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E. B. Hershberg Award Address

My Odyssey in Drug Discovery†

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Introduction

I am deeply gratified by the honor the American Chemical Society has accorded me in its decision to name me the first recipient of the E. B. Hershberg Award for Important Discoveries in Medicinally Active Substances.

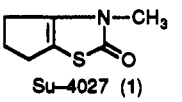
As a prologue to my main lecture, I want to record a few comments concerning Emanuel B. Hershberg. Although I only met him once at a North Jersey American Chemical Society meeting, I knew much about him through his work and from his colleagues at Schering Laboratories. It is clear that Dr. Hershberg was a man of tremendous scientific acumen with a deep love for organic chemistry and its power to lead to useful drugs as is evidenced by the great success of Schering Laboratories in becoming a leader in natural product research in the pharmaceutical industry. During his tenure as Director of Research, Schering discovered and brought to the medical profession prednisone, betamethasone, gentamycin, and sisomycin, to name a few. But more importantly, in the words of one of his colleagues: "E.B. gave us the courage and conviction of the scientific soundness of an idea and its pursuit to completion. In addition, he was a gentleman, a scholar, and a most effective research leader who was highly esteemed by his co-workers."

Odyssey

My odyssey in drug discovery goes back many years to my childhood. From my earliest recollection I had always wanted to be a chemist. I recall my mother encouraging this desire by presenting me with a chemistry set at the age of 12. In 1936 these chemistry sets were first becoming popular. Many an hour was spent mixing various substances, noting changes in colors, formation of precipitates, and the bubbling over of gaseous materials. Much of these phenomena, though not understood, left memorable impressions and gave substance to one's youthful imagination. This was manifest one quiet summer afternoon when I mixed several chemicals (their identity has long been forgotten) and to my astonishment, a white milklike solution was obtained. As chance would have it, the family cat entered at the time and it occurred to me that my discovery could be incorporated in the cat's milk bowl. This was done. The cat voraciously drank the milk with its additional contents, then hesitated for a moment, its back went up in typical defensive form, gave a howl and raced out of the house. My first medicinal chemistry experiment and I knew not what I had wrought! Fortunately, our cat returned a few hours later, a bit haggard but feeling better and prepared to live to a ripe old age.

Reflecting back on this event, I certainly do not suggest other 12 year olds to do the same. I recount it merely to tell how, on that quiet summer afternoon, some 55 years ago, I began this journey which has taken me to sharing this experience with you today.

I joined CIBA in 1955 at a momentous time in its history. Emil Schlittler of CIBA, Basel, had recently arrived in Summit, New Jersey, to head up the Chemical Research Department of CIBA Pharmaceutical Company. He engaged me to join the newly formed synthetic organic chemistry group. The first project I was assigned was the search for a nonnarcotic analgetic. Little did I realize the enormity of the challenge. In fact, the analgetic problem consumed my interest on and off for more than 10 years. One of the first compounds I submitted for analgetic testing was Su-4027 (1). This substance proved to be very



Su-4027 (1)

effective in all animal analgetic tests but exhibited a narrow therapeutic ratio. After an extended SAR study

† This is the text of the E. B. Hershberg Award Lecture which was delivered by Dr. George deStevens at the 201st National Meeting of the American Chemical Society in Atlanta, GA, on April 16, 1991.

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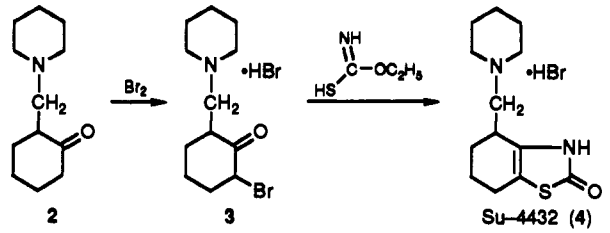
Scheme I

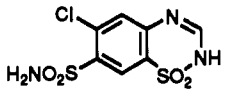


Su-4432 (4) was synthesized as shown (Scheme I). This substance was found to have potent analgetic effects with a wide therapeutic ratio. It was submitted for evaluation in humans, and at doses of 100 mg per day in 100 patients for 6 months, it proved to be equivalent to codeine in reducing pain. However, it was also found to cause inflammation of the optic nerve in a small number of patients, a side effect which was not noted in animals. Fortunately, this effect was reversible. Su-4432 was removed from further clinical trials and for obvious reasons this series was no longer pursued.[1]

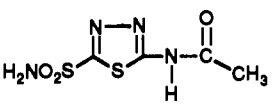
The lesson learned from this early experience was that drug discovery is a difficult and demanding endeavor which requires a great deal of persistence, patience, and tenacity. However, in my view, disappointments and setbacks, such as shown with Su-4432, serve to strengthen the resolve of the medicinal chemist to solve new problems.

During this time Schlittler[2] and his collaborators had elucidated the structural complexity of reserpine, a drug which was gaining much attention and use as a neuroleptic agent, and in addition, as noted from the animal pharmacology, it significantly lowered blood pressure in hypertensive patients. This coupled with the finding by Yonkman and Plummer that hydralazine elicited potent antihypertensive effects established CIBA as a pioneer in cardiovascular research.[3]

Of the several projects I worked on, I was particularly intrigued with cardiovascular problems as they related to diabetes and hypertension. To this end, I was involved in the synthesis of a variety of sulfonamides and sulfonylureas. It was in early 1957 that we at CIBA became aware of the research of Novello and Sprague[4] of Merck Sharp and Dohme on the synthesis of disulfonamides and in particular of chlorothiazide (5). Chlorothiazide was



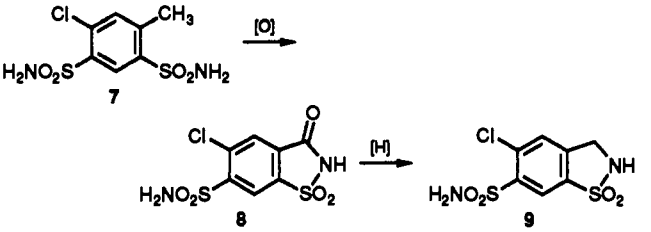
chlorothiazide (5)



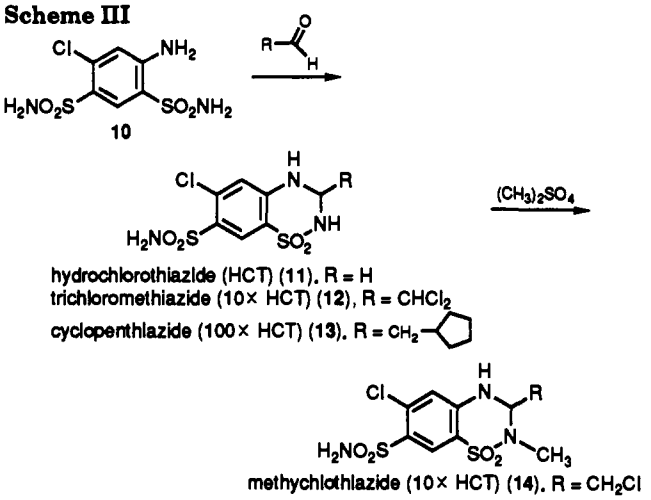
acetazolamide (6)

important since it was the first non-mercurial orally active diuretic drug not dependent for its activity on carbonic anhydrase inhibition, such as acetazolamide (6). Its potential as an antihypertensive agent was generally recognized, although its high dose (250–500 mg twice daily) and some tendency at high doses for eliciting carbonic anhydrase inhibition were considered limiting factors at that time.

Scheme II



Scheme III



hydrochlorothiazide (HCT) (11). R = H
trichloromethiazide (10× HCT) (12), R = $CHCl_2$
cyclopenthiazide (100× HCT) (13). R = CH_2

methychlothiazide (10× HCT) (14). R = CH_2Cl

An initial approach taken in our laboratory was to synthesize a disulfonamide structurally related to saccharin. Thus *m*-chlorotoluene disulfonamide (7) was oxidized to the corresponding saccharin derivative (8), which in turn was reduced to compound 9 (Scheme II). These showed some degree of diuretic activity but clearly were not comparable to chlorothiazide.

Shortly thereafter, I synthesized hydrochlorothiazide (11), which was found to be 10 times more potent than the unsaturated derivative. It was introduced into medical practice in 1959 and within a short time became the drug of choice in the treatment of mild hypertension (Scheme III).

Working with my collaborator, Lincoln Werner, and two able assistants, Sal Ricca and Angelina Halamandaris, over a period of 3 years, we prepared over 400 derivatives of this class from which a number of significant factors evolved:

(1) Whereas in the chlorothiazide series, only the prototype showed any significant activity, in the hydrochlorothiazide series substitution in the 2- or 3-position of the benzothiadiazine 1,1-dioxide gave rise to representative derivatives (12–14) with equivalent or greater potency than hydrochlorothiazide.

(2) The members of the hydrochlorothiazide series showed greater chloride excretion and lesser carbonic anhydrase inhibition than chlorothiazide.

(3) A lipophilic substituent at position 3 gave very potent compounds. Cyclopenthiazide (13) is 100 times more potent than hydrochlorothiazide. In any event, hydrochlorothiazide was widely accepted in clinical medicine, and until the advent of the ACE inhibitors a few years ago, it was the most widely prescribed drug, alone and in combination, for the treatment of hypertension.[5]

(1) deStevens, G.; Hopkinson, A. F.; Connelly, M. A.; Oke, P.; Schroeder, D. C.; Investigations in Heterocycles. IV. Substituted Cycloalkeno[*d*]thiazolin-2-ones. *J. Am. Chem. Soc.* **1958**, *80*, 2201–2204.

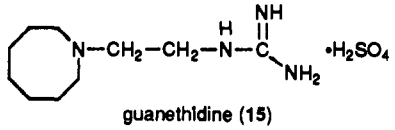
(2) Schlittler, E. The Chemistry of Rauwolfia Alkaloids. In *Rauwolfia*; Woodson, R. E., Youngden, H. W., Schlittler, E., Schneider, J. A., Eds.; Little, Brown and Co.: Boston, 1957; pp 50–108.

(3) deStevens, G.; Wilhelm, M.; Antihypertensive Agents. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhauser Verlag, Basel; 1976; Vol. 20, pp 197–259.

(4) Novello, F. C.; Sprague, J. M. Benzothiadiazine Dioxides as Novel Diuretics. *J. Am. Chem. Soc.* **1959**, *79*, 2028–2029.

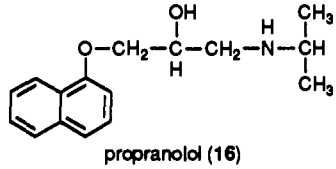
(5) deStevens, G. *Diuretics: Chemistry and Pharmacology*; Academic Press: New York, 1963; pp 81–119.

In the meantime, my associate, Robert Mull,[6,7] working with pharmacologist Robert Maxwell had discovered a most unusual guanidine derivative which in the clinical hands of Irvine Page was found to be very effective for treating severe hypertension. It is well known that guanethidine (15) is an indispensable drug when severe high blood pressure resists all other treatments.

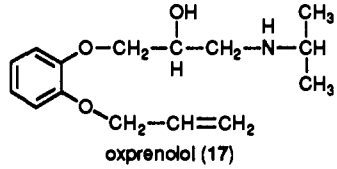


guanethidine (15)

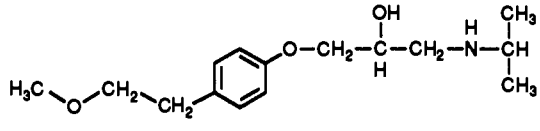
It is quite evident that by the mid-1960s, CIBA had established quite a strong franchise in the cardiovascular arena. β-Adrenergic antagonists were now being prescribed in Europe and in England as antihypertensive agents, and although oxprenolol (17) was considered competitive with propranolol (16), it was the conviction of the research management of the merged CIBA-Geigy U.S., to which I had been appointed Executive Vice President and Director of Research, that a cardioselective β-blocker would offer much more benefit to the hypertensive patient. As a result, we consummated a joint research agreement with Hässle, Sweden, an organization with a strong program in cardioselective β-adrenergic antagonists. Thus, by adding strength to strength we brought metoprolol (18) into



propranolol (16)



oxprenolol (17)



metoprolol (18)

clinical trials in the United States. All toxicology, considerable amounts of pharmaceutical development work, and Phase I and Phase II clinical trials were done in the United States. Hässle carried out most of the pharmacology, biochemistry, and Phase III clinical trials. The objective in all of this effort was to introduce metoprolol in as many markets as possible, with the target that metoprolol should be the next β-blocker to be introduced in the U.S. The NDA approval for metoprolol for the treatment of hypertension was obtained in the summer of 1978, approximately 4 years after our collaboration with Hässle on this project began. Metoprolol was the second β-blocker to be approved in the U.S., and it was the first of these agents to be approved by the FDA as a cardioselective agent.[8]

(6) Maxwell, R. A.; Mull, R. P.; Plummer, A. J. Guanethidine, a New Antihypertensive Agent. *Experientia* **1959**, *15*, 267.
(7) Mull, R. P.; Egbert, M. E.; Dapero, M. R. Guanidines with Antihypertensive Activity. *J. Med. Chem.* **1960**, *25*, 1533–1536.
(8) deStevens, G. Medicinal Research: Retrospectives and Perspectives. In *Progress in Drug Research*; Jucker, E., Ed.; Birkhauser Verlag: Basel, 1985; Vol. 29, pp 97–120.

Table I. Fixed Combinations with Hydrochlorothiazide (HCT)

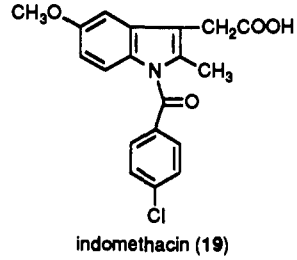
reserpine-HCT	Serpasil-Esidrix
hydralazine-HCT	Apresazide
guanethidine-HCT	Esimil
reserpine-hydralazine-HCT	SerApEs
metroprolol-HCT	Lopressor-HCT

With the introduction of metoprolol, the CIBA-Geigy franchise in cardiovascular medicine was more firmly entrenched. This was particularly emphasized since our discovery of hydrochlorothiazide permitted the additional introduction of fixed combinations of our antihypertensive agents and the diuretic (Table I). However, the use of hydrochlorothiazide alone and in combination, though most useful for controlling blood pressure and ensuring compliance, nevertheless over an extended period of treatment gave rise to hypokalemia.

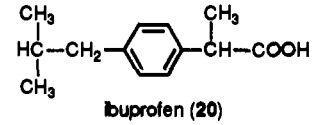
This problem got us into drug delivery system research and led to the development of Slow-K. The unique feature of Slow-K was that for the first time it permitted the safe administration of a potassium chloride supplement to hypertensive and edematous patients on long-term diuretic therapy. This was accomplished by means of the slow release of potassium chloride from a sugar-coated wax matrix. The consequence was that the salt was not dumped out in one large portion in the stomach or in the small intestine—as was the case with the enteric coated form—thus preventing mucous inflammation, ulceration, and stenosis.

The immediate success of Slow-K caused us to expand our drug delivery research program and its viability was further enhanced in 1977 by a joint venture of CIBA-Geigy and Alza. This collaboration led to a further extension of our cardiovascular commitment with the development of Transderm-Nitro for the treatment of angina. Our pioneering effort in transdermal delivery systems has enlarged the scope of medicinal administration.

Another main pillar of research for CIBA-Geigy has been inflammatory disease. After the significant discovery of corticosteroids, their widespread use revealed that though they were effective for the treatment of arthritis, their many side effects made them less than desirable for the long-term treatment of this crippling disease. The Merck Sharp and Dohme research management led by Max Tishler recognized that alternative approaches, such as nonsteroidal antiinflammatory agents, could be more fruitful. After several years T. Y. Shen and co-workers discovered indomethacin (19), which since 1965 has gained



indomethacin (19)



ibuprofen (20)

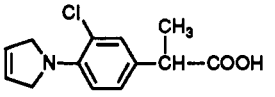
wide use as an effective antiinflammatory drug. Shortly thereafter, Boots introduced ibuprofen (20), and it was quickly ascertained that the acetic acid portion was the common feature in both of these molecules. As a consequence, a virtual explosion of research ensued in the synthesis of acetic and propionic derivatives for evaluation of their antiinflammatory properties.

At the time of the CIBA-Geigy merger in 1970, we had three such compounds ready for clinical evaluation. Due to the importance of this therapeutic area, the international research management agreed to move forward with

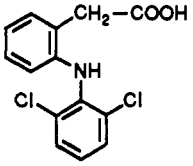
Table II. Drugs and Their Indications

rifampicin	tuberculosis
cephacetril	broad spectrum antibiotic
carbamezapine	epilepsy
baclofen	spasticity
maprotoline	depression

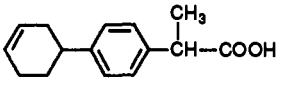
all three clinical candidates. Within a short time, Ba-41,027 (23) dropped out because of carcinogenic effects in rats. Diclofenac (22) in early clinical trials in Europe



pirprofen (21)



diclofenac (22)



Ba-41,027 (23)

proved to be effective although gastrointestinal side effects were of some concern. When we in the U.S. sought to submit an IND for diclofenac, all sorts of obstacles were encountered with the FDA. The animal toxicology in rodents, dogs, and monkeys was quite severe at all dose levels. The FDA imposed such excessive demands for additional animal work that our Research Management in Summit decided to withdraw pursuit of this substance in the U.S. and to seek to register it only in selective markets in Europe to ascertain the response. It was only after 3–4 years of successful clinical usage in Europe and Japan along with much basic biochemical work when it was learned that the pharmokinetic profile of diclofenac is quantitatively different in animals than humans. As a result, it appeared that the alarming animal toxicity did not carry over into man. On the basis of these findings, the IND for diclofenac was submitted to FDA by CIBA-Geigy in 1978. The final NDA approval for diclofenac came in 1988 and since that time it has proven to be widely accepted for the treatment of inflammatory conditions. The NDA for pirprofen (21) was approved in 1979 and was introduced in several European countries primarily as an analgetic.

In the postmerger period between 1970 and 1979, our Research and Development Department in the U.S. also was responsible for introducing into clinical medicine rifampicin, a cure for tuberculosis, and cephacetril, a broad-spectrum cephalosporin antibiotic.

In addition, our extensive program in central nervous system research led to the introduction of carbamezepine, a very effective antiepileptic substance which has gained wide acceptance as the drug of choice to control seizures. Baclofen was also brought into medical use for the treatment of spastic conditions and maprotoline was shown to be a useful antidepressant (Table II).

What I have presented to you this morning represents the efforts of my colleagues and myself at CIBA, and CIBA-Geigy from 1955 to 1979. To this end I wish to acknowledge the following associates for their tremendous efforts and loyal support during those years. The honor you accord me is also reflected upon them (Table III).

Table III. Research Associates

Lincoln Werner	William Darrow
Angelina Aretakis	Rosina Dixon
Sal Ricca	George Ohye
Robert Mull	Joseph Mollica
Robert Maxwell	Lewis Leeson
Jerome Chart	
Albert Plummer	
Neville Ford	
Richard Carney	
Robert Diener	
Max Wilhelm	

Perspectives

In 1979 I retired from CIBA-Geigy and was appointed Research Professor of Chemistry at Drew University. Since then, I have maintained my strong interest in medicinal chemistry through a number of programs and associations; namely, the founding of the international journal, *Medicinal Research Reviews* and also The Residential School of Medicinal Chemistry and The Charles A. Dana Research Institute. These programs have permitted me to stay in touch with the latest developments, and to this end, I would like to share with you in my closing comments some thoughts concerning the challenging opportunities available to the medicinal chemist in the coming decade and beyond.

Intrinsically associated with the birth of molecular biology has been the perception that the predominant force in modern drug discovery is no longer chemistry but biology. Another way to express this is: All drug research is biology driven with chemistry serving as a support to the needs of the biologists. In fact, on many occasions my students have questioned the wisdom of pursuing a career in organic chemistry. The argument is that organic chemistry is a mature science and its future in drug discovery is limited. My answer is that organic chemistry and in particular organic synthesis, in and of itself, and as it has been practiced in some quarters, *is* a mature science; however, with the advent of molecular biology, all has changed.

The revolution in biology brought about by the Watson–Crick model of DNA indeed has altered and expanded our knowledge of the life sciences in general, and biology and genetics in particular. But, essentially, we are dealing with organic chemistry since the building blocks of DNA are well-defined chemicals, namely, nucleotides, and the substances which are a consequence of the translation of the DNA code are proteins and resulting enzymes, which are vital to all mammalian life processes. And so what has molecular biology done? It has expanded our knowledge of biochemistry, cell organization, and cell function and it is beginning to give us a detailed understanding of chromosome structure and gene function. Recombinant DNA technology also permits us to prepare in large quantities important cell components, the absence or deficiency of which are responsible for many disease states. The biosynthesis of a gene and its incorporation into an individual deficient in that gene will lead to a correction of specific genetic defects. All of this is happening and will continue to evolve. And part of that evolution will be the determination of the structure of cell-surface receptors.

A detailed outline of the structure of the receptor is of immense value to the organic chemist whose mission is the design of a biologically active molecule. Only the chemist who understands the interacting bonding forces, which are a result of the tertiary structure of the macromolecule folding together in a specific way and giving rise to the surface receptor, can study the possible chemical shapes of molecules which can fit within that receptor site, bind accordingly, and in turn elicit the desired agonist or antagonist action. Receptor site structure information will also facilitate the process of structure–activity studies. Under these circumstances the medicinal chemist will be much more selective in the synthesis of derivatives of a

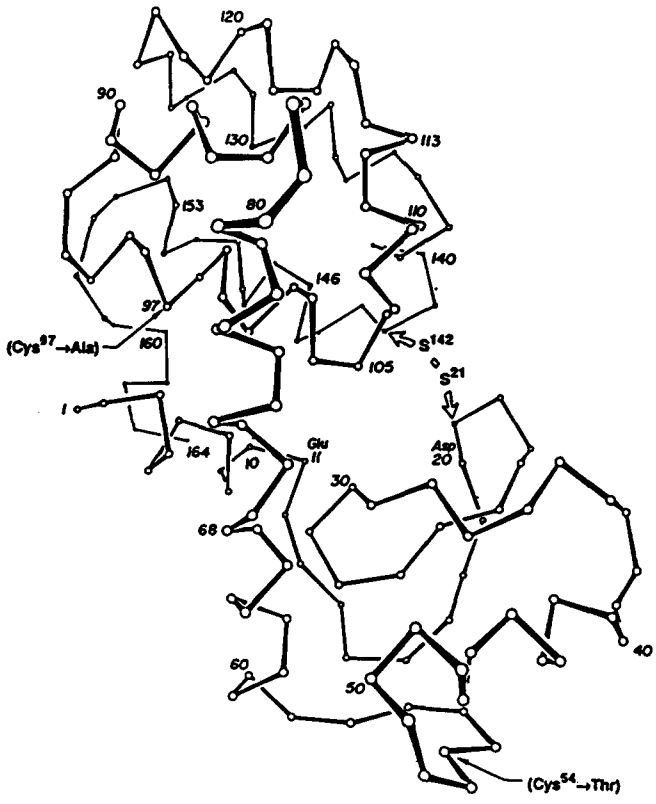


Figure 1.

lead discovery compound. The time frame from lead discovery to clinical candidate will be greatly shortened.

Another application of molecular biology in drug discovery is the study of the active site of an enzyme. By means of recombinant DNA technology certain amino acid junctures at the active site of an enzyme can be altered. Such changes in turn give much information on the nature of the active site and how its enzymatic alteration of a substituent is facilitated. An example of such an approach is the work of Matsumura and Matthews.[9]

It is well known that bacteriophage T-4 lysozyme (1,4-β-*N*-acetylmuramidase) catalyzes the hydrolysis of the 1,4-β glycoside linkage between the alternating units of *N*-acetylmuramic acid and *N*-acetylglucosamine in bacterial peptidoglycan.

As shown in Figure 1, by means of genetic engineering Matsumura and Matthews replaced threonine at positions 21 and 142 with cysteine. This change permits, under specific redox conditions, the opening and closing of the mouth of the active-site cleft (oxidation will form the disulfide bridge, reduction leads to the thiol moiety). Thus, the cysteines after undergoing oxidation forming the disulfide bond have essentially caused a gate to be put across the entrance to the active site. Under these circumstances the catalytic activity of the oxidized (i.e. cross-linked) T-4 lysozyme was completely lost. However, exposure of the cross-linked inactive enzyme to a reducing agent regenerates the non-cross-linked lysozyme which exhibited full enzyme activity. This research is a marvelous example of how the marriage of molecular biology and organic chemistry can lead to significant information on the nature of the active site. More of this kind of work will be forthcoming and will be of immense value to the medicinal chemist in discerning the subtleties of the receptor and the design of drugs to elicit biological activity. Therefore, molecular biology will be a tool by which the organic chemist can better understand substrate binding and function at the receptor site of a protein macromolecule. In other words, molecular biology deals with the structure of biological systems; that is, DNA, RNA translation of the genetic code to give rise to proteins and enzymes which are responsible for cellular functions. Thus, the chemist, whether he/she be biochemist or medicinal chemist, or both, is interested in fundamental reactions at the cellular level, the significance of these reactions in cell function, how these reactions serve the well-being of the organism as a whole, and how the overt changes in the reactions leading to disease states can be corrected or brought back to normal via the intervention of drug therapy.

Our next question then is: *How does biochemistry impact on the research of the medicinal chemist*? Very simply, biochemistry is concerned with all the molecules of the cell and organism and their function. In this regard, one may consider biochemistry as the forerunner of molecular biology, and both depend on the language of organic chemistry. Leopold Ruzicka[10] in 1964 expressed this most eloquently: "Biochemistry requires at least as much organic chemistry as does organic chemistry." The medicinal chemist, to function effectively, must have a good understanding of biochemical principles. This presumes an excellent understanding of enzymology, cell surface receptor theory, receptor-binding assays, drug–receptor geometry and drug–receptor bonding, the interrelationships of proteins, carbohydrates, lipids, coenzymes in cell structure and function, and how all of these factors influence motor and sensory functions of the central and peripheral nervous systems. Obviously, a corollary to this background is a working knowledge of drug biotransformation (metabolism). It is obvious from this brief outline that the medicinal chemist of today would have little understanding of where to begin in drug design without an appreciation of the guiding focal direction of biochemistry.

The power of biochemistry for understanding life processes and to alleviate, correct or cure disease, has recently been emphasized by Kornberg[11] in his book *For the Love of Enzymes*: "In recent years, the popularity and power of genetic engineering, dominated by molecular biology, have eroded the ranks and important roles of biochemistry. Without attention to biochemistry, the basic issues of cell growth and development, of degenerative disease and aging, will not be resolved. Molecular biology has successfully broken into the bank of cellular chemistry, but biochemical tools and training are needed to unlock the major vaults."

In another context, developments in the past decade in computer graphics and spectrographic analysis have had and will continue to have profound effects on how the medicinal chemist approaches and executes drug design. Let us look at this retrospectively so that we can see where we have been and where we are going.

It has been known since the time of Louis Pasteur and then Emil Fischer that the shape of molecules is closely associated with biological activity, an idea which prompted the suggestion of the "lock and key" effect. Ehrlich was saying essentially the same thing when he spoke of "pharmacophoric groups" attracted to receptors and implicit in these proposals is that the shapes of the active substance and the receptor are complementary.

Since the turn of the century, chemists have been intrigued with the shape of biologically active molecules and how the shape affects activity. The shape obviously must

(9) Matsumura, M.; Matthews, B. W. Control of Enzyme Activity by an Engineered Disulfide Bond. *Science* **1989**, 792–793.

(10) Eschenmoser, A. Leopold Ruzicka—From the Isoprene Rule to the Question of the Origin of Life. *Chimia* **1990**, *44*, 1–20.

(11) Kornberg, A. *For the Love of Enzymes*; Harvard University Press: Cambridge, MA, 1989; p 274.

be considered in three-dimensional terms and consequently was expressed by means of molecular models. Models became a necessary part of the medicinal chemist's armamentariums in his/her quest for new drugs. However, their use was in many respects self-limiting insofar as bond distances, bond interactions, rotational and electronic influences on surface–membrane interactions, and drug–receptor fit parameters were concerned, since all were subject to some speculation and approximation. This limitation was quite apparent after a lead discovery was made, since scores of analogues would have to be synthesized in order to arrive at a meaningful structure–activity relationship (SAR).

A significant change in drug design and SAR studies has come about in the past 20 years due to a marked improvement in physical methods for determining three-dimensional structures of organic molecules. These involve X-ray diffraction analysis of the crystalline state, NMR spectroscopic methods for the liquid or dissolved state, and quantum mechanical calculations for the isolated states. Application of these methods gives rise to what appears to be an almost insurmountable volume of information on the conformation of a molecule.

Now enters the computer! In recent years medicinal chemists in all major pharmaceutical companies have for their personal use a graphics microcomputer linked to a mainframe computer. Such a computer graphics system allows the chemists to inspect on a screen the most favored conformational structure of a molecule, visualize it in various three-dimensional modes, and, in so doing, to assess van der Waals forces, hydrogen-bonding volume, and possible cationic interactions. A lead discovery compound can be modified and the resulting biological data will be of great value in determining SAR studies. By superimposing the modified structure or structures on the lead discovery compound on the graphics terminal, the chemist can readily visualize the three-dimensional compatibility of the compounds. The superposition of structures, which is readily feasible with a computer graphics system, gives hints and suggestions on the receptor allowed volume and the possible shape of the receptor site. Such visualization also is a guide to the chemist in the synthesis of analogues and, in fact, facilitates the whole SAR process. The computer will not of itself design new drugs, but it will surely be of tremendous help to the medicinal chemist, reducing the time and effort of transforming a lead discovery into a clinical candidate.

Finally, a large number of receptors has been cloned and sequenced, and some have been crystallized. Eventually, the conformational structure of all of these will be determined by means of X-ray analysis. Such information with the aid of computer graphics will be of immense value to the medicinal chemist in designing drugs to fit the receptor as agonist or antagonist.

The foregoing has demonstrated most emphatically the significant and central role which chemistry plays in modern and future drug research. It does not mean to diminish the important role of biology, but it does serve to show that chemistry is not merely a support for the needs of biology but is a powerful driving force in itself. The two disciplines are essentially interdependent and each relies on the other for success in drug design, discovery, and eventual delivery of a useful medicament to the patient.

Finally, the medicinal chemist today is faced with as many if not more formidable challenges in medicinal research as his counterpart of a generation ago. The sciences of genetics, molecular biology, neuropharmacology, and electrophysiology have expanded the knowledge base of cellular function many fold. This new knowledge when coupled with the fundamental role of biochemistry in outlining in chemical terms both normal and abnormal cellular events offers the researcher a much more sophisticated appreciation of the cause of disease states. Knowing which enzymes or receptors are involved is a crucial step toward correcting the malfunctioning cellular condition.

With powerful new methods for determining the three-dimensional structure of molecules and computer graphics which give insight on rational drug design and modification, the medicinal chemist can explore with greater confidence than ever before the road to new drugs. The new biology, the new physical methodology, and the computer have enhanced the role of chemistry in modern drug research and have given the medicinal chemist a more profound grasp of cellular aberrations leading to disease. This knowledge is a golden rod in the hands of an imaginative chemist in the search for innovative drugs.

Is there a future for the medicinal chemist in modern drug research? The answer is a resounding *yes*!