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Review article

Trends in the organization of drug research: interfacing industry and universities[1]

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Abstract

This article shortly describes some of the current social, political and scientific developments that are considered to be of relevance for the future organization of drug research in Europe. Attention is paid to the social-political changes that affect the academic and industrial research teams. These developments will inevitably lead to a closer and more structured collaboration between universities and pharmaceutical/chemical companies, for example, in the fields of drug delivery research, molecular pathophysiology and clinical drug studies. The creation of national research networks aimed at drug innovation in specific therapeutic areas is anticipated given the current evolution in this field in the Netherlands. The impact of modern technology in computational chemistry, molecular biology, and drug delivery are discussed together with the impact of drug utilization studies on drug design and development. A currently developed model for drug innovation in which multidisciplinary teams work in specific therapeutic areas, while receiving feedback from the clinical practice, is presented and discussed in relation to the creation of post-graduate research schools in the Netherlands. Such research organizations as, for example, the Groningen Utrecht Institute for Drug Exploration (GUIDE), are natural partners for the innovative drug industry and provide a stimulating environment not only for forming specialists, but also for training more multidiscipline orientated (integrative) scientists in drug research. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction: social changes and their impact on drug innovations

The present world is changing rapidly, both socio-economically as well as scientifically [1,2]. These changes will undoubtedly increase uncertainty, but will also offer new challenges and hope for the future. A central issue here is the transition from a public to a more private system. The public system is characterized by a responsibility which is delegated by the individual to a public organization. In the private system more individual responsibility and flexibility based on collaboration will be necessary. Along with these social aspects, economic factors will undergo major changes. One example is the more global competition due to increasingly open borders. These changes will have an important impact on the development of new drugs and drug formulations in the pharmaceutical industry [3].

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Costs of research will markedly increase, among others because of the use of 'high tech' instrumentation and the necessary heavy investments in cellular biology based technologies. This methodology will, for instance, play an important role in the study of complex diseases such as neuro-degenerative disorders and chronic immune-diseases.

In addition, it is anticipated that the reluctance of insurers and governments to reimburse mediocre pharmaceutical products will increase so that when developing new drugs, major efforts in pathophysiological research will be necessary. In principle, the scientific opportunities to discover entirely new therapeutic agents seem better than in any other period in the past [1]. Yet, in recent years the number of new chemical entities (NCEs) that reach the market is declining and real 'breakthroughs' can only be attained at high costs and tedious research efforts [4].

The pharmaceutical sciences are rapidly changing, and immunology, molecular biology, structural biology in combination with biotechnology and molecular nanotechnology are all highly promising areas for future pharmaceutical developments. Molecular nanotechnology is a technology which provides highly versatile and inexpensive methods for synthesizing and manipulating molecules. In contrast with biotechnology, no dependency exists on rules dictated by cell biology. For example, atoms such as Si instead of C are used as the basis of self-assembling molecules that in turn can be employed as a factory for synthesizing the (non)-biological building blocks for nanosystems. It is expected that the field of molecular nanotechnology will be strongly stimulated in the fifth EU innovation research programmes.

The elucidation of pathophysiological processes on the molecular level combined with advances in chemistry and molecular biology should provide the basis for the development of a completely new generation of drugs.

2. The relation between the pharmaceutical industry and academia

Due to further concentration in research activities and sharper competition between companies, resulting in the abovementioned socio-economic trends, the pharmaceutical industry will be encouraged to collaborate more closely in partnerships with universities. Strategic alliances, implying long-term commitments between academia and industry on specified goals in the field of biomedical research, are being established. Such industry—university partnerships provide excellent opportunities for both parties to gain access to novel technology and fundamental biomedical research [2,3,5].

University scientists and their industrial partners work to push further the frontiers of science in order to create products that improve the quality of life. An integrated multidisciplinary approach is required to make possible an effective and causal pharmacotherapy for neurodegenerative and chronic diseases.

For a research program to be effective, a thorough long-term planning of execution is required. Clearly, long-term planning does not mean a simple extrapolation from the present to the future. A thorough scenario-analysis (an estimation of possible future situations based on an analysis of the 'driving forces' which underlie expected shifts in society) is necessary to prepare the research organizations and government bodies for possible future situations [1].

To be innovative in the field of drug development, both original scientific ideas and a motivated management with a vision are necessary. To be successful, the management must be able to identify the relevant socio-economic 'understreams' in society. Examples are the changes in global political relations and the impact of the current political pragmatism, in addition to the rapid evolution in 'high tech' activities and electronic communication networks as well as the current debates on energy resources and environment.

Research depletion is the 'horror' scenario for the pharmaceutical industry, and in fact implies the drying up of the resources for innovation [1]. This phenomenon could be brought about due to a lack in real scientific breakthroughs, or as a result of an inadequate or insufficient 'cultural transformation'. The latter includes changes in the social 'appreciation' of disease and, in relation to this, long-term cost-benefit analysis of drug use.

The necessity of shorter cycles for drug development encourages the pharmaceutical industry to collaborate more extensively with academia. In order to speed up the whole process of drug design and development and to shorten the costly research programs, a versatile and flexible infrastructure is needed in which the technical and scientific know-how of academia and industry are brought together. This also enables pharmaceutical companies to focus and concentrate their research efforts and still keep in touch with potential 'leads' in therapeutic areas somewhat more distant from their primary objectives.

Collaborations with the mere aim of product-renewal can be organized on a local (national) basis, but collaborations with the aim of fundamental innovation will more and more tend to have a global character. In the latter case, an elaborate, well organized research infrastructure is a 'conditio sine qua non'. Areas in which knowledge transfer from universities to industry is needed includes: new animal models for pharmacological and toxicological testing, new biological targets

based upon an improved insight in pathophysiological processes, new approaches in the field of drug administration and drug delivery and new procedures in the field of clinical pharmacology. In addition, new technologies in medicinal chemistry, based on molecular diversity and (bio) molecular recognition as well as more reliable predictive toxicological models, are required. It is generally recognized now that classical LD_{50} screening and routine chronic toxicology testing on various laboratory animals are of limited usefulness for predicting the effect on humans. There is also an increased need for advanced pharmacoepidemiology and postmarketing-surveillance research for an earlier identification of unforseen interactions and unexpected side effects. In this respect, pharmaceutical companies will pay more attention to pharmaco-economics and 'quality of life' research. Finally, the development of very sensitive bioanalytical and biosensor techniques will prove to be essential for the 'online' monitoring of pathology markers, drug levels and therapeutic outcomes [2,12].

3. Trends in drug research in Europe

In such an environment, collaboration in the European context, i.e. EU research programmes will become attractive. New opportunities can also be created for collaboration between countries in Eastern and Western Europe.

The 'European scene' will also further develop because of the Europeanization of drug registration and drug safety monitoring. The European Medicines Evaluation Agency in London will play an important role: the registration of a new drug will hold only for 5 years. After this period the registration will expire automatically. The original registration will be extended only, if the manufacturer complies with the new rules for pharmacovigilance during the 5 years post-registration period and is able to prove that the new drug has an acceptable benefit-risk profile in the free market. These requirements can only be met by a concerted action of pharmaceutical companies and clinical research teams supported by pharmaco-epidemiologists. Professionally acquired post marketing surveillance data on long-term drug efficacy and safety should subsequently be translated into new programs for basic research teams either to work on more optimal drug formulations and dosing regimens or to create congeners with an improved therapeutic index.

Traditionally, Europe has a relatively strong position in the innovative pharmaceutical sector. Drug design and development is a high tech activity sector par excellence and, traditionally, is strongly R&D oriented. It also represents a relatively 'clean' activity with a high level of employment. In Europe, a major effort is required to maintain and further strengthen this international position [3]. Both the industrial and academic research teams are in a process of adaptation, creating the platform for the formation of adaptable research networks. For example, the recent establishment of research schools and research institutes in the Netherlands was the result of the increasing need for improving the quality of research training in a multidisciplinary environment. Other goals of such research organizations are a higher efficiency in the use of the available resources and matching the research priorities to current social needs in health care. Such an organization can adapt to sudden changes in government science policy, to budget decline and sharper competition, as well as to the increasing dependence of drug research on expensive research instrumentation. The necessity of research reorganization was also triggered by the increasingly multidisciplinary nature of the pharmaceutical sciences and the abovementioned globalization of drug innovative activities [2,3,5].

In the Netherlands, two schools for drug research were created and were recognized by the Royal Netherlands Academy of Sciences and Arts: The Leiden-Amsterdam Centre for Drug Research (LACDR) and The Groningen-Utrecht Institute for Drug Exploration (GUIDE). In the LACDR, the bio-pharmaceutical aspects of drug research are emphasized while GUIDE is part of a medical school so that preclinical/pharmaceutical aspects can be integrated with clinical aspects of drug innovation.

In the near future, research networks for drug research should be created in Europe, based on such research clusters. The intention is to strengthen the international position of academic drug research and to improve the conditions for long-term organized collaboration with the pharmaceutical industry [2,3]. There is an increasing tendency in the international pharmaceutical industry to acquire fundamental knowledge and new technologies from research institutes such as universities, at acceptable costs. The industry's aim is to enter into strategic alliances, often in the form of agreements covering several years, on the basis of predefined goals. Companies should be in a front-line position with respect to their chosen competencies. Academic institutions can offer skills and scientific concepts that are complementary to those of the industry.

A characteristic of such strategic alliances is that researchers from both sides commit themselves to joint research projects on a voluntary basis, and that they evaluate research result and map out research strategies together. A recent survey on collaboration between academic institutions and industry in the area of life sciences revealed that among 210 companies, including

all of the prominent pharmaceutical companies, 90% of them worked with one or several academic institutions in 1994, 59% supported research, providing an estimated US$ 1.5 billion , or about 11.7% of all industrial R&D funding in that year [5].

Pharmaceutical scientists clearly played their part in these developments in the Netherlands.

In 1987, the 'Netherlands Association for Pharmaceutical Sciences' (NVFW) was founded, not only to stimulate this rapidly evolving research field but also for the advancement of national pharmaceutical research programmes. In 1990, this led to a new initiative: the creation of the Dutch Platform for Drug Research integrating the National Associations of Pharmacologists, Clinical Pharmacologists, Medicinal Chemists and Pharmaceutical Scientists, with the aim to stimulate collaboration in drug research between scientists working in different disciplines. This body collects nationwide information on drug research and makes it available to the government, to policy makers, to national research organizations and the pharmaceutical industry. In general, the reactions from both the authorities and the pharmaceutical companies were favourable: it was mutually agreed that research policy in this area should be upgraded and be better focused in order to strengthen the position of the Netherlands in the field of innovative drug research and to create more favourable conditions for the expansion of this 'high tech' industrial activity.

In 1995, these activities led to a concerted initiative from the government, through the ministry of economic affairs and ministry of education, culture and science, aiming at producing a national priority programme for innovative drug research, organized on a multidisciplinary basis. These activities are now controlled by a national research organization called the 'New Drug Research Foundation' which coordinates the work of the national research organization (NWO), the university drug research centres and the pharmaceutical industry, by creating national research networks that operate in various therapeutic areas. Apart from fundamental research in the drug design and development, more attention will be paid to industrial protection: new drugs and new drug formulations should be protected as soon as possible through patent filing and financial incentives should be given to the scientists involved. It is generally agreed that in this type of collaboration, academic research should maintain much of its own character. However, the focus on applicability and value (product) creation has to be increased. Needless to say, university teams, in spite of the closer contacts with industry, should maintain their independent position as academic evaluators of drug therapies [2].

Similar trends have been reported in other European countries [3]. In the US and UK, there is a very long tradition of industry-academia collaboration. Especially in the US, venture capital is available to fill the gap between the fundamental and the development phases in drug research. To ensure an adequate supply of new technologies, new concepts and new products to the pharmaceutical industry, small high-tech companies need to be helped and encouraged. In Europe, favourable conditions for industry-university collaboration exist especially in Sweden and the UK. In Sweden, there is an active exchange of scientists between academia and industry. Also, the universities seem to have a natural inclination to focus on the needs of the local industry. This attracts (new) industrial activities to the university's environment. In the UK, especially the university centres of Oxford, Cambridge, and London have a rich tradition of university-industry collaboration.

The specific national efforts to stimulate innovative drug research will certainly achieve a more European character. In this respect, the foundation of the European Federation of Pharmaceutical Sciences (EUFEPS) should be mentioned. The objectives of EUFEPS are to seek more coherence in the pharmaceutical sciences in Europe and to provide a platform for the exchange of information between the individual pharmaceutical scientists. In this respect, EUFEPS should develop in a direction exemplified by the American Association for Pharmaceutical Sciences (AAPS) which plays a central role in the advancement of pharmaceutical research.

4. Trends in research programmes in pharmaceutical sciences

Entering the century of molecular biology and gene technology, clearly a more optimal collaboration between basic and clinical scientists is required. Novel targeted molecules for use as drugs can be identified with these technologies. However, such activities should be part of an integrated therapeutic approach.

In spite of these new scientific opportunities, many diseases at present cannot be adequately treated with drugs. Especially, curing or preventing chronic diseases with therapeutic agents is more wishful thinking than medical reality. Although in the field of immunopharmacology (interferon, interleukines) clear progress was made, for major disorders such as certain viral infections, chronic inflammatory diseases, neoplastic and cardiovascular disorders, effective therapeutics are still eagerly awaited.

A number of reasons for this can be mentioned, among others:

- the lack of understanding of pathological mechanisms at the molecular level

- some drugs may not enter the target cell type in sufficient amounts

In addition, some general aspects may play a role: further progress is hampered by a lack of integration of scientific concepts (the impact of specialization) as well as by considerable scientific data noise, for instance, arising from unnecessary phase IV (seeding) trials. Through an integrated, multidisciplinary approach and a professional organization of research teams, such problems can now be successfully tackled. It is anticipated, therefore, that in spite of difficulties, many new and safer therapeutic agents will eventually find their way into the medical practice in the near future.

5. The molecular basis of pathophysiology and rational drug design

The basis for rational drug design resides in the basic understanding of the chemistry of the drug in its interaction with its potential receptors: macromolecules that may be key enzymes or crucial membrane proteins that, in concert with their endogenous substrates, carry out certain physiological functions. Quantitative or qualitative changes in such key molecules can lead to perturbation of such functions and may give rise to diseases or drug resistance. Well-known examples are point mutations in protein molecules which, for instance in the case of reversed transcriptase, can lead to the rapid development of resistance to nucleoside-analogues in anti-HIV treatment.

In the whole organism, many of such potential drug receptors and their substrates are present and in the future will be further identified and characterized in detail at the molecular level. Examples are cytokine receptors, transcription factors, lipid mediator receptors, metabolic enzymes, adhesion molecules and tumour antigens [6,11].

Drugs with high efficiency and proper safety can, in principle, be designed on the basis of knowledge of the three-dimensional structure of the identified pharmacological receptor and that of the drug itself. Molecular modelling and computational chemistry will greatly improve the rational design of drugs and will enable the further fine tuning of therapeutically active compounds. Yet a spatial conformation in a crystalline structure does not always represent the relevant three-dimensional structure as it occurs in the living organism. Obviously, this high tech approach has intrinsic limitations and among others, it does not take into account essential pharmacokinetic considerations. Consequently, even in the 21st century, improved (intelligent) screening procedures will be extensively used. In this research, pharmacophore functional groups in lead molecules, originally from natural sources or produced by organic chemistry and recombinant techniques, can be systematically varied. In fact, screening procedures are undergoing a revival, since they can be used for the fast screening of libraries, consisting of many compounds (e.g. peptidomimetics). The synthetic strategies to prepare these often large libraries of tens of thousands of compounds are referred to as combinatorial chemistry [7]. This technology now is attracting interest in many pharmaceutical companies. The so-called biased libraries, in which a knowledge of pharmacophoric functional groups is included, derived among others from computer molecular modelling, will play a crucial role in the finding of new leads as well as for lead optimalization [7,8] and will increasingly replace 'random' synthesis and screening procedures.

In vitro test systems will increasingly include human material: isolated cells, tissue slices, and cellular fractions enriched with plasma membranes and cell organelles [9]. Pharmacologists in the future will, therefore, be less animal pharmacologists and more investigators using human material. Although the use of human material for such purposes can be considered as questionable, a properly argumented and technically optimal use of such material can convince medical ethics committees and the public. In this respect, it is anticipated that the pharmacokinetic, dynamic and toxicological screening of drugs in human tissues will largely speed up the costly process of drug development and at the same time may greatly reduce the need of experimental animals [9].

6. New drug formulations: programmed release and cell-specificity

The physicochemical features of drug molecules that determine their pharmacological activity at the same time dictate their distribution and elimination from the body. Often body distribution is not optimal in relation to the required therapeutic profile: the major fraction of the drug dose arrives in non-target tissues (side-effects!) and delivery to the target cells may not be optimal. Other well-known problems are poor bioavailability and rapid elimination, for instance, in the case of oligopeptides and anti-sense nucleotides. In the last decades, research on drug delivery has flourished and potential solutions to these problems are the subject of extensive investigation both in the pharmaceutical industry and in universities. Apart from programmed sustained-release preparations for enteral and transdermal administration, a large variety of targeting preparations and drug-carriers have been designed to ensure a cell-specific delivery of drugs.

Many of these carriers are based on specific antigen recognition, or are accommodated by various receptor-mediated endocytotic mechanisms [10,11]. The rapidly growing knowledge on cell adhesion molecules may

enable a specific targeting of vascular endothelia of tumours and other diseased sites [6,11].

These concepts have been applied to the targeting of drugs to the various cell types in the body, by which a higher concentration is attained in the vicinity of the pathological process (active targeting) and/or distribution to sites of side-effects is reduced (passive targeting). Applications are found in the areas of antiviral- and antifibrotic therapy, among others [10]. Evidence is increasing that carrier systems with a long circulation time can accumulate at least to some extent at diseased sites, such as tumours as well as at sites of infection and inflammation. Examples of this approach include the delivery of antitumour drugs, antibiotics and radionuclides incorporated in long-circulating liposomes [6].

Intrinsically active drug carriers that, apart from delivering the coupled drug, can also contribute to the therapeutic effect themselves to provide an increased efficacy. Such drug targeting preparations with 'dual action' have been developed for various therapeutic purposes, and they include antiviral and antiinflammatory polypeptides [10].

One area in which particularly sophisticated delivery means need to be used, is that of gene- and anti-sense nucleotide-therapy, in which a proper cellular and intracellular delivery is a crucial issue. An increasing number of studies show that it is possible to reprogram cells in the intact body to produce therapeutic peptides by intravenous injection of genetic material targeted by appropriate homing devices. Major problems still lie in the efficiency, persistence of expression, and regulation of gene activity.

7. On-line monitoring of drugs, diagnostics and biochemical markers

Generally speaking, it can be said that new or improved therapeutical agents can only be created with the simultaneous development of improved diagnostic methods for the disease to be healed. Advanced bioanalytical and clinical chemical methodology is available now for monitoring the drug levels and to monitor the concentration of disease markers. Clinical practice not only requires rapid data acquisition but also expert interpretation of such data.

For the adequate treatment of certain diseases it would be of great help if both the evolution of the pathological process and the impact of drug treatment could be monitored. Biosensors for the continuous measurement of glucose in certain diabetic conditions have already been developed by various groups. In the light of the ongoing technological revolution in the field of highly sensitive and selective immunological assays that can be combined with implantable bio-chips, it seems possible to transfer signals from the body to data collecting equipment. It is, therefore expected that on-line measurement of relevant pathology markers and of organ function test-substances will become possible. This would be especially attractive if the collected data relating to the blood levels of multiple substances could be adequately evaluated at the same time, using advanced curve-fitting procedures. For instance, software containing various nonlinear-fitting facilities and population-based feedback in drug monitoring have been developed for practical clinical pharmacy in our institute and that of others [12]. Such programmes could be further developed into expert systems that include clinical interpretation of the data.

The functional status of organs and the evolution of pathological processes could in this manner be continuously monitored by simultaneous on-line measurement and analysis of a number of markers or test substances. This type of technology could largely contribute to improving the therapeutic outcome of drug treatment in individual patients.

8. Efficacy and side effects of drugs

Drug innovation is often viewed as the creation of more potent and more selective drugs. As mentioned above, this encompasses the creation of new drug formulations ensuring an improved delivery of drugs to the target organ(s) or tissues, and/or better pharmacokinetic properties. Especially if the basic mechanisms of a pathology are unravelled, opportunities arise for the design of new drug molecules. However, to the question of whether the therapeutic goals of the newly developed drugs are really met or, in other words, of whether the novel drugs really do contribute to the pharmacotherapeutic arsenal in the long run, proper answers based on hard facts are seldom available [1]. Obviously, this is a time consuming process. Retrospective analysis of long term efficiency and safety of drugs have, in some cases, revealed that well-accepted and widely administered 'therapeutic' agents do not significantly improve the quality of life nor prolong patients' lives. In some cases, these drugs were even shown to cause additional problems (severe side-effects) to the treated patients. A rapidly expanding discipline in this respect is that of pharmaco-epidemiology. Long-term effectivity data may not only arise from well organized and professionally designed clinical studies, but can also be obtained through systematic data collection carried out by physicians and pharmacists in the daily practice [13]. This important part of the overall process of drug innovation process is usually called 'post-marketing surveillance research'. This type of investigation can provide essential information to the research scientists, who in designing improved therapeutics should also rely on actual field data concerning the efficiency

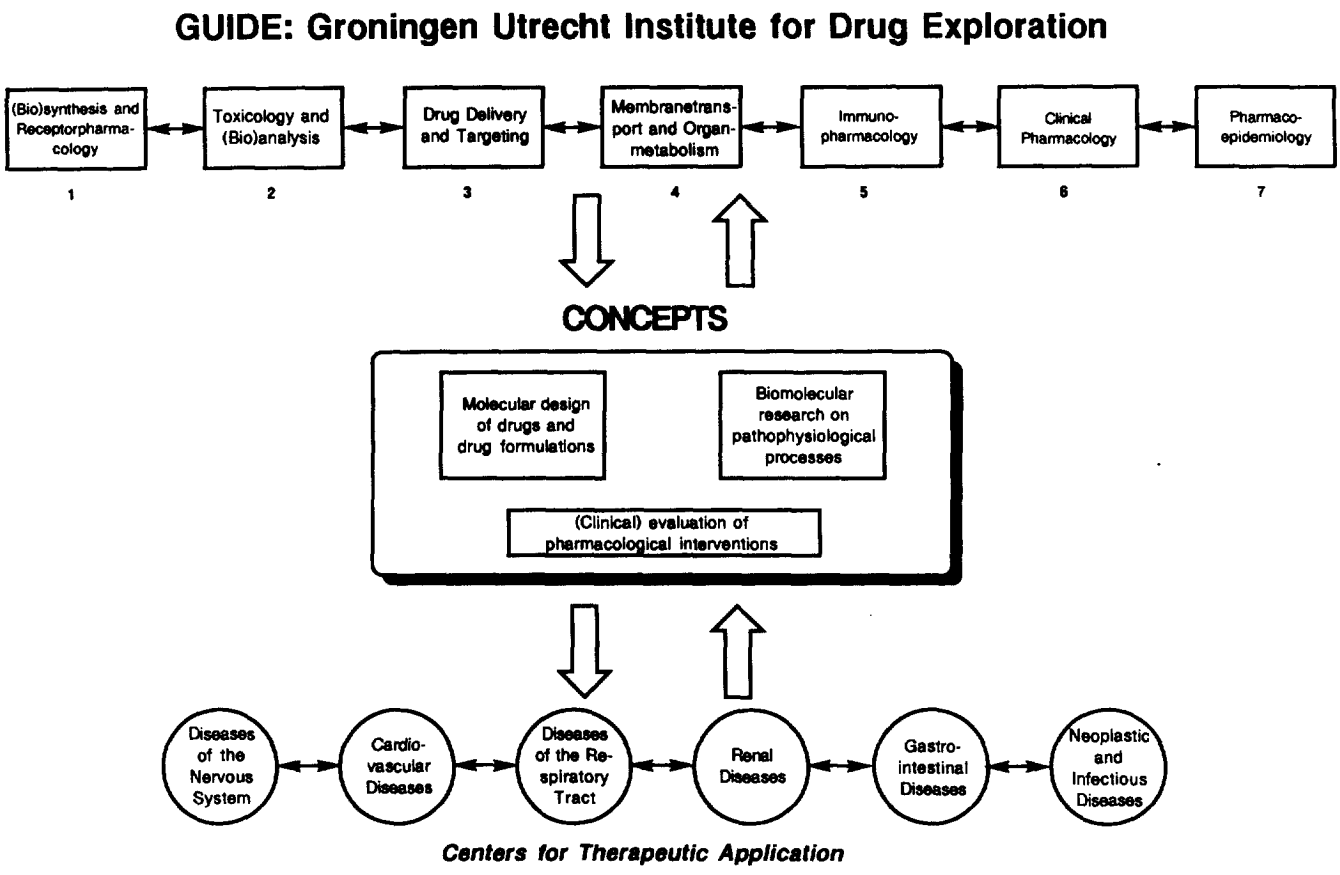

Fig. 1. The research activities of the research institute/post-graduate school GUIDE are focused on three central themes: (a) the biomolecular basis of pathophysiology; (b) the clinical evaluation of pharmacotherapeutic interventions; and (c) the molecular design of drugs and drug formulations.

In the institute, the clinical (disease-orientated) research centres from the medical faculty (circles, lower part) interact with expertise centres from the two pharmaceutical faculties as well as with the preclinical centres of the medical faculty (squares, upper part). The latter carry out basic research on drug innovation methodology while the clinical groups, apart from evaluating drug therapies, employ drugs as tools to study the nature of diseases at the cellular level and provide essential feedback on drug efficacy and safety to the expertise centres. For instance, the research centre investigating diseases of the respiratory tract, brings together scientists from basic pharmacology, clinical pharmacology, bio-analytical chemistry, pharmaceutical technology, pharmacoepidemiology as well as clinicians from the major CARA research centre of the academic hospital of the medical school. This type of organization induces intensive contacts between clinical and preclinical/pharmaceutical disciplines with feed-back of therapeutic data from clinical and drug utilization studies. This combined knowledge should lead to new concepts in the field of pharmacotherapeutic practices as well as in the design of new drugs and drug formulations.

and safety of marketed drugs [15]. Post-marketing surveillance research, therefore, is as important as structure-activity relation (SAR) studies: physicians and pharmacists do not only apply pharmacological knowledge, they also develop pharmacotherapeutic know-how that is necessary for therapeutic decision-making. This has been demonstrated, among others, in the fields of cardiovascular and psychopharmacological research [13–15]. This type of research will find increasing support from authorities in the future since inappropriate drug use can not only lead to failure of treatment, but also to avoidable injury of patients and in general to a waste of resources. The public does and will not tolerate that drugs carrying significant risks be marketed. In the coming decades, pharmacy-based drug utilization data combined with information from other health-related data bases will not only be essential for the daily therapeutic practice, but can lead to the identification of both beneficial and adverse effects of drugs in large patient groups as well as the detection of patient populations at risk from certain drugs [1,13]. Exposure ascertainment and record linkage has led to the concept of PHARMO (PHARmaco-MOrbidity linkage). Studies on drug utilization review and quality of pharmacotherapy have been carried out with a special focus on validation of the quality evaluation scores and review methods. Record linkage will be expanded to non-hospital settings. In the future, special attention will be paid to the contribution of pharmacoepidemiology to pharmaco-economics, quality of life and drug policy. Expertise on scenario analysis constitutes a link between these various fields of the pharmaceutical sciences [1,13–15].

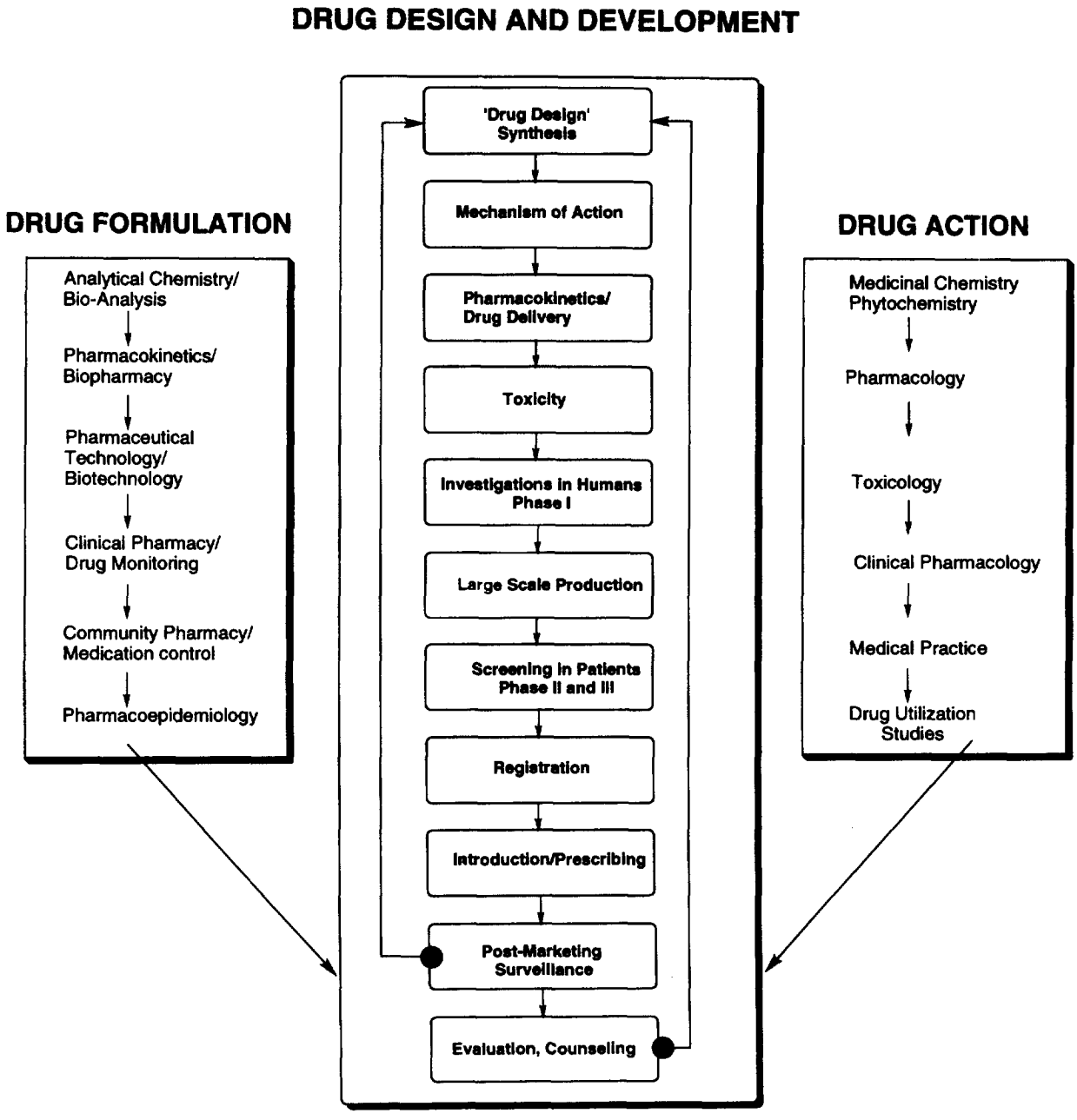

Fig. 2. A schematic representation of the various stages of drug design and development and their relation to the medical and pharmaceutical professions. The classical (linear) flow scheme in the central part represents the well-known research activities going from medicinal chemistry and pharmacological/toxicological testing to pharmacokinetic profiling and clinical studies including drug utilization studies in medical practice.

The left part of the flow scheme indicates the predominant contribution of pharmacists in bio-analysis, and pharmacokinetics in relation to drug formulation as well as the advisory role on drug dosage forms and dose regimens. The latter aspect is supported by, among others, drug monitoring programmes. The right part reflects the basic pharmaceutical/medical disciplines involved in the characterization of drug action and the professions dealing with therapy and drug utilization studies.

The upwardly directed arrows indicate the continuous flow of clinical and drug utilization data back to the basic sciences sections as provided by pharmacists and doctors in medical practice. This gives rise to a somewhat circular model, in which feedback from clinicians and pharmacists is an essential aspect of the drug innovation process.

9. More optimal organization of drug research

Part of the above mentioned aspects of drug innovation were derived from the current research programmes of the Groningen Institute for Drug Studies (GIDS) and the Utrecht Institute for Pharmaceutical Sciences (UIPS). GIDS and UIPS form the national post-graduate research school Groningen/Utrecht Institute of Drug Exploration (GUIDE) in the Netherlands. This institute accommodates about 80 senior scientists

and 180 post-graduate students who work on their thesis. GUIDE employs scientists from both the pharmacy faculties of Groningen and Utrecht as well as a large number of scientists from the Medical Faculty of Groningen (among others, specialized in anaesthesiology, nuclear medicine, cardiology, nephology, oncology, immunology, and hepatology). Within the institute, much of the drug research is organized themewise, according to therapeutic application areas (see Fig. 1). One of the institute centres of GUIDE is the Research Center for Liver, Intestinal and Metabolic Diseases in which pharmacologists, physiologists, biochemists and pathologists work together on new liver drugs together with hepatologists, gastroenterologists, liver surgeons and radiologists. This integrative approach produces a bidirectional flow of ideas and data between the clinical sciences and the basic research groups.

This particular organization is the materialization of the vision prevailing within GUIDE concerning the nature of the process of drug innovation [14]. In this study a concept of drug discovery was proposed, according to which the design of new medicines is the result of interaction between the knowledge concerning drugs and the knowledge concerning diseases, in which clinical therapeutic expertise is a source of feedback which is indispensable to the drug discovery process. In other words: the origin of novel medicines lies in the interface of development in the laboratory and the application of therapy in the medical practice. This theory criticises the generally assumed 'linear' drug innovation model in which the process is a one-way operation from molecular drug design to pharmacological and toxicological evaluations and finally to clinical testing and registration. The historical analysis of the evolution of beta blockers and calcium antagonists, for example, revealed that a circular model is more adequate for describing the process of drug innovations (see Fig. 2). In this innovation process, clinicians provide both expertise on essential pathophysiological aspects and data on therapeutic effects. They may also produce new ideas on alternative therapeutic indications for existing drugs that were previously developed for completely other purposes (drugs looking for diseases!) [14]. The abovementioned integration of preclinical (and pharmaceutical) sciences with clinical drug research in GUIDE leads to an even more optimal integration of disciplines and results in many fruitful collaborative projects. Recent examples are the strategic alliances that have been created between the industry and sections of GUIDE in the field of CARA research (with Glaxo/Wellcome) and psychopharmacological research (with Solvay/Duphar). It is estimated that the research teams of GUIDE receive altogether more than US$ 15 million annually from non-governmental sources.

As mentioned earlier, in the coming century, costs of drug research will rise sharply and a further concentration in research activities will be unavoidable. Pharmaceutical companies, can, in spite of the necessary focus on a limited number of research topics, maintain their overall flexibility in research planning by strategic alliances with university research centres [2,3,5]. In this framework, more long-term contact research will replace the short-term contract research that was more methodology-oriented. Such collaborations between industry and academia enable substantial investments in new research areas of pathophysiology, immunology, molecular biology, molecular diversity and drug delivery research [2,3,5].

Modern research organizations such as GUIDE can also improve the quality of research training in a multidisciplinary environment and in an international context. Among others, apart from highly qualified specialists, there will be an increasing need for 'generalists' in the drug innovation process. Reductionist activities that can lead to a lack of integration of scientific data through poor interdisciplinary communication should be counteracted by educating a category of scientists that are able to build bridges between the various disciplines and have a global view of the entire process of drug innovation.

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