What Information Does the Medicinal Chemist Really Need? Projections for the Future*

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Screening of chemicals in combination with the chemist's imaginative and skillful capacity to alter chemical structures and to relate structural groups to biological activity has been the source of most of our therapeutic agents over the past 35 years. How this approach can be made more effective is discussed.

Very recently I had the occasion to compare the third revision of the text "Medicinal Chemistry" released about six months ago with the second edition published 10 years ago. Both editions were prepared under the able editorship of Alfred E. Burger, one of the pioneers of our time who helped to convert the amorphous collection of seemingly unrelated data on chemical therapeutics into a meaningful and productive discipline—Medicinal Chemistry. I was impressed with the revision because of its contents and because of the enormous sense of accomplishment. The 1970 edition was no longer a single volume but rather consisted of two volumes even though much of the substance in the earlier edition was excluded from the new revision.

I was impressed by the publication in 1970 of another text on medicinal chemistry of equal size and quality by Gustav Ehrhart and Heinrich Ruschig entitled "Arzneimittel." Having witnessed during the past 30 years nearly all of the research covered in these two texts, I experienced a sense of pride as I examined these texts. I was stirred by the pedagogy and by the enormity of knowledge pertaining to chemical structure and pharmacological activity. The past 30 years have been wonderful ones for chemistry and biology in the discovery and development of therapeutics. These sciences made a deep impact on man's relentless struggle against disease and unlocked prodigious stores of knowledge undreamed of when I began my career in the pharmaceutical industry. To appreciate this progress we need only recall medical therapeutics before the discoveries and developments in the nutritional diseases, the infectious diseases, diabetes, and the degenerative diseases related to the cardio-vascular and renal systems.

But as I read sections of these books, I also had a strange feeling of nostalgia for I began to realize that the next edition of "Medicinal Chemistry" may be quite different if measured in terms of therapeutic agents both in their number and in their quality. It is in this context that I discuss the question: What information does the medicinal chemist really need to continue to discover and develop new drugs?

Before we delve into this question, we need to remind ourselves of how we got here. If we know from whence we came, perhaps we can answer the question of whither.

We sometimes forget that the oldest source of useful drugs is nature itself. Tissues of living organisms—plant and animal—have been an ageless fountain of therapeutic agents. And plants manifested today by such alkaloids as morphine, quinine, atropine, pilocarpine, and the cardiac glycosides—digitoxin and ouabain—are a few of nature's pharmacodynamic agents which are still priceless ingredients of the physician's armamentarium.

There can be no question about the importance of the discovery of these drugs and their impact on subsequent discoveries, even in our time. The intellectual ingenuity and the humanitarianism associated with the discovery of opium for pain, digitalis for cardiac insufficiency, and cinchona bark for malaria have not been surpassed by any of the therapeutic advances of modern times. For these drugs and many others we shall never know with certainty the lay pharmacologist or medicine man to whom credit for the original discoveries belongs. We inherited these drugs without records of demonstration in the experimental sense of efficacy and safety as we know them today.

The 19th century saw the beginnings of organic chemistry and its growth into a science destined to play a major role in the understanding of living processes and their control. Development of isolation techniques, of structure determination of natural products, and of methods of synthesis of complicated molecules led to new chemical structures with specific value in therapy. By the late 1800's synthetic compounds such as the salicylates, acetanilide, amyl nitrate, ether, and chloroform had found their way into pharmacological testing, usually in human subjects. And chemists were learning from nature the importance of molecular modification in terms of pharmacological response.

The early 1900's saw the introduction by Ehrlich of the experimental procedure for chemotherapeutic research, which in spite of the magnitude of subsequent medicinal research had changed remarkably little since then. Even Ehrlich's stimulating theory of side-chain and cell-receptor theory advanced when essentially nothing was known about cellular biochemistry recalls his greatness and prophetic insight. However, it was not until Domagk's discovery of the antibacterial activity of *Prontosil rubrum* in 1934 during an experimental screening program that medicinal chemistry reached its true measure as a discipline and that the screening approach to chemotherapy was accepted universally. The methods of Ehrlich and Domagk became effective experimental tools for medicinal chemists.

Screening of chemicals on a random basis in experimental disease, combined with the chemist's imaginative and skillful capacity to alter chemical structures and to relate structural functional groups to biological activity, has been uniquely productive and, in fact, has been the source of most of our therapeutic agents discovered and developed during the past 35 years. What followed Domagk's screening program was amazing in terms of useful drug therapy. It not only had a profound effect on infectious diseases but it led to drugs with related structures effective in the control of edema, hypertension, gout, diabetes, and leprosy.

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It was a long way from Protosil, both on temporal and chemical bases, to probenecid, the thiazides, and the sulfonylureas. In a similar way, we owe to screening, discoveries in the fields of antibiotics, the antihistamines, and agents for mental health.

Where does screening or the empirical approach to new drugs belong in the years ahead? Somehow I feel that screening is rapidly losing its eminence and will, unless checked by some unforeseen event, disappear as a major operation during the next few years. Chemists are beginning to believe that this source is no longer productive. This is a pity in view of the record. Let us not forget that even in the chemotherapy of cancer, screening has been the major approach. Up to a few years ago—and the situation is not much different today—every drug used in the treatment of cancer had been found by screening procedures.

Rather than losing faith, we should direct our efforts toward reorganizing and improving the empirical approach. Biologists and chemists need to devise better in vivo assay techniques—ones that will require tiny quantities of chemicals. Every modern instrument used in physical and analytical chemistry should be called in to give better and more rapid data. Tying into the in vivo studies such instrumental techniques as thin layer chromatography, VPC, IR, NMR, electrophoresis, automated and computerized should expand the capacity of screening techniques.

I continue to be optimistic about the empirical approach because of the enormous expansion of chemistry that has taken place in the past 15 years. Somehow, I feel that we have scarcely brought this new knowledge into the laboratories of the medicinal chemist. I am amazed at the breadth of photochemistry and the types of compounds it spawns. The expansion of inorganic chemistry—the enormous literature on all kinds of metal alkyls and the organic compounds which can act as ligands with metal cations—is almost staggering to one who has failed to follow the literature during the past decade. Today, we have compounds in which carbon is bonded to nearly every element of the periodic table. Nitrenes, carbenes, and arynes are essentially new reagents from which completely new chemical structures can now be derived. It was not long ago that allenes were rare indeed and interestingly, from the point of view of the medicinal chemist, an allene (α-D-2,3-decadienoyl *N*-acetyl cysteamine) has been discovered by Konrad Bloch and associates to be an inhibitor of the enzyme β-hydroxydecanoyl thioester dehydrase. From the point of view of new chemical structures, medicinal chemistry has probably never had more exciting opportunities than it could have now.

The biochemical approach to new drugs understandably is today receiving the major share of our research effort. And as our understanding of homeostasis of living systems is expanded, the greater becomes the stimulation and excitement. The motivation for medicinal chemists to act is at its peak, whenever normal and abnormal physiology can be delineated in terms of biochemical events for now a rationale for attacking the disease becomes apparent.

The deficiency diseases—nutritional and humoral—were early recognized as biochemical problems, and their control forms an impressive volume in the medical history. The nutritional diseases whether due to vitamins, minerals, or specific amino acids respond quickly to supplementation with the deficient nutrients and need not ever again be a problem to mankind.

Deficiency diseases arising from inadequate levels of nonpeptide hormones such as cortisone and thyroxin again are well controlled largely because these hormones are readily available through synthesis. But the peptide hormones—particularly those of the pituitary gland—constitute a different story. We know very little about growth hormone, prolactin, follicle stimulating hormone, luteinizing hormone, thyrotropin, parathyroid hormone, and calcitonin because we have had very limited supplies of each. To fill this gap in our knowledge, we need vastly improved methods of preparing these peptides—either by extraction or synthesis—and each substance must be nonantigenic and active in man. While our methods of synthesis of peptides are quite sophisticated today, we are still very far from practical methods of producing large quantities of pure peptide hormones by chemical synthesis. And beyond the hormones of these endocrine glands, there are the hypothalamus releasing factors, which seem to play an important role between the central nervous system and pituitary functions. We need to know about each releasing factor present in the hypothalamus since, indeed, each may be a key to homeostasis and a more direct and economical way of controlling the different hormonal diseases.

Perhaps the greatest challenge to the medicinal chemist is what to do about enzymes and the cellular nucleic acids. We have already learned to control some disease states which are characterized by over-active enzyme systems. Hypertension, gout, and hyperthyroidism are examples of this type of abnormal metabolism, and these defects respond well to treatment with compounds that bind to specific enzymes and reduce the amount of substrate undergoing a specific biochemical reaction. However, this approach must always be critically assessed, and compounds which block or depress enzyme action must be approached with considerable caution. Interference of biochemical reactions is a complex and fundamental event. If a particular step in a biosynthetic pathway is blocked we must find out immediately what intermediate metabolite piles up and whether the body can handle this metabolite safely. We have seen an unexpected and frightening toxicity manifest itself not too long ago with an anti-hypercholesterolemia drug prescribed freely to patients because of a build-up of an intermediate metabolite. I hope that we have learned well from this experience and that a situation of this sort can never occur again.

We are all reminded from time to time that the achievements in medicinal chemistry fall short in the area of chronic and degenerative diseases. While control of symptomatology can be frequently attained, cures are lacking. What are the prospects for breakthrough in this area? They are indeed encouraging! With the development of molecular biology we are beginning to obtain completely new concepts of the etiology and pathology of disease on a molecular level and with it a new degree of confidence in the future. One day, and I suspect it will be soon, we shall understand how to apply molecular biology to the conquest of disease. Presently, we have no clear view on how to move ahead and apply our knowledge of DNA-enzyme interrelationship, although we are beginning to make some real progress. What are the paths that lie ahead and which ones will lead to the aurora?

Our comprehension of genetics and somatic mutations in terms of molecular biology leads us to believe that enzymes will be useful as therapeutic agents. This is a stimulating concept but fraught with enormous difficulties, and its development will tax the ingenuity of chemists and biologists as never before. We shall need to know how to produce large quantities of enzymes and how to administer them. We shall also need to overcome or to avoid the problems of antigenicity. While chemists will one day emulate nature in the way it performs the synthesis of enzymes, that time is far off. And a practical total synthesis of an enzyme in kilogram quantities is even further away. Will we have to rely on microorganisms for our therapeutic

enzymes much as we are doing today for the enzyme asparagine? And if so, how shall we remove the antigenic properties from a protein made by a microbe? And how will we bring the enzyme to the tissue or cell that needs it? There was a time when we regarded these needs as almost impossible objectives.

The situation is changing rapidly, and, I believe, this approach now looks more hopeful. There are already indications that affinity chromatography may be a practical way for isolating enzymes from fermentation broths and that enzymes bound covalently or electrostatically to a solid matrix may be a feasible and economical way of using enzymes in therapy. One of the encouraging aspects of enzymes bound to solid matrices is the stability of the enzyme. In a recent publication on a RNA polymerase bonded to a solid matrix, the combination of this enzyme-matrix was reused for polymerizing a nucelotide over 30 times without significant loss in enzyme activity. There is also the concept that enzymes can be trapped within a gel lattice with pores large enough to permit only the substrate and the product to enter and leave freely. If we can demonstrate that this system can be made operative and made free from antigenicity—because no enzymes can pass in and out of the gel—we have come upon an exciting development. If we succeed in this first step then the development of an efficacious therapeutic agent out of an enzyme is a certainty.

Another equally exciting, but difficult, objective is to treat inborn or mutagenic errors of metabolism with some form of genetic surgery—excising an erroneous gene and replacing it with one that is true. Can the deficient or missing gene which is responsible for the synthesis of an essential enzyme be exogenously supplied to the cell? A number of basic and practical concepts are now available to encourage us in the development of macromolecules for the treatment of inherited diseases and probably degenerative diseases as well. In the genetics of microbes, this approach is manifest in the bacterial transformation and in phage transduction, and these achievements are striking. However, the problems associated with the introduction of a gene into the genetic mechanism of *Bacillus subtilis* and *Escherichia coli* are vastly simpler than those of introducing a gene into the more complex genetic apparatus of the mammalian cell. We already know that DNA viruses destroy a cell by entering the nucleus and taking over from the hosts DNA management of the cell.

There is another way the DNA virus can become involved in the cell's welfare. In this case, the DNA virus or a portion of it can become incorporated into the host's chromosome. This transformed cell has an altered morphology and differs from the normal cell in other characteristics as well. The hope is to use this knowledge and to produce pseudoviruses for DNA therapy which are made up of specific genes with a protective protein coat and to use them to repair defective chromosomes. There are several approaches to the preparation of pseudoviruses being investigated extensively. One way would be to synthesize and isolate a specific mammalian gene just as Beckwith and his associates at Harvard Medical School had done in 1969 with a microbial gene. These authors isolated a gene and used it as a template and, together with nucleotides and DNA polymerase, were able to synthesize that gene in significant amounts. To complete the preparation of a pseudovirus of a mammalian gene the addition of a protein coat is essential for without the coat the synthetic gene would be destroyed by the DNA hydrolytic enzymes present in plasma. While we now have cell-free systems for the synthesis of bacterial and phage proteins, this is not the case for mammalian proteins. If we are to move ahead in this area of genetic disease therapy, we need to discover and to develop a cell-free system for the synthesis of mammalian proteins.

Another approach suggested by Tatum is the transplantation of normal cells or tissues in a gene-deficient animal. Spectacular progress in transplantation of organs gives feasibility to this approach.

To sum up, what we need to know or solve if we are to develop DNA therapeutics are easy and reproducible methods for gene isolation, effective biosynthetic or total synthetic methods for DNA, and biosynthetic or total synthetic methods for protein production.

Up to now I have talked about the technical aspects of drug discovery and development as seen by the medicinal chemist. But this is only a small part of the whole story. As I perused the recent books on medicinal chemistry already referred to, I could not help but wonder about the total relevance of all the data contained in them. We have built up an enormous repertoire of facts and skills pertaining to chemical structures and pharmacological activity, and we are proud of this achievement. In fact, we see ahead even greater capacity for defining chemical structure in terms of pharmacological activity with the use of mathematical models and computers. Those engaged in this kind of research are confident that this approach will be useful for drug design for it ought to allow predictions of the biological activity of a compound prior to its synthesis. Purcell, Beasley, and Clayton of the University of Tennessee have recently reported a success with this approach. If one adds to this the very recently reported scholarly treatise of Lermont B. Kier of the Batelle Memorial Institute entitled "Molecular Orbital Theory in Drug Research," one senses new excitement. Notwithstanding the sophistication of these new approaches to medicinal chemistry, I see little in them which can bring forth better drugs in terms of patient utility nor can increase the introduction of new pharmaceutical products over the performance of the 10 years. I don't believe that we are in a post golden age in the uncovering of new drugs and that medicinal chemistry is finding it more difficult to find compounds with interesting pharmacodynamic activity. Rather, I am of the opinion the FDA with its regulations, philosophy, and power has seriously impaired drug discovery and development by injecting into the sequence of steps from concept to drug therapy a rigid requirement for an enormous amount of pharmaceutical, animal, and human data.

The cost in terms of manpower, facilities, materials, animals, patients, and clinics is so great that it has frozen our initiative, our motivation, and even our imagination. Faced with the huge task in preparing a compound for eventual submission to FDA approval, it is doubtful that we shall take a drug to the clinic because of an inspirational concept or because we want to determine the significance of an exciting animal observation. Unless we can predict the value of a potential drug before it is studied in man and can measure it in terms of patients utility, we are apt to give up early in drug development. The chances of serendipity will become very much less under such conditions. And as I look back over the past 30 years, I am struck by the fact that many of today's important drugs would have never reached the clinic based on today's sophistication. Who would have been willing to pay the costs and invest so much manpower and facilities to synthesize cortisone and make it available for clinical studies with only Addison's disease as expected to respond to its usage.

What does this mean to medicinal chemistry? First, I feel that we need to emphasize more strongly than before that the mission of medicinal chemistry is to create substances which can treat a disease efficiently and safely.

Medicinal chemists have done wonderfully with the efficacy. They need now to do something about the second parameter—safety.

If medicinal chemistry is to fulfill its mission it needs to work closely with the biologists in particular, with the pharmacologists and toxicologists, and to develop more meaningful ways of assessing the potential of a new pharmacodynamic before bringing it into the clinic. New and imaginative approaches are essential, and this can only be obtained by an even greater involvement of medicinal chemists in the experimental work in animals.

The time has come to include toxicity and side effects in our textbooks dealing with chemical structures and therapeutic activities. We should begin to correlate data collected over the years and begin to treat these data much in the same way we are treating biological activity. Let us use our computers and every sophisticated tool at our disposal to expand our capacity to predict animal efficacy and toxicity in terms of man. It is timely to begin learning the relationship between the way different species metabolize a drug in terms of the parameters efficacy and toxicity. We must learn how to correlate these data with the behavior of the drug in man. Perhaps we shall begin to know why drugs may be ineffective or toxic to a few patients but not to most and why individuals handle drugs differently. If we can build up a store of knowledge in pharmacogenetics, perhaps we shall be able to predict which patient should or should not be treated with a particular drug. In short, we must learn to know how different patterns of metabolism dictate the usefulness of a drug.

This is the way I view what medicinal chemistry will need in the years ahead, but, as I say this, I realize that scarcely any two discoveries have been made in the same way. As we go down the list of morphine, insulin, sulfa drugs, antibiotics, steroids, and psychopharmacological drugs, what impresses me most is the ingenuity of man. I believe that this power of the human mind will overcome the obstacles we see in our paths today. There are many, great holes in the physician's armamentarium, and we have the capacity to fill them. This is the challenge on which depends the future not just of medicinal chemistry as a science but, more importantly, of drug discovery and development.

Primary Transmission of Scientific Information—Today and Tomorrow*

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The question of content of medicinal chemical journals is discussed. Medicinal chemists require information from clinical, health science, pharmaceutical science, and chemical science areas to carry out their work. Changes which may occur in journals in the future are considered.

Decisions in economic areas—e.g., printing costs *vs.* methods, subscription rates, and page charges—are relatively easy in comparison to the question of journal content. Alfred Burger has said that he does not want the *Journal of Medicinal Chemistry* to be a journal of second rate organic chemistry. I know that all of us agree with this and are glad that he had the courage and will to make it much more than that. But what then should be the content of the Journal?

The primary transmission of scientific information is of crucial importance in all aspects of the process of the preparation of new drugs. It is clearly of importance in the planning stages of this work, and it may not be overstating the point to say that prior information, taken together with individual creativity, are the two most important factors in the design of new drugs. In some fields, the primary scientific information required for the planning of a new project may encompass a limited scope. Individuals who work in such fields, therefore, have a relatively simple task in selecting the journals necessary to satisfy their informational needs. All of us here are aware that this is not the case in medicinal chemistry.

The medicinal chemist must have information from four broad areas even to be able to plan a project in medicinal chemistry. He must, in the first place, have information from the clinical area, because the design of a new drug is clearly a response to a clinical problem. He must, secondly, have information from the area of the basic health sciences—physiology, pharmacology, biochemistry, pathology, microbiology, and biophysics. This information is required for the chemist to understand the clincal problem in molecular terms. In a few cases, we may even have a fairly good idea of the molecular processes underlying a disease state. However, this is usually not the case. More often, we have some scattered information on the physiology and biochemical basis of a disease state and must make assumptions concerning the rest. In any case, the rational design of new drug entities requires the full application of all the basic health sciences to the problem at hand.

Thirdly, the medicinal chemist requires information from the pharmaceutical sciences. It is now well known that the type of dosage form may markedly influence blood levels of a therapeutic agent. The type of tablet employed in an oral form, or the type of vehicle utilized in a topical preparation, may influence the activity of a substance to the point of causing an active compound to give a negative result in a biological test. This rapidly expanding area, therefore, is one which must be understandable to the medicinal chemist in the course of his design studies.

Finally, the medicinal chemist must have the traditional

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