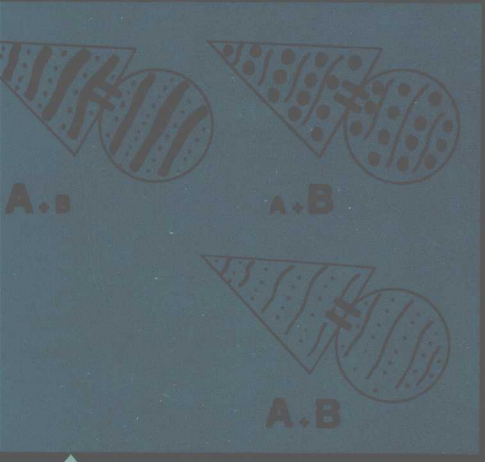
Decision Making in Drug Research



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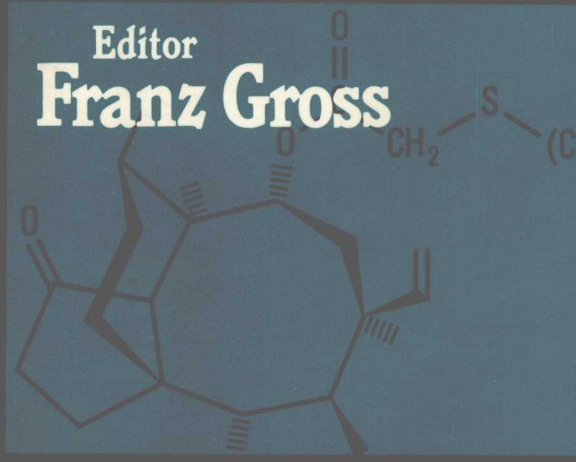

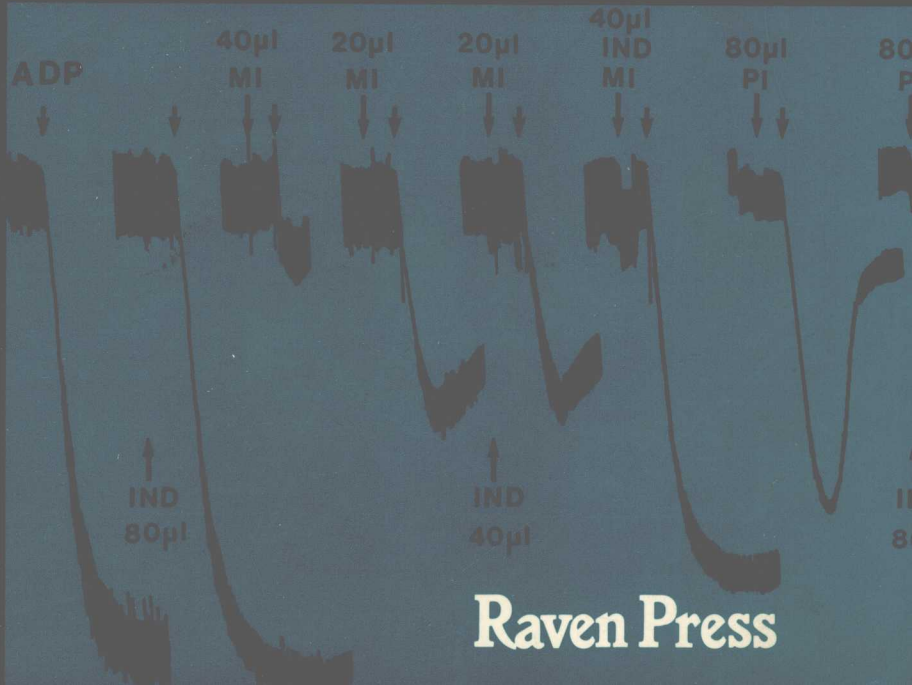

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Decision Making in Drug Research

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DECISION MAKING IN DRUG RESEARCH

Preface

Research is the powerhouse of the pharmaceutical industry. Every reputable drug company has a research department, or at least a research division, and claims to be actively engaged in research. However, the term "research" is not at all well defined and covers manifold activities, quite a number of them having little to do with exploring new areas, synthesizing new molecules, or studying how to make use of basic new discoveries in the biomedical sciences. There are only a few companies in the world, concentrated in a handful of countries, in which inventive drug research is pursued and from which real progress arises. Originally, I estimated their number to be as few as about 20,* which is somewhat on the low side and should be corrected to about 30–35. This figure is still far below the number of those who claim the status of a research-based company or a corresponding enterprise.

Developmental operations may also contribute substantially to progress and may serve in various respects to improve medicines and expand therapeutic possibilities better than the results of many original research efforts. Besides these warranted definitions of research, which also include to a certain degree development, it has to be admitted that, for numerous companies that call themselves "research-minded" and issue corresponding statements, the term "research" is but a fig leaf or clever window dressing to distract from reality or hide the true nature of the company. Such self-upgrading is quite common in the heterogeneous "drug industry." One should be aware of this fact and discern what may be hidden behind the ambitious term "research laboratories."

The symposium published in this volume dealt with genuine drug research, with problems facing the important research departments of big companies, and with the methods used for the discovery and the development of new medicines. The various possible approaches to drug research, the numerous factors that influence the choice of area on which to concentrate effort, the selection of sophisticated methods, and the continuously increasing competition affect the decisions and the whole decision-making process in directing drug research. They also influence the structure of the research departments, the choice of personnel to be employed, as well as the budget allotted to research. It was the aim of the meeting to define some of these problems and to show ways and means of solving them. Right from the beginning, however, it was obvious that no simple answers to the complex questions could be expected, only some general principles that would need adaptation to the individual situation.

* F. Gross, The present dilemma of drug research. *Clin. Pharmacol. Ther., 19,* 1–10, 1976.

Undoubtedly, industrial drug research is in a phase of fundamental change and of new orientation, a state of transition between successful history and uncertain future. On the one hand, the well-proven methods cannot be abandoned completely, but on the other, they do not suffice to guarantee further success. It is easy to criticize the inefficiency of industrial drug research during recent years, but it is difficult to make constructive and helpful proposals for the improvement of an unsatisfactory situation. The meeting on which this book is based was an attempt to bring together people directly involved and interested in drug research, with the aim of discussing some of the major problems and of trying to find ways to get out of the present predicament before it becomes an impasse.

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Introduction: The Present Situation of the Search for New Drugs

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In recent years, industrial drug research has definitely become less productive than it was in the golden fifties or early sixties. Despite rapidly rising expenditure, the discovery of new drugs has been slowed, and drug innovations are rare events today. Although quite a few new chemical entities appear on the market each year, the therapeutic progress resulting from them is in most cases modest, and a breakthrough in the treatment of a disease is a rather exceptional incident. The beta-adrenoceptor blocking drugs, the blockers of histamine-2 receptors, the inhibitors of the angiotensin converting enzyme, or the slow calcium-channel blockers are the best-known examples of late. On the other hand, great research efforts in areas such as the prostaglandins or the antiatherosclerotic drugs, have not, at least as yet, resulted in success.

Various explanations have been given for the unsatisfactory situation of drug invention, and—as may be expected—not only one, but several factors are responsible for it. It has been stated that the "easy discoveries have been made" (4), and that the lack of imagination, both conceptual and methodological, is counterproductive (5); regulatory constraints on industrial drug research have been accused of increasing the cost and delaying the launching of new medicines without, however, compensating these negative influences by greater safety (2). Further alleged factors are: the increasing need to defend the position of a successful drug in view of the heavier competition in a limited number of areas of special economic interest; the shift of resources available for research and development toward the latter; and, last but not least, a growing influence of marketing and marketing research on the selection of fields and research projects, as well as a rapidly expanding administration, which has to be satisfied by frequent submission of plans, proposals, reports, and other paper work.

The rising cost of research and the falling number of products have repercussions on the return on investment, and a new drug may have to be charged with a disproportionate share of the total expenses. In yesterday's issue of the *Frankfurter Allgemeine Zeitung* it was stated that, according to a British manufacturer, the cost of a new drug approaches 350 million DM or about 150

million US$—a figure which may be exaggerated for some, but not for all new medicines.

Since research efforts can only succeed if a division or department has well-qualified personnel and modern equipment, it is obvious that the curtailing of expenses will sooner or later result in a fall below the critical mass that is necessary for proceeding with a research project within a reasonable amount of time and with adequate prospects. Various small or medium-sized companies have already been forced to close their research laboratories, owing to their inability to continue the necessary investments and to meet the steadily increasing requirements (5). Even in the large companies, the present-day difficulties of drug research have left their traces in the form of hiring restrictions, freezing of expenses, and the abandonment of long-term projects whose chances of yielding promising results in the near future are limited. It is not unusual for these restrictions to go far beyond the streamlining of programs, which is necessary at regular intervals, and to affect the structure and potential of the research department. Of course, the situation is not critical in the large multinational companies, but all of them must consider ways and means of facing the problems that may arise quite unexpectedly.

The problems that confront industrial research today are rendered more serious by an increasing interest of the public, represented by consumer organizations or similar groups, which suspiciously observes drug manufacturers and their products, always ready to attack, but not to acknowledge. Reproaches are not only voiced against the marketing practices of industry, but also directed toward research, which is accused of not paying sufficient attention to the development of drugs for incurable diseases. Instead, projects are said to be fostered which may yield drugs that are unnecessary, but perhaps of commercial interest. This negative attitude against industrial research is found widely among medical students and among certain groups of doctors who have only a faint knowledge of drug research and its inherent difficulties. Recent unfortunate incidents with drugs such as practolol, ticrynafen, and benoxaprofen have received great publicity and have resulted in the general blaming of industrial drug research. The continuous attacks by certain news media and consumer organizations as well as the scrutiny of drug regulatory agencies have created an atmosphere of uncertainty in drug research. Drug manufacturers are scared of adverse reactions and some promising drugs have been dropped because of positive results in preliminary tests for mutagenicity, carcinogenicity, or other potentially dangerous side effects (3).

It was against the background of this intricate situation that the symposium and this subsequent volume were conceived, keeping in mind the goal of presenting useful proposals and conclusions that will lead to improved conditions in drug research. The areas thus targeted for examination and review were the methods employed in drug research, the organization of corresponding departments, and the selection of projects. It is obvious that no general

solution of all or even part of the present-day problems in drug research can be expected from this volume, given its exploratory goals. However, the need is very great today for the preliminary step of defining and analyzing the predicament of industrial drug research, in order to stimulate thought directed toward future solutions.

In an editorial, published in the *Lancet* nearly a year ago (1), it was stated: "Gone are the days when a fortune could be made by patiently sifting a lorry load of soil. Pharmaceutical research now has to be rational, and that means science-based." This, of course, is a truism today and has been accepted for many years. However, the statement continues: "Few companies can afford it on the scale required and few are in a position to benefit from the innovations of the molecular biologists." This is certainly correct, but it leaves out one most important factor for successful drug research, that is, the better understanding of the pathogenesis of most of the diseases. The immense and admirable progress in molecular biology has so far contributed little to unraveling the pathophysiological processes underlying the various diseases, and advances in clinical medicine are not comparable with those in the biological sciences. Nevertheless, we are at the dawn of exploiting the results of biological advancements; biotechnology will render immense services to drug research, and it may be anticipated that further insight into molecular biochemistry will also contribute to improved understanding of mechanisms and disturbances underlying disease. New ways of discovering drugs will be found, and industry will make its contribution in the future as it did in the past.

REFERENCES

1. Editorial (1981): Drug licensing or innovation. *Lancet,* ii:788.
2. Gross, F. (1979): Constraints of drug regulation on the development of new drugs. *Arch. Toxicol.,* 43:9–17.
3. Gross, F. (1981): The scientific basis of drug safety regulations. In: *Sécurité et Médicament, Progrès et Controverses*. Proceedings of the IVth International Congress of Pharmaceutical Physicians, edited by M. Aurich, J. Burke, and J. Duchier, pp. 9–18. Pergamon Press, Paris.
4. Weatherall, M. (1974): Limitations on the discovery and supply of medicines. *Proc. R. Soc. Med.,* 67:1287–1290.
5. Weatherall, M. (1982): An end to the search for new drugs? *Nature,* 296:387–390.

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Opening up New Fields

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In discussing the opening up of new fields, it is useful to consider the existing fields and the extent to which they have already been explored. Table 1 shows a classification of discoveries that have been made or which can be foreseen as desirable. The methods of discovery for each class have been appreciably different, and new strategies may be planned accordingly. This point will become clearer when the classes are considered separately.

The chemotherapy of infectious diseases has had a rational foundation (1) ever since the microorganisms responsible were recognized and identified. The target for therapeutic purposes is not part of the host's tissues, and the prospects for selective toxicity are very good. Research tactics are based largely on the study of organisms grown, if possible, *in vitro* and may follow the combination of biochemical analysis and screening in whatever proportion seems appropriate to the investigator (9). Of course it is necessary to ensure that active compounds are not toxic in required doses to the host. This difficulty applies to all new drugs and it will be mentioned again later. This field of innovation has been immensely successful from Ehrlich's "Salvarsan" onward. As long as microorganisms continue to become resistant to existing drugs, the need for new agents will continue. Some diseases may be eliminated by a combination of vaccination and public health measures, like smallpox (3), but the failure to eradicate malaria suggests that such events are not very likely.

Infections with viruses are much less easy to deal with. The range of effective antiviral drugs is very limited, but the very obvious problems of discovering new agents are gradually being overcome, sometimes with some subtle surprises, as in the way acyclovir acts (8). The applications of antiviral chemotherapy may grow enormously if viruses causing such common diseases as diabetes (11,12) or rheumatoid arthritis (7) are discovered. Whether this is likely is open to speculation, just as it was once speculative whether microorganisms were in any way related to infectious diseases. But the therapeutic implications of eliminating, for instance, juvenile onset diabetes by use of a chemotherapeutic agent are very considerable.

The etiological role of viruses in the development of particular animal tumors is more or less well established (17), but in general the chemotherapy of neoplasms is directed against tumor growth itself, rather than against the

TABLE 1. *Fields of drug discoveries*

1. Chemotherapy—Diseases due to infecting organisms
2. Chemotherapy—Neoplasms
3. Replacement therapy—Nutritional deficiencies
4. Replacement therapy—Internal deficiencies (hormones, transmitters, enzymes, antibodies, etc.)
5. Pharmacotherapy—Adjustment of functioning of organs (anesthetics, cardiotonics, diuretics, etc.)
6. Immunizing agents—Promoting natural defense mechanisms
7. Immunomodulants
8. Antidotes to poisons and to radiation
9. Drugs for diseases of unknown or uncertain cause

cause of its growth. The target is not clearly distinct from the tissues of the host. The problem of achieving selective toxicity is much greater (14), and antitumor drugs are, in general, seriously toxic. The route to discovery is not very encouraging, in spite of much enthusiastic work (4). Neither massive screening programs nor the prodigious quantity of cancer research is doing more than erode the problem. But perhaps it will in the end be completely eroded, without the dramatic breakthrough as was the case with prontosil or penicillin.

The discovery of the role of vitamins has been an important advance in therapeutics, but it does not seem likely that more accessory food factors will be found, or that their discovery will have substantial practical implications. Current nutritional research is more concerned with the effects of known nutriments, often in excess (16), when the therapeutic problems are quite different.

Similarly, the ordinary list of human endocrine glands and, broadly speaking, their hormones is probably complete. Considerable possibilities still exist for devising simpler synthetic substitutes for natural hormones, for finding stimulants or inhibitors of their secretion, potentiators of their action, or blockers of the receptors on which they act. All these discoveries are more accurately regarded as improvements on existing treatment than as the opening up of new fields. But other internally generated substances are essential to health, in the sense that deficiency is associated with disease and replacement with restoration of well-being: for example, dopamine and levodopa in Parkinson's disease (6). The inborn errors of metabolism or genetic deficiencies of specific enzymes fall into this class and present so far insuperable problems of substitution therapy. And there may well be other internal deficiencies, not yet identified. This is initially an area of research for the experimental and investigative clinician, and perhaps for biochemical physiologists in the laboratory. Until key substances are identified, it remains an inaccessible field for orthodox pharmaceutical research.

The discovery of new pharmacotherapeutic agents is, on the other hand, the bread and butter of pharmaceutical research. The tactics of setting up experimental models or screens and investigating a variety of compounds are very