 mg of caffeine) tolerate a 12-oz Coca-Cola (65 mg), but others cannot tolerate even that much. This table can be used to identify caffeine-containing foods and their relative caffeine content.

Food	Unit	Caffeine content (mg/unit)
Prepared coffee	6-oz cup	
Instant, freeze-dried		61–72
Percolated		97–125
Drip		137–174
Decaffeinated coffee	6-oz cup	
Ground		2–4
Instant		0.5–1.5
Tea, bagged or loose	6-oz cup	15–75
Black, 5-minute brew		40–60
Green, Japanese, 5-minute brew		20
Cocoa	6-oz cup	10–17
Chocolate bar	Bar	60–70
Carbonated drinks	12-oz can	
Coca-Cola		65
Dr. Pepper		61
Mountain Dew		55
Diet Dr. Pepper		54
Tab		49
Pepsi-Cola		43
RC Cola		34
Diet RC		33
Diet Rite		32
Drugs	Tablet	
Cold tablets		30–32
Cafergot		100
NoDoz		100–200

TABLE D-9. Patient's Guide to Mild Sodium Restriction

No special foods are needed unless one prefers to substitute a low-sodium product for a high-sodium food, such as low-sodium tuna for canned tuna, low-sodium crackers for regular salted crackers.

Foods allowed with mild sodium restriction

Meat: poultry, fresh pork, fresh fish, fresh beef
Eggs: no more than two per day
Vegetables: fresh or frozen
Natural cheese (examine label carefully)
Fruits and fruit juices
Bread: white, rye, whole wheat
Milk: whole, 2%, skim
Butter or margarine
Desserts
Salt foods lightly during preparation and *do not add salt at the table*.

High-sodium Foods (one food from this list may be used daily)

Canned vegetables
Meats: cured or smoked meats such as ham, lunch meat (bologna, salami, Braun-schweiger), chipped or corned beef, frankfurters, meats koshered by salting, sausage, smoked tongue, canned meats, canned tuna and salmon packed in oil
Processed cheese, cheese spreads, or Roquefort, Camembert, blue cheese
Salted crackers, cornbread, biscuits
Buttermilk

Foods too high in sodium to be included in your diet

Sauerkraut, pickles
Anchovies, caviar, salted and dried cod, herring, sardines
Snack foods: salted potato chips, pretzels, salted popcorn, salted nuts, Fritos, corn curls, Cheez-Its
Salt pork, ham hock, smoked jowl
Miscellaneous: bouillon, commercial canned and dried soups, olives, soup base, pickles, relishes
Convenience meals: Hamburger Helper, TV dinners, canned chili, canned hash, others
Flavorings: salt and combination salts, such as celery salt, onion salt, garlic salt, seasoned salt; Worcestershire sauce, A-1 sauce, chili sauce, Accent (monosodium glutamate), horseradish (prepared with salt), meat extracts, meat sauces, meat tenderizers, soy sauce
Medications: most antacids, Alka-Seltzer, Rolaids (check with your doctor about over-the-counter medications)
Here is a list of the most common sodium compounds added to foods: When any of these compounds are listed on the label of a food, the food has some sodium. The word *soda* or the abbreviation *Na* on the label will often help you recognize a product that contains a sodium compound. More than one sodium compound indicates a high-sodium food.

Salt	Sodium saccharin
Sodium chloride	Sodium citrate
Baking soda	Sodium alginate
Bicarbonate of sodium	Sodium propionate
Sodium bicarbonate	Sodium benzoate
Baking powder	Sodium sulfite
Brine	Sodium hydroxide
Disodium phosphate	

Modified from *Barnes-Jewish Hospital Nutrition Guide*.

TABLE D-10. Patient's Guide to a Weight Loss Diet

These are guidelines to diet changes for persons who are presently eating a balanced diet and want to lose a small to moderate amount of weight (10 to 20 lb). Weight loss with this program will be slow, about a pound a week. These guidelines are suggested modifications of your present diet rather than an entirely new diet.

1. Eliminate or markedly limit concentrated sources of calories. Foods with a high caloric content and little additional nutritive value include the following: sugar, jelly, syrup, potato chips, crackers, fried foods, gravy, cream sauces, regular soft drinks, ice cream, candy, regular chewing gum, cakes, pastries, and doughnuts.

   Alcoholic beverages also have a high caloric content. A 12-oz beer contains 168 calories, and 2 oz of whiskey contains 172 calories. Many people consume 10% to 20% of their calories as alcoholic beverages. Eliminating alcoholic beverages without other dietary changes would lead to significant weight loss in these people.
2. Change methods of food preparation. The caloric content of food can be greatly affected by the method of preparation. Fried chicken has a higher caloric content than baked chicken. The caloric content of French fries is much greater than that of a baked potato. Similarly, the way food is treated at the table affects caloric content. The salad dressing may have more calories than the salad, the gravy may have more calories than the biscuit, and the sour cream may have more calories than the baked potato.
3. Reduce the portion sizes of foods of high caloric content. Fats have a higher caloric content than carbohydrates or protein. Reducing the portion size of foods high in fat (meat, butter, margarine, salad oil) will reduce caloric intake more than will reducing the portion sizes of foods high in carbohydrates (fruits, vegetables, breads, potatoes, pasta).
4. Add high-fiber, low-calorie foods to the diet. A number of foods contain few calories. These include celery, cucumbers, lettuce, carrots, cauliflower, green peppers, bean sprouts, mushrooms, and onions. A plate of raw vegetables with meals or as a snack can satisfy the desire for food without contributing much to caloric intake.
5. Be aware of calories. Successful weight loss with a low-calorie, nutritionally balanced diet requires that the dieter be aware of the caloric content of foods. Buy and use one of the pocket calorie counters that are available at all major bookstores.

INDEX

Page numbers followed by a *t* refer to tables; those followed by an *f* refer to figures.