1.01 Reflections of a Medicinal Chemist: Formative Years through Thirty-Seven Years Service in the Pharmaceutical Industry

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1.01.1 Introduction

It has been my good fortune to have been trained and influenced throughout my career by outstanding mentors and collaborators, both biologists and chemists. Their collective impact is immeasurable. They differed from each other in their fields of expertise, their research philosophy, and their 'Weltanschauung.' Taken together, the thoughts contained in this chapter reflect – to paraphrase Ralph Waldo Emerson[1]– the amassed thoughts and experiences of innumerable minds.

1.01.2 The Training of a Medicinal Chemist

1.01.2.1 Graduate School

Organic chemistry is the foundation of medicinal chemistry. I was very fortunate that Professor William S. Johnson of the University of Wisconsin, Madison, accepted me as a graduate student in 1946. My PhD thesis involved natural product total synthesis, and the target was a steroid. My knowledge of natural product total synthesis made me an attractive candidate for the pharmaceutical industry, for reasons that have remained a tradition widely accepted by big Pharma, but not by biotech companies. The attraction of a natural product as a synthetic target lies in part in the fact that the target was set by Nature, which gives it an aura of legitimacy. The most challenging part in the synthesis of a complex natural product often concerns the retrosynthetic analysis of its synthesis, which is generally determined by the major professor, not by the student or postdoctoral fellow. Successive heads of medicinal chemistry departments in big Pharma were trained in natural product total synthesis and they, in turn, tended to prefer candidates with a similar background when making job offers. This preference tends to become a self-fulfilling proposition.

Nature has evolved expertise in the use of reactions such as aldol condensations and others, and they are used repeatedly. Partly as a result thereof, chemists can rely on volumes of literature dealing with these reactions. To be sure there will be one or several steps in any natural product synthesis that will require creativity, which will ultimately make the difference between success and failure.

The situation is very different in the synthesis of unnatural products, which are today generally designed to display predetermined physical, chemical, or biological properties. There may be little or no prior art to guide the synthesis. Let me give one example: my colleague at the University of Pennsylvania, Professor Amos B. Smith, III, an acknowledged leader in natural product total synthesis, and I initiated a program in 1988 to design and synthesize inhibitors of proteolytic enzymes using pyrrolinone-based mimics of amino acids. Interestingly, chiral pyrrolinone-based amino acid mimetics had not been described. The endeavor proved to be rewarding, in that it led to an inhibitor of HIV-1 protease, which has better pharmacokinetic properties than its peptidal precursor, both because the pyrroline bonds are stable to proteases and because transport across membranes involves a lower desolvation penalty.[2] The x-ray crystal structure of the enzyme-inhibitor complex has also been reported.[2] In a recent publication, Smith *et al.* reported the 'total synthesis' of an unnatural tetrapyrrolinone mimicking the β-turn of the peptide hormone somatostatin. By current standards, and especially by Smith's own standards, it is not an imposing structure. However, the synthesis, including the preparation of the required unnatural building blocks, entailed some 53 steps, and required 46 person months. The synthesis of each of the four amino acid mimicking building blocks required about 11 steps, even though only one of the pyrrolinones contained a functional side chain. Thus, the total synthesis of unnatural products can be challenging. Moreover, the total synthesis of an unnatural product may not be publishable unless it possesses the predetermined physical and/or biological properties. Finally, in natural product total synthesis, very small amounts of material suffice to establish the identity with the natural product. In the case of nonnatural products, considerable amounts of material may be required to determine whether the substance possesses the desired properties. For these reasons I believe that natural product total synthesis should no longer be regarded as the only appropriate training for a potential employee by big Pharma.

My initial synthetic target as a graduate student in Madison was estrone. Because Professors William S. Johnson and Alfred L. Wilds were recognized leaders in steroid synthesis, they were quickly informed of the dramatic results obtained by Dr Philip Hench at the Mayo Clinic in the first clinical trial of cortisone in April 1949. Professor Johnson, therefore, shifted me from the total synthesis of estrone to that of cortisone. I was told only that cortisone "did something" in the clinic. Looking back, I am surprised that I did not ask any further questions of my mentor. Professor Johnson remains for me the perfect major professor, because of his ethical and scientific standards, his dedication to research and to his students, and for his creativity. As a graduate of Oberlin College I had taken relatively few courses in

chemistry. As a first year graduate student in Madison I was, therefore, concerned whether I could compete with fellow students from larger universities, who had taken many more hours of chemistry. This concern did not, however, prove to be a problem, suggesting perhaps that there is only so much chemistry that one can absorb as an undergraduate. Moreover, Dr Johnson was tolerant toward anyone willing to be in the laboratory in the evenings and over weekends. I was also very fortunate that my laboratory accommodated students of both Professor Johnson and Professor Alfred L. Wilds. Professor Wilds kindly took an interest in my training, and contributed significantly to my education. It will be difficult for today's reader of this textbook to comprehend that in 1950, the year I received the doctorate degree from the University of Wisconsin, nuclear magnetic resonance (NMR) spectroscopy was unknown and infrared spectral capability was not available in Madison. It has always amazed me that in the early twentieth century the structures of steroids, both the scaffold and the substituents, were elucidated through very hard and brilliant work, using such unremarkable reagents as potassium permanganate and acetic anhydride. Reading the history of early steroid research thus has always had a very humbling effect on me. I believe that it is sad that modern textbooks, and often classroom lectures in organic chemistry, have generally become dehumanized. It is argued that there is so much to be taught that there is neither time nor space to name the chemists on whose shoulders we stand. Perhaps so, but in my opinion, we pay a high price for this exclusive concern with 'the facts,' at the expense of our invaluable scientific heritage.

In the 1940s ultraviolet spectroscopy was well established as a tool in spectroscopy, but its value to organic chemists was questioned. A notable exception was Professor Wilds. Because he was very generous with his time, UV spectroscopy contributed significantly to my PhD thesis. For example, I was able to use this training to discover that a rearrangement of a double bond had taken place during a saponification step in Professor Johnson's total synthesis of equilenin, which caused a double bond to migrate from conjugation with an ester/acid into conjugation with a ketone. I was so excited by this discovery, that I expected the world to stand still once the news was out. This did not turn out to be the case! Moreover a physical chemist on my oral exam committee was amused that a synthetic organic chemist would take UV spectra seriously. I was to realize only much later, after I had joined the faculty at the University of Pennsylvania, that few, even well-trained organic chemists, make optimal use of UV spectroscopy. To give just one example: few medicinal chemists use UV spectroscopy to determine the precise concentration of a test compound in an aqueous solution prior to a biological assay. I am also amused when graduate students sign up for NMR time, when the UV spectrum would have provided the desired information right away.

In addition to Professors Johnson and Wilds, I also benefited greatly from a course taught by Professor Samuel McElvain on the role of electronic concepts in organic chemistry as developed by Lowery, Kossel, Remick, Ingold, and others. In combination with the research by H.C. Brown on steric effects, the two pillars of twentieth century medicinal chemistry were in place. Finally, it was a privilege to take Professor Homer Adkins' course in advanced organic chemistry. He was the only professor I have encountered who taught a philosophy of science, stressing skepticism as epitomized by his observation that "logic is the organized way of going wrong with confidence."

1.01.2.2 My 37 Years At Merck & Co., Inc.

1.01.2.2.1 The cortisol era

1.01.2.2.1.1 My years in process research

In the fall of 1949, Dr Max Tishler, then Director of Process Research at Merck & Co., Inc., and Dr Karl Folkers, Director of Fundamental Research, came to Madison on a recruiting trip. Before his arrival I realized that Professor Johnson had a healthy respect for Dr Tishler, because my mentor told me not to be too specific about our strategy for the total synthesis of cortisone "lest Dr Tishler figure out exactly what we are trying to do." The interviews were a success, and for the first time, I saw Dr Tishler's eyes flash with excitement. To an extraordinary degree he was both a passionate scientist and a hard-nosed boss. I was offered a position by both Dr Folkers and Dr Tishler. I should not have been surprised, because at that time Merck was interested in chemists with prior experience in steroid chemistry. I accepted Dr Tishler's offer, but I learned that I would be working on a total synthesis of folic acid, a somewhat unexpected assignment.

Several years later Dr Tishler was elected a member of the National Academy of Sciences (NAS) upon nomination by Professor Robert Woodward. It was extraordinary for a Process Research Chemist to be elected to the NAS, and it greatly strengthened his position with corporate management. Dr Tishler also hired a Bryn Mawr graduate trained by Professor Marshall Gates, Ms Lucy Aliminosa, who became my wife in 1951. The Tishlers were good friends of Lucy, and Dr Tishler therefore took an interest in me, I believe.

Thus, in the spring of 1950 I started to work as a Process Research Chemist reporting to Dr Norman Wendler, a kind person and an outstanding organic chemist. My assignment had changed, however. Instead of working on a synthesis of folic acid, I was to develop a new method to convert cholic acid into desoxycholic acid, the first step in the partial synthesis of cortisone. Dr Wendler was to be the first of the 13 sequential superiors to whom I reported at Merck. I learned an important lesson from having so many different mentors. To succeed in the art of directing research, there is not much point in acquiring a supervisor's style. It is best to be one's natural self – for better or worse – because one's subordinates are too astute to be fooled by acting.

I also learned that communication is a challenging art. When one is really excited about an idea, one must be prepared to devote time and energy to convey one's enthusiasm to colleagues. Surprisingly, at the end of a detailed discussion, the two participants often leave a conversation with different impressions of the conclusion that was reached.

It is worth mentioning that the environment at Merck in the 1950s was different from that which prevails throughout the industry today. Dr Tishler was a no nonsense, demanding research director, and I always made sure that I acted promptly on all of his instructions and suggestions. This is not surprising. What is noteworthy is that I was nevertheless free to pursue my own ideas. Some of that work was done in the evenings and over weekends, but some of it was carried out on 'company time.' Importantly, when an unauthorized project produced a useful result, my supervisors were pleased. I have the impression that the environment has changed, because today bench chemists and their supervisors are expected to devote all of their energy to the officially assigned tasks. Clearly the assigned tasks must be the first priority, but when leadership becomes excessively autocratic, and when creative initiative is stifled, something invaluable is lost. I believe that the insightful manager knows which of his associates should be closely supervised, and who should be left some measure of freedom. 'Management by objectives' is a sound concept, but when carried too far, i.e., when it is assumed that all good ideas come from the top or from a committee, productivity is likely to suffer.

Although I was not aware of it, I started my industrial career during one of the most remarkable periods in the history of the pharmaceutical industry. In the 1940s drug discovery at Merck, as at other major pharmaceutical companies, was 'largely based on blind, empirical screening of myriad chemical entities or on extracting compounds from microbial broths derived from soil samples.'[3] The age of 'rational drug design' was yet to come. Arguably the cortisone era served as a bridge between the two. Merck's decision to go forward was based on the faith, intuition, and insightfulness that cortisol, the major constituents of the adrenal gland, must play a major role in physiology, and that cortisol and cortisone might have great potential also in therapy. In addition, there was the false rumor that the Luftwaffe could fly at higher altitudes than our airforce because they were supplied with cortisone. Actually 'rational' analysis of the biological properties of the then known close analogs of cortisone was definitely not encouraging. Cortisone has two hydroxyl groups, at C17α and at C21, and three ketones at C3, C11, and C20. Kendall's compound A, lacking only the 17α hydroxyl of cortisone, and Reichstein's substance S, lacking only the 11-ketone, were devoid of any interesting biological properties even though between them they possessed all of the oxygen functions of cortisone. A rational drug designer should be forgiven had he or she decided that the synthesis of cortisone from cholic acid was not worth the effort of a synthesis of some 36 steps. Yet Professor Homer Adkins' quote (see above) would have been relevant. Fortunately Dr Tishler and Dr Lewis H. Sarett undertook the enormous challenge of making cortisone available by synthesis to make a clinical trial possible. Even though Kendall's compound A and Reichstein's substance S lacked any useful biological properties, the synthesis of cortisone was initiated at Merck in March of 1946.[4] Arguably, Merck and Co., Inc., played the role of a venture capitalist at that time. Nowadays, venture capitalists who have sought my opinion about investing in a given new technology want to be all but assured that success is certain. Merck had no such assurance in 1946.

As reported by Fieser and Fieser,[4] three Merck scientists and a technician processed 577 kg of desoxycholic acid and Dr Edward C. Kendall sent some partially purified desoxycholic acid to Rahway, NJ, for further purification. Cortisone prepared from desoxycholic acid became available just 2 years later, in April of 1948, and was sent to Hench and Kendall at the Mayo Clinic for initiation of the clinical trial the following month. Many persons are under the impression that natural cortisone was used in the successful clinical trial that resulted in the massive effort at Merck. This was not the case. The huge effort had to precede the clinical trial, which fully validated Dr Hench's intuition that cortisone might prove to be an anti-inflammatory chemical entity, based on his astute observation that the condition of women suffering from arthritis improved when they became pregnant. The enthusiasm following the first clinical trial involving a bedridden 29-year-old woman declined somewhat when several side effects associated with steroid therapy became apparent. These include adrenal atrophy, negative nitrogen balance, osteoporosis, 'moon face,' and others. Ultimately these side effects were to lead to the search for and discovery of nonsteroidal anti-inflammatory medications known as nonsteroidal anti-inflammatory drugs (NSAIDS).

Prior to the synthesis by Dr T. Shen *et al.* of indomethacin,[5] the first important NSAID in 1963, attempts were made to discover analogs of cortisol with fewer side effects than those of cortisone or its 11-dihydro analog, the endogenous hormone cortisol. These two steroids are interconverted in vivo. The partial synthesis of cortisol, possessing the critical 11-β-hydroxyl group, was accomplished by Dr Wendler and Dr Robert Graber in Rahway. The decade that followed became my introduction to medicinal chemistry. The goal was to discover an analog of cortisone/cortisol devoid of the side effects of the endogenous compounds. Along with all other medicinal chemists, it took me nearly a decade to appreciate that the strategy to find a safer drug by generating more potent compounds, permitting a reduction in dosage, was doomed to failure because the desired biological effects and the side effects of cortisol were mediated via a common receptor. This is probably the most important lesson in medicinal chemistry that I learned during my first 10 years in industry. More recent research has, however, opened a new window,[6] via novel structures that are devoid of the classic steroid scaffold.[7,8] With hindsight then, it is no surprise that the only side effect of cortisol that was successfully abolished via analog synthesis is salt retention, because it is mediated via a separate receptor, for which aldosterone is the endogenous ligand. That cortisol, an endogenous steroid hormone, can produce significant side effects, reflects the difference between physiologic and pharmacologic doses.

1.01.2.2.1.1.1 Toward more potent and safer analogs of cortisol The search for alternative synthetic routes to cortisol and other research led to an understanding of the structural factors affecting relative glucocorticoid and mineralocorticoid activities, i.e. the desired anti-inflammatory activity and the unwanted salt retention.

Dr Hans Hirschmann, my brother, and his coauthors at Case Western Reserve University found unexpectedly that 16α-hydroxysteroids do not display mineralocorticoid activity.[9] Therefore, Dr Bernard Ellis *et al.* at the British Drug House[10] and Dr Allen Bernstein at Lederle[11] synthesized 16α-hydroxycortisol. These chemists discovered between 1955 and 1956 that the compound displayed considerable glucocorticoid activity, but did not cause sodium retention. Thus, the 16α-hydroxy-steroids represented an advance in steroid therapy.

The search for a route to cortisol via an 11α-hydroxylated steroid led in 1954 to the interesting discovery by Dr Josef Fried and Ms Emily F. Sabo at Squibb, that the 9α-fluoro analog of cortisol showed a ten-fold increase in potency over the endogenous cortisol.[12] The discovery was made possible by the intelligent pursuit of fortuitous observations and their insightful interpretation by Fried and Sabo. The issue was not trivial. On the one hand, there was the desire to remain focused, and on the other, the danger of neglecting unexpected results that might prove to be more significant than the original objective. 9α-Fluorocortisol was of no clinical interest because of its unacceptably high salt retention properties, even in the 1-dehydro series.[13] This problem was later overcome at Schering and at Merck by the additional introduction of 16α- or 16β-methyl substituents, which like the 16α-hydroxyl, blocked the interaction of the resulting steroids with the aldosterone receptor but enhanced affinity at the desired glucocorticoid receptor. This led ultimately to the synthesis of the medically important C-16 diastereomeric 16-methyl-9α-fluoroprednisolone analogs.

The conversion of the relevant 9β,11β-epoxides into the 9α-fluoro-11β-hydroxy-steroids on treatment with anhydrous hydrogen fluoride (HF) in alcohol-free chloroform afforded only a 50% yield. At about that time I was transferred from Dr Wendler's group to that of Dr Robert E. Jones to become more involved in typical Process Research. The yield for the HF reaction was an issue of sufficient importance to the company that Corporate Management was kept informed on a daily basis. I found within a day that the reaction actually afforded much better yields in straight alcohol and in other organic bases, as long as the concentration of anhydrous HF was high enough to permit acid-catalyzed opening of the epoxide.[14] We concluded that the yields were low in alcohol-free chloroform because the concentration of anhydrous HF, and therefore of 'fluoride ion,' was too low to favor fluorohydrin formation over dehydration. Dr Karl Pfister, the inventor of methyldopa, and Head of Process Research at that time, graciously told me that I had taken a big load off his shoulders and that he had wanted me to report directly to him, but since this was not possible for organizational reasons, he transferred me to Dr John Chemerda, the leader of the largest group in Process Research.

At about the same time (1955) the group of Dr John Hogg and coauthors at the Upjohn Company were the first to prepare alkylated analogs of the glucocorticoid hormone. The first,[15] 2α-methylcortisone, was inactive, presumably because the 2α-methyl substituent blocks the in vivo reduction of the 11-ketone to the 11β-hydroxyl. On the other hand, 2α-methylcortisol was a more potent glucocorticoid than cortisol, but it also showed enhanced unwanted mineralocorticoid activity and was therefore not developed. Fortunately, the Upjohn scientists persevered, and the 6α-methylcortisol was found to be more potent than cortisol as a glucocorticoid, and pleasingly it displayed negligible salt retention. Later, the 6α-methyl derivative of prednisolone[13] was marketed by The Upjohn Company.

Given that the glucocorticoidal and mineralocorticoidal receptors represent different proteins, it was not surprising that the first significant clinical advance over cortisol was the discovery of the 1,2-dehydro analogs by Dr Emanuel B. Hershberg

and coauthors at Schering in 1955.[13] These congeners, like the 9α-fluoro cortisol, were more potent than the hormone, but unlike the latter, they displayed reduced salt retention. The new compounds, named prednisone and prednisolone, were obtained by microbial dehydrogenation of the hormones. The use of microorganisms including both bacteria and fungi to achieve chemical transformation was not new and was employed also at Squibb, Upjohn, Merck, and by Wettstein and coauthors. Today it seems amusing that some synthetic organic chemists initially took a dim view of the use of microorganisms in a synthetic endeavor, which they regarded as 'cheating.' The introduction of the 1,2 double bond via the use of microorganisms became routine thereafter.

1.01.2.2.1.1.2 Opthalmic application The ophthalmic application of anti-inflammatory steroids as eye drops had been accomplished via the administration of a suspension of steroidal 21-acetates. Upjohn then developed the 'more elegant' water-soluble 21-succinate ester. I was therefore given the assignment of preparing the 'more physiologic' 21-phosphate. In those days organic chemists dreaded the assignment of a phosphate as a synthetic target because we were used to discarding the aqueous layers in the isolation of our reaction products and we were uncomfortable when the aqueous layer contained the desired product as was the case with phosphates. Dr George I. Poos, a member of my group, developed a practical synthesis of the 21-phosphate of cortisol.[16] The marketed product was attractive also for intravenous administration, but lost its glamour for the ophthalmic market when the patent of the equally effective, albeit less elegant, acetate expired. Not all seemingly 'important' research objectives are truly worth pursuing, especially if their principal appeal relates to marketing objectives rather than medical need.

1.01.2.2.1.1.3 Alternative starting materials Under Dr Tishler's superb leadership the overall yield for the conversion of bile acids into cortisone had become so high that they were hard to believe, even for insiders. Merck, however, kept this achievement a secret and talked only about the complexity of the process. In retrospect this may have been a mistake, because it encouraged the competition, especially at Syntex, to explore starting materials other than bile acids. Indeed, such research was also underway at Merck,[17] typified by the synthesis of allopregnan-3β ol-11,20-dione acetate from ergosterol, stigmasterol, and diosgenin. This research led to—what turned out to be—an interesting in-house competition. Starting with the 12-keto steroid hecogenin (please see below) Mr. C. Stewart Snoddy, Dr Wendler, and I synthesized the corresponding $\Delta^{9,11}$ olefin which was converted into 22-isoallospirostane-3β,9α,11α-triol with osmium tetroxide.[18] At the same time Dr John Chemerda and his collaborators[19] studied the conversion of $\Delta^{7,9(11)}$-steroids into 11-oxygenated congeners. In the critical step Ms Lucy Aliminosa brought the Δ^{7}-9α,11α epoxide into contact with acid-washed alumina during chromatographic purification; in the process the oxide ring is opened by acid catalyzed hydrolysis to afford the corresponding Δ^{8}-unsaturated 7α,11α-diol. Two Merck laboratories had thus achieved the desired 11-hydroxylation. Dr Tishler expressed little joy about my process. He informed me that he hated osmium tetroxide. By that time I knew him to be a good friend, albeit a demanding boss. On the other hand, Lucy Aliminosa was the heroine of the day. As Dr Tishler informed me, "we will do it Lucy's way." I was not unhappy about the outcome.

1.01.2.2.1.1.3.1 The first example of a reaction recognized to be under 'stereoelectronic control' My own 18 years in Process Research were scientifically stimulating and personally satisfying in every way. I enjoyed working in the laboratory with a group of three or four chemists. I was privileged to work with remarkably devoted and gifted collaborators under a research-oriented corporate management. I can recall only one disappointment. Early in my career in 1952 I made what was to become a significant contribution to synthetic organic chemistry. I reduced the 12-ketone of the sapogenin hecogenin and separated the resulting diols. Stereochemical assignments were readily made by then well-established methods and the separated epimers were converted into the corresponding mesylates. Contrary to expectations, solvolysis of the equatorial 12β- mesylate afforded an olefin in high yield whereas the axial 12α-mesylate was recovered largely unchanged. The olefin possessed unexpectedly strong bands as revealed by infrared spectral absorbances at 6.04 and 11.24 μm. Hydroxylation of the presumed 3-hydroxy-11,12-dehydro sapogenin with osmium tetroxide afforded a triol that was quantitatively converted into a diacetate, revealing an OH band in the infrared at 2.8 μm. Saponification of this diacetate quantitatively regenerated the triol, and the latter on cleavage with periodic acid produced formaldehyde in 60–65% yield as determined by chromatropic acid titration and isolation of its dimedone derivatives together with a quantitative yield of a nor-ketone having a single carbonyl bond in the infrared at 5.84 μm and only end absorption in the UV spectrum. We were able to explain the unexpected results and the infrared spectral properties of the olefin by showing that the elimination reaction in the 12β mesylate series resulted in a rearrangement of the steroidal C/D rings affording a C-nor-D-homo steroid. My colleagues Mr. Stewart C. Snoddy, Jr., Dr N. L. Wendler, and I reported in 1952[20] that the formation of the olefin from the equatorial 12β mesylate "represents a rearrangement

path wherein the stereoelectronic requirements are fulfilled only in the case of the natural C_{12}-β-configuration" of the equatorial hydroxyl. We pointed out that "the significance of this geometrical factor is reflected in the extraordinary ease with which this rearrangement occurs." We also noted that 'stereoelectronic control'[20] considerations provide an attractive mechanism to explain the biosynthesis of the alkaloids jervine and veratramine, the structures of which had just been elucidated by Wintersteiner and Fried at Squibb. The concept of stereoelectronic analysis built on the prior work of Derek Barton, who had introduced the concept of axial and equatorial substituents for the A, B, and C rings of the steroid. Barton had thereby rationalized the chemical reactivity of epimeric steroidal alcohols and esters almost overnight. To my knowledge but contrary to the commonly held belief, ours was the first reported use of the term 'stereoelectronic' to describe the mechanistic underpinning of a molecular rearrangement.

1.01.2.2.1.2 Transfer to fundamental research

It had become apparent to Dr Sarett, who had responsibility for new drug discovery, that Ralph Hirschmann, a member of the Process Research team, was 'inappropriately' interested in the synthesis of new compounds for biological testing, the domain of Fundamental Research. In 1958 I was, therefore, transferred from Dr Tishler's Process Research Department to Fundamental Research as one of Dr Sarett's five group leaders for steroid research. The transfer proved to be a high-pressure assignment. Dr Sarett met with the steroid group leaders early every Monday morning. We were expected not only to report on the progress of our laboratories, but also to present new research proposals. This assignment did not make for relaxing weekends. Nevertheless, I have always regarded my internship with Dr Sarett as exceptionally valuable. Dr Sarett's approach was distinct from those of other successful medicinal chemists whom I had observed because it was very systematic. He had realized early on that in medicinal chemistry, all effects are either steric or electronic. Sarett also introduced me to the concept of 'minimum systematic variation' in lead development. If, for example, the biological effects of the introduction of either a chloro or a methyl substituent alpha to a ketone are the same, the effects are steric; if the effects are opposite, they are electronic, etc. Further, if introduction of a methyl substituent decreases potency, there is little point in giving an ethyl group a 'try'.

Dr Sarett stressed that when selecting the next synthetic target, it is important first to write down all possible candidates, and then make a careful selection to ensure that the maximum of information is obtained from the smallest synthetic effort. He taught us never to decide on one's next synthetic target on the spur of the moment.

1.01.2.2.1.2.1 An early example of prodrug design based on a biochemical rationale (MK-700)

Of all the steroids that my group synthesized in the general search for a less toxic cortisol, the most original was the 2-acetamido-2-deoxy-β-D-glucopyranoside of prednisolone (MK-700).[21] To my knowledge, it was the first glucocorticoid that was 'designed' to have a better therapeutic index than prednisolone. The design was based on the assumption that the 21-glucoside, like the 21-methyl ethers, would be biologically inactive and that its conversion to the free steroid (prednisolone) would occur primarily in the synovial fluid of inflamed joints that we and others had shown to have strikingly higher concentrations of *N*-acetylglucosaminidase than normal joints or plasma. This prodrug did indeed display an improved therapeutic index in the rat granuloma assay but lacked oral bioavailability. At least in hospitalized patients, parenteral administration of medicines in solution would not have been a problem. However, the potential of the compound as a parenteral drug was not explored. Its therapeutic potential, therefore, remains unknown. On the other hand, the application of the underlying concept was to become routine. Arguably, making oral bioavailability a *conditio sine qua non*, without considering each case on its merits, is unwise.

On 27 and 28 August 1991, an International Symposium on the History of Steroid Chemistry was held in New York City. Participants included[22] Pedro Lehmann, Arthur Birch, Gilbert Stork, Jeffrey Sturchio, George Rosenkranz, E. R. H. Jones, Carl Djerassi, Leon Gortler, Josef Fried, Ralph Hirschmann, Alejandro Zaffaroni, Seymour Bernstein, Konrad Bloch, Frank Colton, John Hogg, and Koji Nakanishi.[22]

I provided a synopsis of contributions of the Merck laboratories, not mentioned herein, at that meeting.[23]

I have not mentioned the important work of Rosenkranz and others at Syntex, because as a whole it did not significantly relate to my research at Merck. Marker's important work during the early 1940s clarified the structures of sapogenins. His work led to the formation of the Mexican Steroid Industry. I do recall a conversation with Russel E. Marker in my office about the chemistry of the sapogenin hecogenin that he had isolated, and which became an important starting material in my research.[20]

1.01.2.2.1.2.2 The discovery of the steroidal preg-4-eno [3,2-] pyrazoles

The synthesis of steroidal preg-4-eno [3,2-] pyrazoles[24] emerged from my tenure in Dr Sarett's department. I had started the project on my own. Treatment of a 3-keto-Δ^4 -steroid with ethyl formate followed by hydrazine or phenylhydrazine, respectively, led to the desired

heterocycles in high yield. It became an official endeavor only later, and then because of Dr Tishler's support. The pyrazoles, especially the *p*-fluorophenyl pyrazoles, proved to be the most potent activity-enhancing modifications discovered for steroidal anti-inflammatory agents. One of these pyrazoles was marketed in Europe. The pyrazoles also disproved the heretofore held belief that an α,β-unsaturated ketone in the A-ring is required for cortisol-like biological activity.

1.01.2.2.2 Transfer to exploratory research

1.01.2.2.2.1 The total synthesis of an enzyme in solution

When Dr Robert G. Denkewalter, the Vice President for Process Development informed me in 1963 that he was about to assume the newly created position of Vice President for Exploratory Research to undertake basic research in nucleic acid and peptide chemistry, he invited me to head a group of three chemists to establish peptide chemistry at Merck. We started from ground zero. When Smyth, Stein, and Moore published the complete primary structure of ribonuclease A[25] that same year, it became clear just a few months later that my assignment was nothing less than the total synthesis of ribonuclease.

Although in recent years steroid chemistry has regained considerable momentum, in 1963, steroid research was on the decline. This had become obvious to me and, therefore, I gave an immediate and positive response to Dr Denkewalter who had urged me not to make a hasty decision. I was excited about the opportunity to learn about a field of natural product chemistry that was completely new to me. I suspect that abandoning one's 20-year experience in one field of organic chemistry to enter another field may entail a significant risk in academia, but this was not the case in industry.

1.01.2.2.2.1.1 The use of *N*-carboxyanhydrides Denkewalter's reading of the peptide literature led him to a 1950 paper by J.L. Bailey,[26] which reported the controlled synthesis of small peptide esters in anhydrous medium at low temperatures, using amino acid *N*-carboxyanhydrides. These anhydrides were prepared by allowing amino acids to react with phosgene. *N*-carboxyanhydrides had also been successfully employed in polymerization reactions. Bailey's procedure was impractical primarily because of solubility problems in organic solvents at low temperatures. Although we were unaware of the fact at the time, Professor Paul Bartlett[27] at Harvard had explored the use of *N*-carboxyanhydrides in aqueous medium in controlled peptide synthesis without isolation of intermediates, but had abandoned the project because of side reactions that he was not able to control. The appeal of the use of *N*-carboxyanhydrides in peptide synthesis in aqueous solution lies in the fact that the desired coupling reaction proceeds very rapidly. Treatment of the potassium salt of an amino acid with a slight excess of an *N*-carboxyanhydride generates the dipeptide, the new amino group of which is protected as the carbamate potassium salt. Acidification results in the formation of the carbamic acid, which loses CO_2 spontaneously. It takes only about 5 min to generate the desired dipeptide. The cycle can then be repeated with retention of enantiomeric integrity. While we were able to synthesize a crude octapeptide quickly and without isolation of intermediates, purifying only the final product, the method generally failed to afford multiple step products of the desired purity[28] without chromatographic purification.

1.01.2.2.2.2 The state of the art in 1963

In 1906, in a much-quoted lecture, Emil Fischer expressed the view that the daunting challenges of an enzyme synthesis notwithstanding, chemists should at least give it a try. In 1907 he had synthesized peptides containing 20 amino acids, using his own acid chloride method and the azide procedure of Curtius. Nevertheless, little real progress was made in peptide synthesis until Bergman and Zervas[29] introduced the benzyloxycarbonyl protecting group in 1932, which, unlike an acyl protecting group, permitted the introduction of an activated amino acid without loss of enantiomeric purity and which could be removed by catalytic hydrogenation. In combination with other protecting groups and new coupling reactions, du Vigneaud achieved the synthesis of the first compound of biological interest, oxytocin, in 1953.[30] This was a remarkable achievement because this nonapeptide amide contains five functional amino acid side chains including a cystine bridge. It would be a mistake to conclude that with the synthesis of a hormone in hand, the synthesis of any peptide in solution had become routine. Each polypeptide, like any other organic molecule, has its own personality and synthesis of 'model compounds' has gone out of style for just that reason. In 1968, the synthesis of such biologically active peptides as angiotensin, adrenocorticotropic hormone (ACTH), gastrin, insulin, secretin, glucagon, and calcitonin had been accomplished.

The unique role of enzymes was described well by F. H. C. Crick in 1958,[31] who stated that the:

"nearest rivals [of enzymes] are the nucleic acids…. The most significant thing about proteins is that they can do almost anything…[and] the main function of proteins is to act as enzymes…. Once the central and unique role of proteins is admitted, there seems to be little point in genes doing anything else [but protein synthesis]."

1.01.2.2.2.3 The Merck synthesis of an enzyme

The Merck group undertook the synthesis of the 104 membered chain called ribonuclease S- protein, so named because Richards had shown that ribonuclease A can be split by the protease subtilisin into two fragments: (1) S-protein the C-terminal fragment, which contains 104 amino acids including the 4 cystine bridges, i.e., 8 cysteine residues; and (2) the N-terminal 20-membered fragment, named S-peptide. Neither fragment displayed any enzymatic activity, but when the two fragments were mixed in equimolar proportion in aqueous solution, the resulting mixture, named ribonuclease S[1], was active, with an enzymatic activity equal to that of ribonuclease A. Hofmann and associates had synthesized S-peptide in 1966; therefore, the synthesis of S-protein would complete the total synthesis of an enzyme. Importantly, Haber and Anfinsen had shown that fully reduced S-protein can be oxidized in the presence of S-peptide to afford enzymatically active material in 35% yield. Had this not been established, we would not have undertaken the synthesis of S-protein.

It is important to note that at the time we initiated the synthesis of an enzyme, there were only three other laboratories who thought it reasonable to contemplate that objective. These teams were the laboratories of Professor Bruce Merrifield at Rockefeller University, Professor Klaus Hofmann in Pittsburgh, and Dr Christian B. Anfinsen at the NIH. Most of our colleagues, however, thought it likely that our objective could not possibly be achieved for the following reason: ribonuclease contains eight cysteine residues. The final step of any synthesis includes the oxidation of these eight residues to generate four disulfide bridges. In theory, there are 105 different ways in which eight cysteine residues can be combined to form four cystine bridges, only one of which corresponds to ribonuclease. It was generally believed at that time that a template was required to ensure proper folding, i.e., to provide the information required to favor the one isomer out of 105 that is the natural product. This argument is not without merit as evidenced by the subsequent discovery of chaperones that serve that purpose.[32] On the other hand, in 1958 F. H. Crick wrote the following:[31]

"It is conventional at the moment to consider separately the synthesis of the polypeptide chains and their folding. It is of course possible that there is a special mechanism for folding up the chain, but the more likely hypothesis is that the folding is simply a function of the order of the amino acids…. I think myself that this latter idea may well be correct…."

Indeed, White and Anfinsen[33] provided support for Crick's insightful suggestion. They showed that the enzyme's activity, which is lost when the four cystine bridges are reduced under denaturing conditions, is completely restored following dialysis and subsequent reoxidation. The significance of this experiment has been questioned, because the denaturation may have been incomplete. The Anfinsen hypothesis was validated by the total syntheses of ribonuclease.

Clearly the careful design of the strategy for the synthesis was all important. In addition to the question related to the proper foldings of the protein, discussed above, the choice of the protecting groups was of paramount importance. The presence of several sulfur-containing amino acid residues in the proteins argued against the use of a strategy that entailed catalytic-hydrogenation for the removal of any of the protecting groups. Furthermore, protection of the cysteine residue with the widely employed S-benzyl group was unattractive because its removal requires sodium-liquid ammonia, a system not attractive for proline-containing peptides. We had therefore invented the acetamidomethyl group for the protection of the eight cysteine residues.[34] It met our requirements of being stable to trifluoroacetic acid at 25 degrees, to anhydrous HF at zero degrees, and to hydrazine. It can, however, be selectively removed with Hg(II) under mild conditions. The use of the *N*-carboxyanhydrides of unprotected arginine, and unprotected aspartic and glutamic acids as well as the related 2,5 thiazolidinediones (NTAs)[35] for the introduction of unprotected histidine permitted the development of a strategy in which the third functionality needed to be protected only for lysine and cysteine. Thus, rearrangements involving the esterified β-carboxyl of aspartic acid and the γ-carboxyl of glutamic acid were avoided. The formation of the four disulfide bridges subsequent to the liberation of the ε-amino groups of the eight lysine residues was considered to be a desirable feature. For the ε-amino group of lysine we employed the benzyloxycarbonyl protecting group, which can be removed with anhydrous HF. Importantly, S-protein is stable in this solvent at zero degree. This strategy allowed us to use the butyloxycarbonyl group as the acid-labile temporary blocking group for the introduction of amino acids via Anderson's hydroxysuccinimide esters (please see below). Finally, this

combination of protecting groups enabled us to remove all the *N*-blocking groups of the tetrahectapeptide with liquid HF, while leaving the cysteines protected.

To synthesize S-protein we relied on the fragment condensation method. A total of 19 fragments was prepared using NCA's, NTA's, and the Boc-hydroxysuccinimide esters of G. W. Anderson.[36] To permit the use of unprotected ω-carboxy groups of aspartic and glutamic acids, we utilized the azide method for fragment condensation as mentioned above. The plan devised to accomplish the synthesis of ribonuclease S-protein is described in the first[37] of five consecutive Communications to the Editor of the *Journal of the American Chemical Society*. As we pointed out,[38] it is one of the characteristics of peptide chemistry that the success or failure of a given synthetic approach depends to an unusual degree both on the precise experimental conditions, and on the judicious selection of protecting groups and coupling reactions employed. For example, it had been claimed that the hydrazinolysis of peptide esters is not an attractive procedure with larger peptides and that the azide coupling procedure is attended to a large degree by the Curtius rearrangement. Our hydrazinolysis reactions, which allowed us to convert C- terminal ester fragments to azides via hydrazides, were successful because: (1) the β-carboxy group of aspartic acid and the γ-carboxy group of glutamic acid were unprotected; and (2) we developed protocols that avoided side-reactions such as the conversion of arginine to ornithine or of asparagine and glutamine to the corresponding hydrazides. By leaving the β-carboxy group of aspartic acid unprotected, we avoided such side reactions as succinimide formation, which can either survive subsequent reactions unchanged or rearrange to a mixture of α- and β-carboxy linked aspartyl residues.

To study the removal of the eight sulfhydryl acetamidomethyl blocking groups from our synthetic protein we attempted to acetamidomethylate reduced natural S-protein. Using the aqueous conditions that afford the acetamidomethylated cysteine itself, did not yield an intermediate capable of regenerating enzymatically active protein. S-Alkylation in anhydrous HF, however, proved satisfactory. Cleavage of the sulfhydryl blocking groups with Hg (II) in acetic acid afforded the reduced S-protein that could be converted to enzymatically active material. The regeneration of enzyme activity by air oxidation as described by Haber and Anfinsen proceeded in low yield. We were able to improve the protocol for the oxidation step to a nearly quantitative yield. The final coupling reaction was carried out by Dr Ruth Nutt, who had only 1.6 mg of the precious hexacontapeptide at her disposal! The unprotected, oxidized S-protein revealed optimal enzymatic activity only when the oxidation step was carried out in the presence of S-peptide. All other control experiments also gave the expected results.

The successful completion of the endeavor was due above all to the experimental skill of the bench chemists, the leadership of three group leaders, Dr Daniel Veber, the late Dr Fred Holly, and Dr Erwin Schoenewaldt, as well as the spirit of collaboration within the entire team. I am particularly indebted to Mrs Susan R. Jenkins and Dr Ruth Nutt for carrying out the most challenging coupling reactions involving the large fragments. It is also a pleasure to acknowledge the skill of Tom Beesley in using Sephadex gel filtration to purify our growing fragments and Carl Homnick who provided amino acid analyses within a deviation of 3%. To my knowledge such accuracy is no longer available today. These analyses were invaluable in demonstrating purity. An advantage of the fragment condensation strategy is the fact that we were generally confronted with impurities that differed significantly in molecular weight from the desired product. The remarkable spirit of collaboration, which is a great credit to the entire group of chemists, deserves further comment. Because we had chosen fragment condensation as our underlying strategy, a chemist A might have synthesized fragment 1 and a chemist B, fragment 2. To couple these two building blocks, one of the two chemists would have to turn over all of his or her precious material to the other. The further the synthesis progressed, the more precious the fragment that was handed over. To the best of my knowledge, these arbitrary assignments of the fragment coupling reactions did not become a major issue.

I suspect that chemists outside the peptide field may not fully appreciate the role that purification techniques available to us and to Professor Merrifield played in achieving success. In the chemical synthesis of peptides it can become very challenging to detect impurities that may arise, such as diastereomers, or asparagines that rearranged to succinimides, or to β-linked aspartates. More often than not, such impurities do not change the desired properties of the synthetic proteins, but they are impurities nevertheless. Therefore, the more cavalier characterization of synthetic proteins now widely employed leaves something to be desired. In our synthesis of RNase S[1] we went to great lengths to characterize our intermediates as fully as was possible at the time when mass spectrometry was not available. We made extensive use of generating and fully examining enzymatic digests, which permitted us to show that asparagines and glutamines had not been hydrolyzed to the corresponding dibasic acids. Enzyme digests also demonstrated chiral purity.

While reporting to Dr Denkewalter I had one and only one responsibility: to ensure the successful total synthesis of our enzyme. I had no time-consuming administrative tasks. During that period I spent hours discussing the synthesis with Dr Daniel Veber. I made an interesting observation during those months. Dr Veber and I would discuss a particular chemical issue and reach what we thought to be a logical conclusion. Because we had no other tasks, we would consider

the issue further only to realize half-an-hour later that there was a better conclusion than the one we had reached earlier. It is not a reassuring thought, because I had come to realize that when I 'make rounds,' the recommendations I make are often not as good as those I could have made, had we continued the dialog longer.

The chemical syntheses of an enzyme were announced at a joint press conference held at Rockefeller University in January 1969 by two groups, one by Professor Bruce Merrifield and Dr Gutte, and the other by our group at Merck. Brief remarks were made by Drs Merrifield and Gutte, by Dr Denkewalter and by me. One sentence of mine was quoted in the *New York Times* the following weekend: "We all build on the work of those who came before us and we never know what the future will bring."

1.01.2.2.2.4 The Merrifield 'solid phase' synthesis

The Merrifield solid phase synthesis announced in 1962 has revolutionized not only peptide chemistry but also nonpeptide synthetic organic chemistry. Its distinguishing feature, known to every chemist today, is the fact that the C-terminal amino acid is permanently attached to a resin throughout the elongation of the peptide chain. The peptide is cleaved from the resin in the final step and is then purified. Remarkably, Merrifield was able to achieve sufficiently high yields to complete the synthesis of biologically active material without purification of intermediates. Such operations are now completely automated. Unfortunately, the pharmaceutical industry widely embraced combinational chemistry for lead discovery in the late twentieth century before that concept had been validated. As pointed out elsewhere,[39] only Pharmacopeia appreciated early on that libraries, to be of potential value, need to be sufficiently complex to generate structures of potential interest; to ensure adequate chemical purity, the chemistry has to be studied first.

Over 30 years have passed since the completion of the synthesis of ribonuclease A and ribonuclease S. I have been told that the Merrifield/Merck enzyme syntheses were one of only three chemical achievements that were reported on the front page of the *New York Times*.

The impact the Merrifield solid phase approach was to have on synthetic organic chemistry was not anticipated in January of 1969. This is also true of the fact that these syntheses stimulated the pharmaceutical industry to take a fresh look at the potential for synthetic peptides not only in support of basic research, but also for the discovery of marketable products. Thus, the enzyme synthesis stimulated synthetic organic chemists in academia and in industry to take a greater interest in peptides generally, resulting in the development of new technologies, the discovery of invaluable peptidal medicines and ultimately of peptidomimetics.[40,41]

From a purely personal perspective, it has always been a source of satisfaction to me that the relationships between Professor Merrifield and the Merck group, which were competing for the first total synthesis of an enzyme, were always cordial. I remember driving to the shore many years later, when I heard the announcement on the radio that Professor Merrifield had been named recipient of the Nobel Prize. I stopped my car and dispatched a congratulatory telegram to which Bruce responded most graciously.

As pointed out above, we undertook the synthesis of an enzyme because we thought that Dr Anfinsen had shown that the reduced, denatured protein can be oxidized to regenerate enzymatic activity. The validity of this experiment is now questioned because of the possibility that some of the desired tertiary structure is retained even after denaturation. As a result, the most profound significance of the two total syntheses may lie in the fact that only a total synthesis can prove unequivocally that the amino acid sequence does indeed encode the tertiary structure of RNase.

To put the advances made in peptide research during the twentieth century into perspective, it is worth recalling that prior to Dr Sumner's 1926 isolation of urease, no one could have predicted that enzymes would prove to be proteins.[42]

Last but not least, it is remarkable that Merck & Co. supported this enterprise on the recommendation of Dr Max Tishler and with the approval of Mr. Henry Gadsden, Chairman of the Merck Board of Directors. I am deeply grateful to Dr Denkewalter, who initiated this endeavor, for giving me the opportunity to participate in this work. I am equally indebted to all of my collaborators whose expertise as organic chemists and whose experimental skills and, importantly, whose remarkable teamwork assured the success of this very significant endeavor. My next assignment came in 1972, and it came as another major surprise.

1.01.3 The Merger Between Merck & Co., Inc. and Sharp & Dohme

In 1953 Merck & Co., Inc. merged with Sharp & Dohme in Philadelphia resulting in the formation of Merck Sharp & Dohme. The cultures of the two companies could scarcely have been more dissimilar. As pointed out by Drs Lou Galambos and Jeffrey Sturchio,[43] Merck "valued innovative science and high quality products, had experience in industrial sales, but very little experience or capability in marketing. The most important players at Merck were the

medicinal and fermentation chemists, the firm's acknowledged stars." On the other hand, "Sharp and Dohme valued aggressive salesmanship, conducted largely on a face-to-face basis. The business employed marketing techniques that were frequently more effective than informative. "The two cultures were thus sustained by two contrasting status systems."

To this day I am fond of saying facetiously "that the merger between the two companies is proceeding on schedule."

I should like to stress, however, that the first post-merger product was the discovery by the Sharp and Dohme arm of the diuretic chlorothiazide, a major breakthrough. The compound was synthesized by one of Dr James Sprague's chemists, Dr Novello. The biology was headed by Karl Beyer, MD, PhD, a renowned pharmacologist. Chlorothiazide was truly a breakthrough diuretic. Its marketing potential was greatly underestimated for two reasons: chlorothiazide was the first diuretic which, unlike the prior mercurials, was a drug, not a poison, and, secondly, it proved to be not only a safe diuretic but, importantly, also a very effective antihypertensive.

The difference between Rahway and Philadelphia/West Point went beyond the differences identified above. West Point Research was dominated more by pharmacology than chemistry whereas in Rahway at that time chemistry dominated the scene and biology centered on biochemistry and microbiology rather than pharmacology. Research in Rahway referred to West Point as a country club, and West Point Research referred to Rahway as 'Emerald City,' where a constant state of agitation is confused with productivity.

Be this as it may, in 1972 Dr Sprague was approaching retirement. He had built the West Point Medicinal Chemistry Department into a first rate organization, he was the unquestioned boss, and the only department head his chemists had ever known. In 1972 I had set foot on West Point soil only once, that being in 1969 as a result of Dr Denkewalter's hint to West Point management that his peptide chemists would be pleased to give lectures about the synthesis of RNase. Drs Holly and Veber, as well as Dr Denkewalter and I drove to Pennsylvania where Drs Veber and Holly reported on our work.

1.01.3.1 Transfer to West Point, PA

None of this was on my mind in 1972. I didn't even know that Dr Sprague was approaching retirement. Fortunately, Dr Tishler forewarned me and, therefore, when Dr Beyer came to Rahway to invite me to head medicinal chemistry at West Point, I remained fairly calm. At that time, our daughter, Carla, was a senior in high school who obviously did not want to move to Pennsylvania. Therefore, during the first year, I spent my weekends in Scotch Plains, NJ, and the week at the Holiday Inn in Kulpsville, PA. It was actually a good arrangement. I had no knowledge of pharmacology in general, and no information about any of the projects at West Point. Thus, I spent all my evenings trying to learn about the ongoing West Point programs. I immediately recruited Professor Samuel Danishefsky as a consultant in organic chemistry as well as two biochemists, Professors Jeremy Knowles and John Law. Professor Knowles was about to move from Oxford to Harvard, and he alleged that his consultantship income from Merck significantly enhanced his standard of living in the Cambridge, MA area. Professors Jeremy Knowles and John Law brought the all-important discipline of biochemistry to the Medicinal Chemistry Department.

I believe that Dr Beyer offered me the job because he expected, correctly, that peptides would become increasingly prominent in drug discovery. Fortunately, I was one of the individuals on Dr Sarett's list of 'acceptable candidates.' As part of the reorganization, 12 of the 13 members of the peptide group agreed to move to West Point with me, at least in part because housing was cheaper. I shall never forget my first day at West Point. I held a departmental meeting, where I faced a very nervous audience. I wanted very much to reassure my new team and I like to think that the meeting went reasonably well. I said in essence that I had tremendous respect for Dr Sprague and all he had accomplished, but I also said that I was not Dr Sprague, and that I would do some things differently. My main purpose, however, was to assure the group that it was not my intent to see how much chaos and fear I could create during my first week as Department Head. I will always be most grateful to Drs Edward T. Cragoe and Edward Engelhardt, my chief lieutenants, for helping me succeed in my new assignment.

I now reported to Dr Karl Beyer, Jr, who headed West Point Research. The most senior biologist at West Point under Dr Beyer was Dr Clement A. Stone, and my principal biological contact was the pharmacologist Dr Alexander Scriabine, with whom I met at least once a week. It was a marvelous learning opportunity for me.

In 1971, after the synthesis of RNase and subsequent to the retirements of Drs Pfister and Denkewalter, I reported to Dr Sarett, as Senior Director of the newly formed 'New Lead Discovery' group in Rahway. We synthesized, inter alia, the so-called 'renin substrate' as the first step toward the establishment of a renin inhibition program. Dr Veber and his colleagues designed and synthesized cyclic penta- and decapeptides, which Dr Charles Sweet found to be renin inhibitors in vitro and to behave like renin inhibitors in the spontaneously hypertensive (SH) rat. These compounds also induced hemorrhaging. It is not known to what extent the latter effect contributed to the lowering of blood

pressure. Clearly these compounds were not attractive leads, but they attest to the long-standing interest in renin inhibitors by the pharmacologists at West Point and the peptide chemists in Rahway. In 1973 the peptide group had been scheduled to join me in West Point. That had been part of Dr Beyer's desire to bring peptide research to West Point. I was therefore somewhat unprepared when Mr John Horan, who was to succeed Mr Henry Gadsden as Chairman of the Board, and CEO, called me to his office to inquire why the company should move me and my group of 12 chemists from Rahway to West Point. I do not recall what I said during that unexpected interrogation. I must have said something about trying to bring the two sites closer together, because I do remember Mr Horan asking whether the move, then, was to be a 'social experiment.' That was the low point in the discussion, but in the end, Mr Horan gave his approval. I believe, with hindsight, that this was his expectation from the beginning. Nevertheless, I was told subsequently that Mr Gadsden had remarked that "it cost me $1 million to move one man from New Jersey to Pennsylvania." I hasten to add that both Mr. Gadsden and Mr. Horan remained very supportive of me thereafter, and I felt much affection for them.

1.01.3.1.1 Compounds possessing two symbiotic biological activities

1.01.3.1.1.1 Uricosuric diuretics

Dr Sprague had initiated a program to discover potential drugs possessing two different biological properties that would be useful for the treatment of a given medical problem, e.g., diuretics, which also induce the excretion of uric acid. Dr Sprague had identified a lead compound at the time of his retirement that was a uricosuric diuretic. Subsequently, we discovered a compound good enough to be nominated as a candidate for safety assessment. Unfortunately, it failed to pass that critical step.

1.01.3.1.1.2 Vasodilators with β_2 adrenergic blocking activity

We tried a different approach to discover compounds with two symbiotic biological activities. Instead of screening for leads possessing two desired symbiotic properties, we sought to discover them by design. Since the structural requirements for beta adrenergic blockade are reasonably simple, we started with vasodilators and we tried to incorporate β_2 adrenergic blockade by design. In fact, in a 1979 publication, the Medicinal Chemistry and Pharmacology Department at West Point, PA reported the design and synthesis of an antihypertensive beta adrenergic blocking agent that also acted as a vasodilator. We thought that the vasodilating property of this compound was an intrinsic property of the pharmacologic profile and that the vasodilating component was not due to β_2 adrenergic agonism.[44] This molecule was therefore thought to represent an example of the "symbiotic approach to drug design." Later on we concluded, however, that in fact the vasodilating properties of the compounds in question were due to β_2 adrenergic agonism after all. In a subsequent paper[45] we sought to incorporate β_2 adrenergic properties into a dihydrolutidine-type vasodilator. We concluded again, that "the development of a useful bivalent agent cannot be achieved reliably simply by combining pharmacophoric elements," that is to say "the incorporation of an aminohydroxypropoxy moiety into an aryl ring of a vasodilator does not guarantee the introduction of significant beta adrenoreceptor antagonism."

I subsequently abandoned the search for symbiotic medicines because I had concluded that the chances that one could identify a chemical entity where the potencies for the two biological activities are in good balance, are not very good. Further, the differences in metabolism between animals and humans might further complicate the matter. While Merck's physicians liked the concept, i.e., having to prescribe only one pill rather than two, we concluded that it represents a very long shot.

1.01.3.1.2 Methyldopa progenitors

A second significant assignment related to one of Merck's most important products at that time, methyldopa the antihypertensive discovered by Drs Pfister and Stein. Methyldopa had one significant liability: its oral bioavailability varied from patient to patient. Our task was, therefore, to discover an oral prodrug with high and predictable bioavailability. Given the medical importance of this antihypertensive medicine, I made an unusual decision: I put every organic chemist in the department on the problem and launched a crash program. As I had expected, the well-disciplined West Point medicinal chemists responded beautifully. The project, which was termed "ester progenitors of methyldopa" was the subject of a 1978[46] publication by Walfred S. Saari and his collaborators. The program led to the discovery that the pivaloyloxyethyl and the succinimidoethyl esters of methyldopa were more potent antihypertensive agents than methyldopa after oral administration in the SH rat. All esters that were found to be more potent antihypertensives in the SH rat were also hydrolyzed to α-methyldopa at a relatively rapid rate, but Dr W. Saari *et al.* were able to show that the chemical rate of hydrolysis cannot be the sole determinant of antihypertensive potency.

The work demonstrated that in animals the two above-mentioned progenitors were indeed better absorbed and yielded higher plasma and brain levels than the amino acid. In human subjects, however, the pivaloyloxyethyl ester appeared to be more potent than the succinimidoethyl ester; importantly, the latter did not produce the increased potency expected from animal studies. Neither compound became an approved drug.

1.01.3.1.3 The somatostatin program

In 1973 Brazeau, *et al.* reported the isolation and chemical and biological characterization of somatotropin-release inhibiting factor (SRIF-14, somatostatin). At one of the regular meetings of all the department heads, both chemists and biologists, Dr Sarett asked whether there were any ideas that could serve as the basis for a novel antidiabetic program. I was aware of the studies by Dr Luft and his team at the Karolinska Institute that growth hormone (GH) may play a permissive role in the development of retinopathy in diabetes. In addition, Dr Unger[47] pointed out that while glucagon levels are within the normal range in diabetics, they are inappropriately high if one considers the plasma levels of glucose in these patients. Because SRIF-14 suppresses both GH and glucagon release, I had become interested in finding an analog of SRIF-14 with a half-life sufficiently long to test the concept that lowering both GH and glucagon levels in diabetics would be beneficial. Since SRIF-14 also inhibits insulin release, I thought of juvenile diabetics, who lack insulin, as the initial target patient population. Dr Daniel Veber and his colleagues initiated a spectacularly successful program,[48] building on Dr Rivier's alanine and D-amino acid scans. The research at West Point led first to the elucidation of the bioactive conformations of SRIF-14, and then to the design and synthesis of a cyclic hexapeptide (MK-678), which, pleasingly, was more potent and which, as expected, was completely stable to proteases. In addition it displayed some oral activity – a significant advance. Oral bioavailability was, however, less than 5%, presumably because of a high desolvation penalty. Dr E. M. Scolnick, who had succeeded Dr Vagelos as head of Research, like many others, had little or no hope for peptides as drugs, precisely because of their low oral bioavailability. The compound was therefore tested in a cavalier clinical trial and then dropped. Interestingly, however, Sandoz subsequently discovered and successfully developed sandostatin as a parenteral SRIF-14 mimetic, albeit for clinical targets other than juvenile diabetics, showing again that parenteral administration is not inconsistent with commercial success.

1.01.3.1.4 The protease inhibitor program

Two major developments toward a mechanism-based design of protease inhibitors were the identification of protease inhibitors typified by pepstatin[49] by Dr H. Umezawa at the Institute of Microbial Chemistry in Tokyo in 1970 and by a publication of equally profound importance by Professor R. Wolfenden[50] of the Department of Biochemistry of the University of North Carolina, in Chapel Hill, in which he provides his interpretations of Pauling's transition state analog hypothesis. The work of Professor Wolfenden did not receive the recognition that it deserved, in my opinion.

In 1972 Miller and Poper[51] at Eli Lilly reported the exciting observation that pepstatin, a nonspecific inhibitor of renin and other aspartate proteases, lowered blood pressure in rats. Professor Dan Rich of the University of Wisconsin, Madison, immediately recognized the implications of the work at Lilly in terms of the earlier reports by Umezawa and Wolfenden, i.e., that pepstatin might in fact be a transition analog inhibitor. Dr Rich reasoned further that if his speculation proved to be correct, it should be possible to alter the peptide backbone in the regions contiguous to the critical secondary alcohol, thereby creating a new class of protease inhibitors that would be specific for the protease of interest. Such compounds would have great potential for drug discovery. These concepts were, however, sufficiently unconventional that Dr Rich's NIH proposals did not fare well. In 1978, I became the second member of the Study Section with a background in peptide research, and therefore one of the two assigned principal reviewers of the proposal. I believe that my enthusiastic review played a role in the decision by the Study Section to recommend approval and funding of the proposal. Dr Rich thus pioneered what has become a seminal, novel approach to protease inhibitor design. It may be worth noting that the discovery of enzyme inhibitors incorporating transition state analogs exemplifies that nature is one of a medicinal chemist's best teachers.

I first met Dr Dan Rich in 1969 while he served as a postdoctoral fellow with Professor W. S. Johnson at Stanford University. We went for a long walk that became the beginning of a lasting friendship. I invited Dr Rich to consider joining Merck. My colleague Dr Patchett, who had an opening, offered Dr Rich a position at Merck Rahway, an offer that Dr Rich declined, because he had decided to pursue an academic career.

Independently, Dr Veber, like Dr Rich, had considered that pepstatin might represent a transition state analog, which led him also to consider incorporating its statine residue generally into protease inhibitors. In the meantime, Dr Rich had written identical letters to twenty different industrial medicinal chemistry departments, asking for financial support. Nineteen replies were very polite expressions of "no interest," but I was very interested and offered

to support a postdoctoral fellow to work on the design of transition state analog-based inhibitors of renin under Dr Rich's direction in Madison. Later, the project was expanded to involve aspartate protease inhibitors generally. Equally important, these developments led to Dr Rich's appointment as a consultant and to a highly productive collaboration between "the two Dans," Drs Rich and Veber. Although bioavailable renin inhibitors are now being tested in the clinic, renin inhibitors discovered in the 1970s and 1980s were not sufficiently bioavailable after oral administration because of their inappropriately high molecular weight and/or large number of rotatable bonds. Renin inhibitors, unlike angiotensin I-converting enzyme inhibitors, will not block the metabolism of bradykinin and may thus be free of one side effect: coughing induced by converting enzyme inhibitors.

Dr Rich, supported by both the Wisconsin Heart Association and Merck, also provided experimental support for the transition state analog concept. The hydroxyl group in the central statine residue contributes four orders of magnitude of binding affinity of the statine residue, and he and his group showed it to be a tight binding inhibitor; competitive with substrate. The Merck-Wisconsin collaboration developed potent and highly selective inhibitors. Particularly noteworthy is the elegant paper by Dr Joshua Boger (now CEO of the Vertex Corporation) and his Merck associates, published jointly with Drs Rich and Bopari in 1983.[52] This paper reports that the net gain in binding energy through the incorporation of the transition state analogs is greater than 4–5 kcal. This observation was followed 2 years later by a second paper[53] by Drs Boger and Payne and their collaborators, which reported incorporation of a novel analog of statine and afforded a subnanomolar renin inhibitor. In a 1990 paper Dr Veber and his coworkers reviewed the design of long-acting renin inhibitors.[54]

Dr Rich is in the process of writing a Perspectives Article for the *Journal of Medicinal Chemistry* which will also be the subject of his Smissman Award Lecture this year. He will point out that in 1970 only five crystal structures of peptides had been solved, none of them aspartic acid proteases, and that around 1980 the approaches to discover protease inhibitors generally followed the antimetabolite strategy of Drs Hitching and Elion, but with little success. Further, as I pointed out elsewhere[39] "in the 1980s the recognition that 'rational design' of enzyme inhibitors is a fruitful approach to drug discovery, led to the belief that knowing the tertiary structure of active sites of such enzyme targets would greatly facilitate the discovery process" [of enzyme inhibitors]. "Significant time and effort was invested in this approach by several companies before it was recognized that the x-ray structure of uninhibited enzymes is likely" [to be of little value].[39] I believe that this effort illustrates that the broad acceptance by the scientific community of an unvalidated concept can actually slow down the discovery process. The same mistake was made again 10 years later, when the industry put its reliance for the discovery of new leads prematurely on an unsophisticated use of combinational chemistry.[39]

1.01.4 P. Roy Vagelos, MD, Successor to Dr L. H. Sarett

In 1974, P. Roy Vagelos, MD accepted an offer to move from Washington University in St. Louis, MO, to assume the position of Senior Vice President for Basic Research with the Merck Research Laboratories. Dr Vagelos had studied with the renowned biochemist Dr Earl Stadtman at the NIH and thus became an expert in lipid metabolism. Dr Vagelos' office was located in Rahway, but his initial responsibilities as Senior Vice President were at West Point with both Dr Clement Stone and I reporting to him. It had also been agreed that after 1 year Dr Vagelos would succeed Dr Sarett as the Head of Research. These developments were to have an important impact on my career. At that time some reorganizations seemed called for in Rahway at the levels below those of Drs Sarett and Vagelos.

I received a phone call in my office at West Point from Dr Vagelos in which he discussed this latter problem quite openly with me, and he concluded the conversation by asking me to return to Rahway as Vice President for Basic Research. I attributed this promotion to two unrelated factors: one was the synthesis of RNase, which gave me broader visibility than the synthesis of some more conventional natural product, i.e., the glory belonged to the enzyme, not to me. The other was the fact that Dr Vagelos considered it to be an important responsibility of any department head to have identified individuals in the department, who could serve as one's replacement, should the need arise. I was most fortunate that under the two Senior Directors reporting to me at West Point, I had four outstanding back-ups as potential heads of the Medicinal Chemistry Department. They were Drs Paul Anderson, John J. Baldwin, Robert L. Smith, and Daniel F. Veber. All were excellent and experienced medicinal chemists. Dr Anderson had exceptional administrative skills. Indeed, he succeeded me as the Head of the Department and he was elected President of the American Chemical Society a few years later. I have long considered Dr John Baldwin to be the most knowledgeable medicinal chemist I have met. Dr Smith, whose recent untimely death was a great loss to his family, friends and to the company, brought tremendous creativity and enthusiasm to all of his projects and Dr Daniel Veber was even then recognized as one of the world's most respected peptide chemists. Taken together, I suspect that the enzyme synthesis, and the stature of my West Point lieutenants played a role in my being offered the position of Vice President of Basic Research in 1976.

1.01.4.1 A New Assignment: Vice President of Basic Research

As Vice President I was to retain responsibility for the West Point Medicinal Chemistry Department. Since my wife and I had only recently moved into a new house in Blue Bell, PA, in December of 1972, and Lucy had started to build beautiful gardens, moving back to New Jersey in 1976 was not attractive. Dr Vagelos gave me the option of remaining in Blue Bell and commuting by limo to Rahway on a daily basis. He made it clear, however, that my responsibilities would be the same, even if I commuted. I accepted this proposal, generally spending one night a week in New Jersey. I remember using the 90 min ride on the Pennsylvania and New Jersey Turnpikes from home to Rahway to read the latest journals, and promptly falling asleep on the way home after a typical day in Rahway! There was never a dull moment.

In my new position two Rahway basic research departments in chemistry were to report to me as well as microbiology under Dr Jerome Birnbaum. My immediate assignments were to restore calm among the chemists and to recruit heads of biochemistry and immunology. Dr Eugene H. Cordes, the chair of the chemistry department at Indiana University, Bloomington, IN, and Dr Alan Rosenthal, then a research fellow at the National Institute of Allergy and Infectious Diseases at the NIH, who had clarified the role of the macrophage in immune response, agreed to join Basic Research in Rahway.

I also appointed Dr Burton G. Christensen, a long-time associate and a renowned expert in beta lactam chemistry, to the position of head of the Department of Synthetic Organic Chemistry. Dr Arthur A. Patchett continued as Head of New Lead Discovery. New responsibilities related to program reviews in Terlings Park, UK and Montreal, Canada, which were also attended by Dr Stone.

In the pharmaceutical industry some companies promote scientists based on their administrative skills. However, this was not the case at Merck, where scientific potential was considered more important. Thus, at my senior staff meetings, the emphasis was definitely on scientific issues. There was one exception: I had realized that the heads of chemistry were more demanding than their biology counterparts when they evaluated their subordinates. I made the assumption that chemists and biologists as a group were equally competent at Merck, and I instituted a rating system based on that premise, which Dr Vagelos eventually adopted for all of research.

1.01.4.2 A Breakthrough at the Squibb Institute of Medical Research

The first acute challenge to face Basic Research after the reorganization was the breakthrough discovery of captopril, the first potent, orally bioavailable, competitive inhibitor of the angiotensin-converting enzyme by Drs Ondetti and Cushman and their collaborators at the Squibb Institute of Medical Research in Princeton, NJ, in 1977.[55] The discovery of an inhibitor for this carboxydipeptidase represented the first successful blockade of the renin-angiotensin system, thus all but validating also renin as a target for enzyme inhibitor design. Captopril proved to be an important new medicine for the treatment of hypertension.

When the Squibb discovery of captopril was announced, Dr Arthur A. Patchett had already started an angiotensin-converting enzyme inhibitor program of his own, which, like that at Squibb, was based on Wolfenden's work with carboxypeptidase A.

I mentioned earlier that of my many mentors, Dr Sarett taught me the most about medicinal chemistry. I believe that Dr Vagelos was the mentor from whom I learned the most in terms of basic strategic concepts. One of these was to appreciate the importance of recognizing significant breakthroughs made by our competitors and to respond promptly and with sufficient manpower to be effective. In the case at hand, the discovery of captopril led to an increase in manpower in Dr Patchett's Department working on the angiotensin-converting enzyme inhibitor program from two chemists to about 20 almost overnight, reminiscent of the methyldopa crash program at West Point referred to above.

The angiotensin-converting enzyme is a zinc-containing exopeptidase. In the design of captopril, Drs Ondetti, Cushman, and their collaborators, built on the presumed similarities of this enzyme and carboxypeptidase A. As pointed out by Dr Cushman *et al.*[56] angiotensin-converting enzyme may play a role in blood pressure regulation both because it 'converts' the biologically inactive angiotensin I to angiotensin II, which raises blood pressure, and because it metabolizes, i.e., inactivates, the antihypertensive bradykinin. As mentioned above, and as clearly acknowledged by the Squibb team, the observation by Drs Byers and Wolfenden[57,58] that D-2- benzylsuccinic acid is a potent competitive inhibitor of carboxypeptidase A was the point of departure for the converting enzyme inhibitor program at Squibb. The Squibb workers designed and synthesized the first angiotensin-converting enzyme inhibitors, including captopril, wherein the sulfhydryl group powerfully bound the enzyme's zinc atom. The one fairly common side effect of captopril, loss of taste, was attributed to the free sulfhydryl group. This side effect provided us with an opportunity to discover an improved second generation chemical entity.

1.01.4.3 Improved Second-Generation Converting Enzyme Inhibitors

By having now some 20 chemists on the angiotensin-converting enzyme inhibitors program, Dr Patchett was able to pursue simultaneously several independent approaches toward an improved second-generation product. Dr Patchett has commented on these in detail. From my perspective, the reason why Dr Patchett succeeded where others failed is that their unsuccessful approaches looked for a replacement of the sulfhydryl by a functionality able to bind the zinc atom of the enzyme as tightly as the sulfyldryl. No such replacement has been found. In designing enalapril maleate, Dr Patchett accepted a carboxyl group as a much weaker ligand for the zinc atom, but compensated for the resulting loss of binding affinity by introducing the phenethyl function, which increased the binding affinity of the enzyme inhibitor.[59] Dr Patchett also designed and synthesized lisinopril, which incorporates the same phenethyl substituent.

After my retirement from Merck, when consulting for various biotechnology companies and also for big Pharma, I would encounter situations where a breakthrough had been achieved either by those companies themselves, or by their competitors. When I urged them to act on these events more expeditiously, I was sometimes told that switching manpower would be bad for the morale of the scientists being transferred. I do not believe that this assessment is generally valid, because the company's interests may demand such action and also because medicinal chemists prefer to be on a 'hot project' rather than a lukewarm one. Both of these considerations guided the decision at Merck to increase manpower dramatically on the angiotensin-converting enzyme inhibitor program. Patchett's success paid off handsomely for many hypertensive patients and, in the process, also for Merck & Co., Inc.

Taken together, enalapril and lisinopril strikingly remind us of the wisdom of one of the giants of the pharmaceutical industry, Mr George W. Merck, who founded Merck & Co., Inc. during the depth of the depression and whose famous passage from a speech given at the Medical College of Virginia (now part of Virginia Commonwealth University) in Richmond, Virginia is quoted below. He gave that speech on 1 December, 1950, less than a year after I started working for Merck. It made a deep impression on me at that time.

> We try to remember that medicine is for the patient. We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear. The better we have remembered it, the larger they have been.
>
> Nor is medicine for the politicians, except in so far as they are statesmen. I could add that medicine also is not for the professions, unless it is for the patient, first and last! How can we bring the best of medicine to each and every person? It won't be solved by wrangling with words, and it won't be settled by slogans and by calling names. We will fall into gross error with fatal consequences unless we find the answer – how to get the best of all medicine to all the people. It is up to us in research work, in industries, and in colleges and other institutions, to help keep the problem in focus. We cannot step aside and say that we have achieved our goal by inventing a new drug or a new way by which to treat presently incurable diseases, a new way to help those who suffer from malnutrition, or the creation of ideal balanced diets on a worldwide scale. We cannot rest till the way has been found, with our help, to bring our finest achievement to everyone.

1.01.4.4 The Concept of 'The Champion' in Drug Discovery: Benign Prostatic Hypertrophy and the Inhibition of 5α-Reductase

From time to time, a person in a non-managerial position will have a marked impact on the research organization by single handedly becoming the champion for a specific research project. To those who were privileged to interact with him, Dr Glen Arth served as a splendid example of a champion. Dr Arth, an outstanding experimentalist, had been one of the important players in Dr Sarett's total synthesis of cortisone, which was the only practical rather than 'formal' synthesis of this hormone. Later, Dr Arth championed the search for a treatment of a disease that burdens many elderly men, known as benign prostatic hypertrophy (BPH). In the 1950s, Merck started to take an interest in investigating the role of androgens in several disorders linked to male sex hormones such as prostate disease, acne, and 'male pattern baldness.' Critical to the eventual success of the program was the recognition in the late 1960s that the enzyme 5α-reductase converts the male hormone testosterone into the more potent androgen dihydrotestosterone (DTH) in which the steroid A/B rings are *trans*-fused. Dr Arth and his Merck collaborators (biochemists, chemists, and biologists, as well as consultants) appreciated the potential advantages of 5α-reductase inhibitors over the more toxic anti-androgens. It was, however, a report in 1974 by Dr Julianne Imperato-McGinley and Dr Ralph Perterson at Cornell Medical College and another by Drs Patrick Walsh and Jean Wilson at the University of Texas Southwestern Medical School that put

Dr Arth and his associates into high gear, because these studies demonstrated clinically that DHT and testosterone played distinct roles in the sexual differentiation of a fetus and in the development of males during puberty. As a result, the Merck Research Coordinating Committee (RCC) agreed to start screening for 5α-reductase inhibitors. Sadly, Dr Arth died unexpectedly in 1976. His colleague, Dr Gary Rasmusson, referred to him rightly as the "sole personality through the late 1960s and early 70 s [who drove the BPH project.]." Dr Rassmusson and Glenn Reynolds eventually synthesized MK-906, a steroid 5α-reductase inhibitor devoid of any intrinsic hormonal activity. Dr Eugene Cordes (please see above), the head of the Biochemistry Department, shepherded MK-906 through the critical remaining preclinical programs. Finally in 1992, MK-906 was approved by the FDA. It is marketed as finasteride. As is always the case, FDA approval was the result of dedicated interdisciplinary research, but to my knowledge, no one has questioned that the BPH project owes its beginning and early successes to the insightfulness and enthusiasm of Dr Glenn Arth.

1.01.4.5 Hypercholesterolemia: A Challenge for the Pharmaceutical Industry

To be a contributor to the discovery of a new medicine that reduces morbidity and mortality and thereby enables a large percentage of our population to lead productive lives is surely highly satisfying. Lovastatin, a cholesterol biosynthesis inhibitor, is such a medicine. It was approved by the FDA on 31 August 1987. The events that culminated in that FDA approval go back nearly 200 years. Louis F. Fieser and Mary Fieser in their 1959 edition of 'Steroids'[60] attribute the "discovery of cholesterol to Michel Eugène Chevreul, who in 1812 first differentiated between saponifiable and nonsaponifiable animal lipids."

Cholesterol has long been known to be the dominant sterol of all higher vertebrates. Mammalian sterol, except for the gastrointestinal tract, is nearly pure cholesterol. The nervous tissue, especially brain, is rich in cholesterol. But it has also been known for over 100 years that cholesterol plays an important role also in pathophysiology. My former colleague, Dr Jonathan A. Tobert of the Medical Affairs Department at Merck pointed out[58] that more than 100 years ago, the German pathologist Dr Virchow observed that patients who had died of diseases such as heart attacks had arteries that were often thickened by deposits of a yellowish fatty substance now known as cholesterol, a condition termed atheroma. Although it was known that feeding cholesterol to rabbits rapidly produced the equivalent of atheroma, the idea that there is a cause-and-effect relationship between dietary cholesterol and coronary heart disease (CHD) was not readily accepted by the medical community. However, the well-known Framingham study in the 1950s established a correlation between plasma cholesterol levels and CHD, especially in the US and in northern Europe. This cause-and-effect relationship was attributed mainly to low-density lipoprotein (LDL) cholesterol, which thus became known as the bad cholesterol, in contrast to high-density cholesterol, which correlated inversely with CHD mortality. This led directly to the proposition that reducing LDL cholesterol will reduce the incidence of myocardial infarction. This hypothesis was, nevertheless, not immediately accepted by the medical community although "a good case could be made that lowering cholesterol reduced the risk of coronary events."[61] In 1984, some 70 years after the demonstration that feeding cholesterol to rabbits rapidly induced the equivalent of atheroma, an NIH Consensus Conference concluded that lowering elevated LDL cholesterol levels with diet and drugs would reduce CHD.[62]

The Medical Community, notably the National Institutes of Health, had done its part. It remained for the pharmaceutical industry to take the lead.

1.01.4.5.1 A breakthrough at Sankyo: the discovery of compactin

As Dr Jonathan Tobert pointed out, "early attempts to reduce cholesterol biosynthesis were disastrous."[61] In the 1960s triparenol, also known as MER-29, entered clinical trial as an inhibitor of cholesterol biosynthesis. The complex biosynthetic pathway leading to cholesterol is well understood. It is a process involving more than 30 enzyme-catalyzed steps. Unfortunately, triparenol inhibits that process at a late step and thus leads to the irreversible accumulation of desmosterol which is more harmful than cholesterol. It thus became clear that any drug that would safely inhibit cholesterol biosynthesis should block an early step in the pathway and one that does not result in the build-up of an intermediate. The enzyme β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) reductase catalyzes the rate-limiting step in the conversion of HMG-CoA into mevalonate. Therefore, it appeared an attractive target for inhibition, since its inhibitors would be expected to be devoid of any mechanism-based toxicity such as is exhibited by triparanol.

In 1976, the Japanese microbiologist Akina Endo and Masao Kuroda of the Fermentation Research Laboratories at Sankyo Co Ltd., Japan reported that citrinin, which had originally been isolated as an antibiotic from *Penicillium citrinum* in 1914 by Raistrack and Smith,[63] inhibits cholesterol synthesis from ^{14}C-acetate in rat liver.[64] The Japanese workers emphasized that unlike clofibrate, citrinin did not cause an increase in liver weight. Later that same year Endo *et al.* reported in the same journal[65] that subsequent work in search of cholesterol biosynthesis inhibitors produced by microorganisms led to the isolation and chemical characterization of three chemically closely related metabolites

named ML-236 A, ML-236 B, and ML-236 C, respectively. ML-236 B, also known as CS 500 or compactin, was the major metabolite and also the best inhibitor. They reported that its effect at a dose of 20 mg kg^{-1} in the rat was to lower cholesterol levels by 30% and that the effect lasted for 18 h.

Earlier Drs Z. H. Beg and P. J. Lupien, at the University Loval in Quebec had reported that 3-hydroxy-3-methylglutaric acid (HMG) inhibits a specific step in cholesterol biosynthesis that is mediated by HMG-CoA reductase.[66] As mentioned in an excellent review article by Mr Albert W. Alberts,[67] the discovery of ML-236 B represented a breakthrough in the search for a selective, competitive inhibitor of HMG CoA reductase, precisely because it leads to the accumulation of HMG CoA, a water soluble intermediate "capable of being readily metabolized to simpler molecules."[66]

1.01.4.5.2 The discovery of the first approved β-hydroxy-β-methylglutaryl-CoA reductase inhibitor, lovastatin

Fortunately, Merck was in an excellent position to respond quickly and effectively to the reports from Sankyo that compactin is effective in lowering LDL-cholesterol levels in humans. This was due in part to the fact that, as mentioned above, the head of Research at the time, Dr P. Roy Vagelos, an authority in lipid metabolism and Mr Alfred W. Alberts, a long-time associate of Dr Vagelos, had both moved from Washington University in St. Louis to Rahway, providing critically important expertise. Equally important proved to be the fact that Dr Arthur A. Patchett had initiated a fermentation product for screening project (FERPS) at Merck in 1974 to supply microbial extracts for both in vitro and in vivo screens.[68] Indeed, in 1978 that program achieved a major breakthrough very quickly, leading to isolation of lovastatin (then called mevinolin). Initial concerns that Merck's HMG-CoA reductase inhibitor might be Endo's compactin were laid to rest when it was shown to differ from Sankyo's ML236B (later called mevastatin) by the presence of an additional methyl substituent. Interestingly, the isolation of lovastatin was guided by Dr Carl Hoffman, who had isolated,[69] characterized,[70] and synthesized[71] mevalonic acid in 1956 and 1957. The development of lovastatin was halted when Sankyo announced that it had discontinued clinical studies with compactin. Fortunately, Nobel Prize winners Dr Michael Brown and Dr Joseph Goldstein of the University of Texas Health Science Center in Dallas were able to persuade Dr Vagelos to reinitiate the development of lovastatin, pointing out that it is in fact life saving in patients with uncontrolled very high levels of plasma cholesterol. Even more importantly, based on safety studies in animals and in humans, the formal clinical studies were resumed, leading ultimately to regulatory approval.

1.01.4.5.3 The discovery of simvastatin

As mentioned above, compactin and lovastatin differ from each other in the presence of an additional methyl substituent in the latter in the naphthalenyl ring. The two enzyme inhibitors have in common a chiral 2-methylbutanote ester side chain that is required for enzyme inhibition, but which is lost in vivo by ester hydrolysis. Interestingly, the potency of the inhibitor is the same irrespective of the enantiomer of the butanoate that is incorporated. This observation led the Medicinal Chemistry Department at West Point, under the leadership of Dr Paul S. Anderson and the late Dr Robert L. Smith, to replace the 2-methylbutanoate side chain of lovastatin by the gem dimethyl analog[72] to afford simvastatin, which does not contain a chiral carbon in the side chain. Importantly, it is more resistant to inactivating ester hydrolysis for steric reasons and is twice as potent.

1.01.4.5.4 Lipitor

Today, Parke-Davis' 'Lipitor,' also marketed by Pfizer, is the most widely prescribed HMG-CoA reductase inhibitor.

1.01.4.5.5 A new mechanism to lower plasma cholesterol levels in humans: the discovery of ezetimibe at Schering

More recently ezetimibe was discovered at Schering. The drug lowers cholesterol levels in humans by a mechanism that is complementary to that of the statin: it blocks intestinal absorption of cholesterol and related phytosterols. The fixed combination of ezetimibe/simvastatin, which is marketed as Vytorin, represents a valuable new approach toward optimizing lipid-lowering treatments.

It is of interest to note that combining antihypertensive medicines that lower blood pressure via diverse mechanisms represents a widely accepted regimen. Indeed, a combination of two or more different modes of action are required in some patients to achieve adequate control of blood pressure. The fixed combination ezetimibe/simvastatin is another example that shows that combining drugs that approach a medical problem via two different biochemical/pharmacologic mechanisms can be beneficial. The concept is not new and is used extensively also in the treatment of cancer, asthma, and congestive heart failure.

This fixed combination approach raises the question whether patients (and therefore the industry) would benefit if a greater effort were made to find novel biochemical and/or pharmacologic pathways to treat diseases for which we currently have only one modality of treatment.

1.01.5 The Discovery of Imipenem/Cilastatin, a Life-Saving Fixed Combination Antibiotic

1.01.5.1 Introduction

The discovery of HMG-CoA reductase inhibitors as antihypercholesterolemics, as described in the preceding section, may be said to have been reasonably straightforward from the initial discovery of the desired biological activity in Japan to approval of lovastatin in the US.

In contrast, the road from the initial discovery of the exciting antibacterial profile of thienamycin to FDA approval of imipenem/cilastatin proved to be an unexpected obstacle course. The fixed combination (Primaxin) has been described in an in-house publication[73] as "one of the most difficult, most costly, most frustrating, and most rewarding in the history of Merck research."

The discovery of benzylpenicillin was a breakthrough in the history of antibacterial agents. For a long time, different beta lactam antibiotics had a common scaffold characterized chemically by the fusion of a four- and a five-membered ring. Cephalosporin C, which is produced with penicillin *N* by a *Cephalosporium* sp., cultivated from sea water on the coast of Sardinia near a sewage outlet, has a broader spectrum, i.e., it is active against a larger number of bacteria. It differs chemically from penicillins in its scaffold. Both penicillins and cephalosporins interfere with the synthesis of the bacterial cell wall, an attractive mechanism, since human cells lack that structural feature. One therefore expected correctly, that beta lactams would not prove to be toxic to humans. Chemical changes in the structures of beta lactams resulted in antibiotics differing in their antibacterial profile. The discovery of the cephamycins provided protection against Gram-negative bacteria, but at the cost of a trade-off, since they lacked efficacy against Gram-positive pathogens.

Further chemical modifications of the cephamycins afforded cefoxitin, the first beta lactam antibiotic that was effective against anaerobic pathogens.

1.01.5.2 The Discovery of Thienamycin, an Unstable Antibiotic with a Remarkably Broad Profile as an Inhibitor of Bacterial Cell Wall Synthesis

In the late 1970s, a soil sample that had been collected in New Jersey, was evaluated by Dr Sebastian Hernandez and his associates in the Merck Laboratories in Spain. The culture that contained the antibiotic thienamycin attracted the attention of Dr Hernandez's staff because it had an unusual lavender blue pigmentation. Further screening in Spain revealed the presence of inhibitors of bacterial cell wall synthesis. The organism was sent to Dr Edward Stapley, Executive Director of Basic Microbiology in Rahway, NJ. Dr Sheldon Zimmerman, Associate Director of Analytical Microbiology, concluded that the culture contained not only two known antibiotics, but also one new chemical entity. In another Rahway laboratory, Frederick and Jean Kahan were searching for cell wall synthesis inhibitors in Gram-positive bacteria, such as *Streptococcus* and *Staphylococcus*. The Kahans encountered what became the first major challenge of the thienamycin problem: its chemical instability. At the same time that the antibacterial profile of the new antibiotic aroused great interest in its chemical structure, the stability problem made it clear that the chemical challenges would be formidable. Dr Helmut Kropp, a Senior Research fellow, made the exciting discovery that partially purified thienamycin protected mice that had been infected by *Pseudomonas*. At about the same time (1974) Dr Jerome Birnbaum was appointed Vice President for Microbiology and Agricultural Research and thus assumed overall responsibility for the biology of the program. The Kahans skills as biochemists matched their tremendous dedication to the thienemycin project; working around the clock, they were able to generate a small amount of purified material, which they made available to Dr Georg Albers-Schönberg and Dr Byron Arison for structural studies. The latter concluded that thienamycin is the first member of a family of antibiotics possessing a des-thiacarbapenem nucleus that has a thioethylamino side chain attached to the unsaturated 5-membered ring. Dr Arison's colleagues were reluctant to accept his structure for the antibiotic. Nevertheless, Dr Karst Hoogsteen and Mr. Jordan Hirschfield confirmed the Arison structure by x-ray crystallography.

The optimal stability of the new antibiotic was found to be in the pH range of 6–7. Above that pH the unprotected primary amino group attacks the beta lactam functionality of another molecule of the antibiotic, resulting in the loss of the antibacterial activity.

1.01.5.3 The Discovery of *N*-Formimidoyl Thienamycin (Imipenem), a Stable Molecule with a Superior Profile as an Inhibitor of Bacterial Cell Wall Synthesis

Given the exciting antibacterial profile of thienamycin on the one hand, and its unacceptably poor stability on the other, it became the task of the medicinal chemists under the direction of Dr Burton Christensen, Vice President of Basic Chemistry, to design and synthesize a more stable analog of thienamycin, which would retain the antibacterial properties of that beta lactam. The task proved to be a formidable one. It should be kept in mind that thienamycin, the starting material, was in very short supply and that it was also very unstable. Nevertheless, over 300 derivatives were synthesized over a 3-year period. These derivatization experiments were carried out on a 1 mg scale. Mr Ken Wildonger was the first to achieve the desired goal with the synthesis of *N*-formimidoyl thienamycin (imipenem), which was crystallized by Mr Thomas Miller. The antibacterial properties of imipenem were actually superior to those of thienamycin. With a possible product candidate in hand, the next challenge facing Dr Christensen and his associates was to generate adequate amounts to supply Safety Assessment and Clinical Research, both located at West Point. Supplies of imipenem were initially transported from Rahway by chartered plane!

At this juncture another totally unexpected problem arose. It was discovered that imipenem and thienamycin are metabolized rapidly in vivo in several mammalian species. The metabolic degradation was found to occur in the kidney. Scientists working with beta lactam antibiotics expect to find metabolism by bacterial enzymes. The Merck team was now confronted by the ironic fact that an antibiotic stable to bacterial beta lactamases is rapidly inactivated by a mammalian enzyme bound to kidney membranes, known as dehydropeptidase I. Going forward with imipenem would mean that the new Merck antibiotic would not be useful in the treatment of urinary infections.

Thus, two major problems remained: (1) how to deal with the susceptibility of imipenem to degradation by the dehydropeptidase I in the kidney; and (2) the supply problem of the starting material, thienamycin. As it turned out, both of these problems were solved by the organic chemists in the Basic Chemistry Department.

It was expected that the yields of the fermentation process that provides thienamycin would increase steadily until an adequate supply was assured. Atypically this turned out not to be the case. It was finally recognized that thienamycin would have to be supplied by total synthesis, and the process would have to be economically practical. The Merck team, including the Process Research chemists led by Dr Seemon Pines (in particular, Drs Len Weinstock and Victor Grenda and their colleagues) were up to the task. The total synthesis of thienamycin was first achieved by Dr Christensen, Dr Salzmann, and their associates[74] who developed a stereocontrolled, enantiomerically specific total synthesis. The synthesis from L-aspartic acid entailed novel chemistry. This was required because of the unique structure of thienamycin, which differs from the lactam structure of the penicillins and the cephalosporins by its highly strained ring system, which lacks a sulfur atom. In addition, the ring substituents are also unlike those of the conventional beta lactams.

The second problem, susceptibility of the imipenem to degradation in the kidney required that the antibiotic be combined with an enzyme inhibitor to prevent the renal metabolism in animals and in humans by dehydropeptidase-1. This led to the design and synthesis of cilastatin, a highly substituted heptenoic acid derivative inhibitor. Importantly, the pharmacokinetic properties of cilastatin match those of the imipenem. Pleasingly, cilastatin provided a fringe benefit: it excludes the entry of imipenem into the proximal tubular epithalium of the kidney where it might cause tubular necrosis. The fixed combination of imipenem – cilastatin completes the tour de force, made possible by the splendid interdisciplinary research of the industrial chemists and biologists. An excellent paper[75] gives a detailed account of the development of imipenem – cilastatin, which overcame all of the many shortcomings of thienamycin, an antibiotic with an unusually broad spectrum including a high order of bactericidal activity against *Pseudomonas aeruginosa*, *Serratia*, *Bacteroides fragilis*, *Enterococci*, and other species resistant to other antibiotics. Because imipenem is resistant to hydrolysis by bacterial beta lactamases and because of is extraordinary spectrum, the new fixed combination represents to this day a remarkable contribution to therapy.

1.01.6 Ivermectin: from the Discovery of an Animal Health Anthelmintic to A Wonder Drug for the Developing World

1.01.6.1 Introduction

The discovery of an animal health medication faces an obstacle not generally encountered in the search for a new medicine for humans: the issue of the cost of producing the drug. Generally speaking, if a new drug for humans is superior to heretofore available therapy, it will be produced by industry and prescribed by physicians even if it is more expensive than the older treatment. This is not necessarily the case for animal health products. A farmer will carefully

assess the cost/benefit ratio before switching to a superior but costlier medication. This is an important distinction and probably the principal reason why few pharmaceutical companies enter the animal health arena.

As has been pointed out by Dr William C. Campbell of the Merck Institute for Therapeutic Research in Rahway, NJ,[76,77] the anthelmintic program at the Merck Sharp Dohme Research Laboratories (MSDRL) began in 1953. From it emerged thiabendazole, the first of the benzimidazole anthelmintics, as well as cambendazole, rafoxanide, and clorsulon.[76,77] Building on the experience gained from human health directed antibiotics, Merck Research subsequently decided to explore fermentation broths as a source of new anthelmintics. Wisely, the animal health team chose to use an in vitro screen in mice as the primary assay for fermentation products.

1.01.6.2 The Collaboration with the Kitasato Institute

Another major innovation was the decision to enter into a research agreement with the Kitasato Institute in Japan. It was reached in 1974, and involved the shipment of bacterial cultures from Japan to the MSDRL, where they were inoculated in microbiological medium to permit fermentation. The resultant broths were then tested in a so-called tandem coccidiosis-helminthiasis assay. Mice fed on a diet incorporating one of the broths was found to be free of worms. It was established fairly quickly that an anthelmintic had indeed been present in the broth. As Dr Campbell was careful to emphasize, ''had a particular mouse not been examined properly [by a technician]'' a major new drug might have been missed. This serves as a reminder that drug discovery requires, of course, an idea generated by a sophisticated scientist, but it will lead to a drug only if those 'down the line' perform perfectly. In this case that task was the careful examination of a mouse for worms.

1.01.6.3 The Broth from Culture OS3153

Subsequent testing of broths obtained from culture OS3153 confirmed the presence of an anthelmintic. The next tasks were to isolate and to characterize chemically the active components in the culture now named C-076. Mass spectrometry revealed that there were four biologically active components, each of which consisted of a major and a minor component. Using mass spectrometric separations and then NMR spectroscopic techniques, the active principles of C-076 were found to be glycosidic derivatives of pentacyclic 16-membered lactones, similar in structure to the milbemycins. C-076 differed from the latter primarily in that the former lacked two glycosidic attachments. The new anthelmintic was named avermectin.

1.01.6.4 Avermectin

Avermectin fulfilled its promise as a cost-effective animal health anthelmintic. Like every other biologically active compound, it causes side effects. Had avermectin been a drug for humans, one could have launched a major effort to improve on the drug's therapeutic index, regardless of the cost. I remember discussing that issue with the late Dr Michael H. Fisher, an outstanding, softly spoken scientist who was responsible for the chemistry of animal health research at Merck. Given that avermectin has five double bonds, I was not very optimistic that we would be able to increase safety in a cost-effective way. Dr Fisher's more optimistic outlook was fully vindicated by subsequent developments. The medicinal chemists succeeded in selectively reducing the C *22–23* double bond in good yield. The resulting dihydroavermectin (ivermectin) was actually slightly less potent than avermectin B_1, but, to our delight, it displayed a therapeutic index superior to that of its natural product precursor.

1.01.6.5 Ivermectin

The extraordinary potency of the new anthelmintics against *N. dubius* led Drs Campbell and Fisher to explore the potential of the avermectins against a new host of parasitic nematodes. The results proved to be exciting. C-076 was effective against parasitic nematodes occupying all the major segments of the gastrointestinal tract, including nematode strains resistant to benzimidazole anthelminitics.

The Merck chemists under the leadership of Drs Mike Fisher and Helmut Mrozik synthesized more than 1000 analogs, all of which were tested by the parasitologists. None were significantly more potent than the natural product.

It was also exciting to discover that avermectin and ivermectin are not only broad-spectrum anthelmintics, but also insecticides and acaricides. As Dr Campbell pointed out[76] the activity ''against arthropods changed the scientific and commercial prospects dramatically. When ivermectin was eventually launched as a product for cattle, it was offered not as an anthelmintic, but as an antiparasitic agent for the control of endoparasites and ectoparasites.''

As mentioned above, the thienamycin project presented one challenge after another.[73] The avermectin program began with some interesting results and thereafter kept getting better and better. Some of this was good luck. For example, as Dr Campbell pointed out,[76] avermectin and ivermectin were fortunately active against the microfilariae of dog heartworm, but, again fortunately, they were inactive against the adult stage. "The result was not only a successful commercial product for heartworm prevention, but also a …dramatic example of stage specificity in chemotherapy."[74] To be sure it was the excellence of the scientists involved that ensured that all developing opportunities were recognized and then implemented.

What the antibiotic and the anthelmintic programs had in common was the excellence of the research, from the top on down, which ensured ultimate success. Top management cannot ensure success, it can only help set the course and provide the optimal environment; conversely, it can also create an atmosphere that is not conducive to creative research.

The next major development came in April 1978, when the parasitologists made an important observation and fully recognized its potential.[73] To quote from Dr Campbell' s review paper:[76]

> Another observation that had far-reaching consequences was again a matter of the filarial group of worms. In April, 1978 ivermectin was about to be tested against the gastrointestinal nematodes in horses. At the last minute a decision was made (prompted by a suggestion from L. S. Blair nee Slayton) to examine pieces of skin from the treated and untreated horses in order to detect a possible effect on the microfilariae of *Onchocerca cervicalis* – should those horses happen to be infected with that parasite. The horses did happen to be infected, and an effect on the microfilariae was clearly evident (Egerton *et al*. 1981a [as cited in [74]]). The significance of the observation lay not in the importance of the parasite in horses, for it is an obscure parasite that was then considered of no importance whatever, but lay rather in the relationship of the parasite to an important pathogen of man. To those of us who were actively interested in human parasitology, the potential utility of the finding was clear. In the summer of 1978 I sent the drug (and relayed our results) to an investigator in Australia who was conducting anti-filarial drug tests under the sponsorship of the World Health Organization. The investigator, Dr Bruce Copeman, quickly showed that ivermectin was active also against the microfilariae of *Onchocerca spp* in cattle, The information from horses and cattle, together with the toxicological data that had by then been gathered, served as the basis for recommending the testing of ivermectin in man.

1.01.6.6 The Human Formulation of Ivermectin (Mectizan)

The microfilariae of *Onchocerca volvulus* are the pathogens that are responsible for onchocerciasis in humans. These microfilariae cause progressive skin lesions and frequently induce ocular lesions that lead to blindness. This disease affects people in 35 countries in Africa, America, and the Arabian Peninsula,[77,78] and is known as river blindness. Suramin was effective in killing the adult worm, but proved to be very toxic.[78] Diethylcarbamazine citrate similarly proved to be a very unattractive therapy.[78] Ivermectin turned out to be a miracle drug for the treatment of onchocerciasis, not only because of its effectiveness and safety, but also because it only needs to be given to the patient once a year, a matter of great importance in countries where the health delivery infrastructure is fragile. In their assessment of the impact of ivermectin on illness and disability associated with onchocerciasis, Drs James M. Tielsch and Arleyne Beeche[79] concluded that "regular distribution to populations living in endemic areas has demonstrated significant reduction in blinding ocular complications, transmission and disability caused by onchocercal skin disease," not to mention the impact on intestinal helminth infection, lymphatic filariasis, and human scabies infection.[79]

During my tenure as Vice President for Basic Research my colleagues made many significant contributions to human and animal health. None of these is more pleasing to me than the Mectizan Project.

The Merck Mectizan Donation Program has been a source of enormous satisfaction to all Merck employees and retirees since its inception on 21 October 1987, under the leadership of its then Chairman and CEO, Dr P. Roy Vagelos. It was reaffirmed by his successor, Mr Raymond V. Gilmartin. In essence, Merck & Co., Inc. announced its intention to donate Mectizan for as long as it might be needed and whenever it is needed. "This unprecedented decision came twelve years after the discovery of avermectin by Merck scientists and nearly seven years after the first human clinical trials in Dakar, Senegal."[80]

A priori patient compliance would be expected to be a major hurdle. As mentioned above, almost miraculously, Mectizan is effective when administered once a year. The treatment programs are organized as community-directed interventions – entire villages line up for the treatments annually. The program now reaches some 45 million people in more than 88 000 villages in 34 countries. All of the gods of classical antiquity are smiling on this project.

In the chapters and volumes of this book that follow, the state of the art is brought up to date. This textbook should give a sense of pride and satisfaction to every person who has made medicinal chemistry his or her career. It goes without saying that all of the collaborators of medicinal chemists should share in this sense of satisfaction.

1.01.7 Epilogue

This chapter was written by two coauthors who have been associated with the pharmaceutical industry, although one of us (RH) has spent the past eighteen and a half years in academe. It is fitting and proper to devote part of this epilogue to the evolving interactions of academe and industry. Medicinal chemistry has always stood with one foot in the academic world and the other in the industrial world, as many of the examples noted above illustrate. The roles of these two sectors need to be profoundly different if their combined efforts are to benefit the patient. It is the responsibility and function of academe and government to undertake fundamental research, and it is the task of industry to perform the developmental research required if the knowledge generated by the former research is to lead to medicines and vaccines that are available to all of us in our hospitals and drugstores.

Let us be very clear. We believe that our academic and governmental institutions have no monopoly on outstanding research, and is it not unknown for mundane results to come from university or public institutions. This is equally true of industry. What has worked well in the past and will succeed in the foreseeable future is to understand that the perspectives and priorities of academic and industrial research are complementary. To maximize the opportunity for successful innovation, it is critical to ensure that the best fundamental research in academia and government is followed by the best applied research in the industry. Neither endeavor is nobler, or more challenging, than the other. Everyone would agree that it is an enormous achievement for a scientist in academe or government to generate a truly new idea. It may be more difficult for anyone outside the industry to appreciate the equally creative ideas required in successful drug discovery and development. The above discussion illustrates this point. Consider Section 1.01.2.2.1 on 'The Cortisol Era'. The basic research was done by Drs Reichstein, Hench, and Kendall, all academics, but their fundamental research would not have benefited a single patient without the industrial research that followed, which posed equally challenging intellectual puzzles, and also sparked new lines of academic investigation in the process.

We suspect that the easier problems may have been solved first, which may explain in part why the drug company pipelines – though still remarkably productive – seem dryer than they used to be. There may also be other reasons why it is becoming more difficult to generate a new approved drug. One is that for diseases such as diabetes, Alzheimer's disease, and others, there are no good animal models. As a result we have to go from an in vitro experiment directly to a clinical trial without the benefit of an in vivo experiment in animals. Also, the enormous cost of clinical trials has made the development of later entries in a therapeutic class more uncertain. But second and third generation drugs can also lead to significant advances, and it is also true that individuals vary in their response to different drugs that supposedly work via a common mechanism. Since second, but not third generation drugs have generally represented significant advances, the disappearance of 'me-too' medicines may not be that great a loss. It is nevertheless also true that individuals vary in their response to different drugs that supposedly work via a common mechanism.

Sadly, public opinion of the industry is presently at a low point. To a certain degree the industry itself has become a political football, a matter of concern cited by Mr Merck already in 1950. We suspect, however, that even the industry's most severe critics would not wish their families to be deprived of the medications discovered by the industry during the past 15 years. Recent advances for the treatments of rheumatoid arthritis, cancer, asthma, and diabetes, which are the result of excellent research in academia, government, and industry, are a case in point. We have every confidence that the combined efforts of governmental, academic, and industrial research will lead in the years ahead to advances in medicinal chemistry that today we can only imagine.

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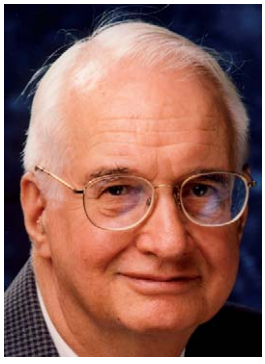
Biographies



Ralph F Hirschmann born in Bavaria, Germany, came to the US in his teens. He graduated from Oberlin College and then served in the US Army in the Pacific Theater during World War II. He resumed his education at the University of Wisconsin (Madison) as the Sterling Winthrop Fellow with W. S. Johnson as mentor (PhD 1950). He joined Merck & Co., Inc. that year, retiring at 65 in 1987, as Senior Vice President for Basic Research when he joined the Faculty at the University of Pennsylvania as the Makineni Professor. At Merck, his team discovered Mevacor, Vasotec, Prinivil, Primaxin, Proscar, and Ivermectin. In 1969 Robert G Denkewalter, Hirschmann, and their collaborators reported the first total synthesis of an enzyme in solution.

He is a member of the American Academy of Arts and Sciences and of the National Academy of Sciences, and its Institute of Medicine. He received the Cope Medal and the Willard Gibbs Medal. In 2000, he was awarded the National Medal of Science from President Clinton.

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