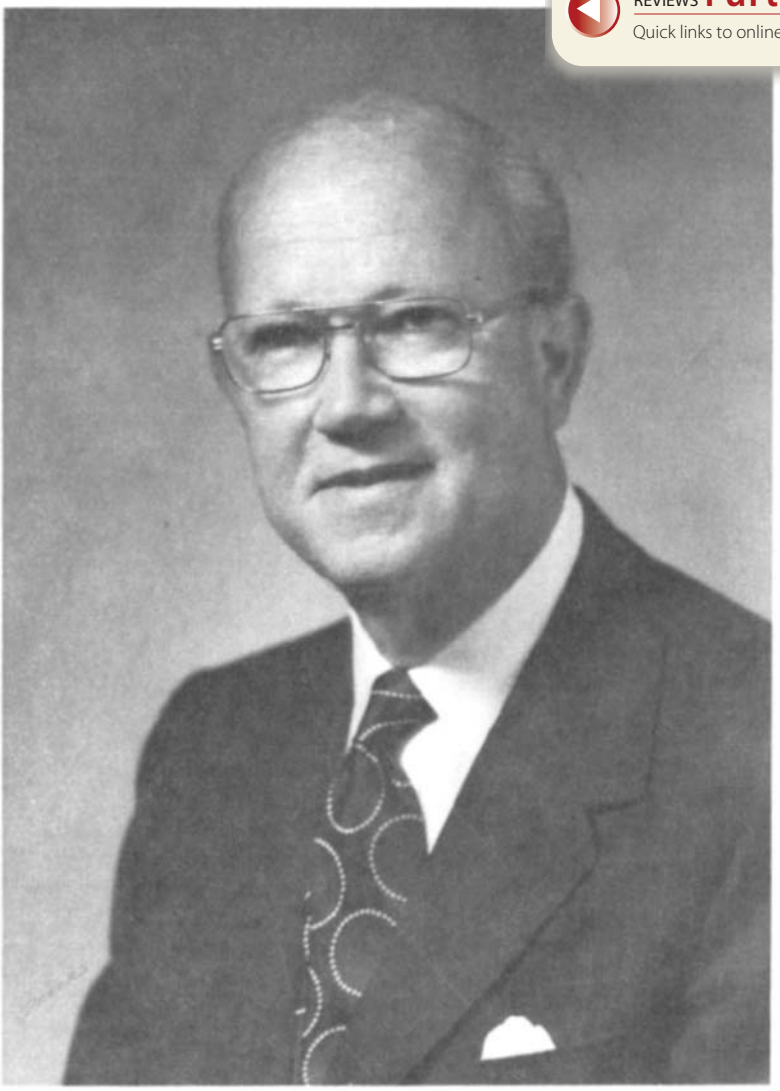

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A CAREER OR TWO

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As I stood on the veranda of the little airport terminal at Hershey, Pennsylvania, watching N254-KB hurl itself down runway 26 under the full power and thrust of its engines, I turned to thinking about this prefatory chapter. What of my life would be interesting to those who actually read these bits of memorabilia?

I had touched down at 9:07 EDT. The week before it had been 9:08, which was pretty good reproducibility for a start on still another new chapter in my life. Tom Gelarden, my assistant, was to pick me up at 9:10 for the ten-minute drive across the lovely valley to our laboratory in the Department of Pharmacology of the beautiful new Milton S. Hershey Medical Center, the Pennsylvania State University Medical School. If such a schedule could be sustained, it might be feasible on Wednesdays to breakfast at Stone House (while a Fogarty International Scholar-in-Residence at the National Institutes of Health, Bethesda), put in a reasonable day's work at the Medical School in Hershey, and spend the evening on correspondence at home, near Philadelphia. Wednesday's schedule. In good humor on that lovely morning, August 14, 1974, it occurred to me that such a recitation might be an interesting way to put this prefatory chapter into perspective—prefatory in the sense of anticipating what lay ahead in the next phase of my career as a scientist.

Before my retirement as senior vice president of the Merck Sharp & Dohme Research Laboratories, I had decided that I might accomplish more in the years ahead if I were to build on what I knew rather than start over in an exciting field of research entirely new to me. Thus, as I write I shall look backward to see how my second scientific career is rooted in the past. These reflections will include some highlights of a career that started when I was twelve and had a makeshift lab bench in my room at home, and may shed some light on the direction of my future career as a scientist and teacher.

But first, a few things about my early days that are not likely to be found in such standard references as *American Men and Women of Science,* or *Who's Who,* etc. I was fortunate to have been born (June 19, 1914) to well-regarded residents of a beautiful historic town, Henderson, Kentucky, set high on the banks of the majestic

Ohio River and very southern in sentiment. Its lovely main streets were the widest I have known. To me the town, whose economy depended on tobacco, reflected the friendly, leisurely character of substantial people to whom the land had been kind. My two younger sisters and I were reared among people to whom manners seemed more important than means. It was not an industrial town. My father was a capable veterinarian (VMD), hard working and sought after professionally in the surrounding counties. Later, he came to love his own land and animals as a preferred way of life. Mother gave as much of her time as she could to the Methodist Church, in which we all were active. Moderation was taught at home and in the community, and what were considered to be excesses of behavior were dealt with firmly. Those were happy days full of much to learn and do. Time has transformed those wonderful days of learning and doing to years, quite a few of which are behind me, quite a few ahead, I hope.

Even before my high school days, with the encouragement of an excellent and enthusiastic science teacher and friend, Mr. C. P. Rhoads, I discovered a love for chemistry that had to be reconciled with the study of my father's (veterinary) medical textbooks and the dissection of various small animals in my little "laboratory" at home. Even then, it was certain that I should be a medical doctor.

Still another fine teacher and friend, my professor of organic chemistry at Western Kentucky University, Dr. J. T. Skinner, obtained for me from his alma mater a Wisconsin Alumni Research Foundation scholarship in medical physiology (1936). This was exactly what I needed. Dr. Walter J. Meek, my professor and Head of the Department of Physiology at the University of Wisconsin Medical School, made it possible for me to take courses as I pleased and to create my own multifaceted research program as I ranged among the tremendous resources within the university.

Perhaps I should explain that I had taken a double major in chemistry and biology at Western Kentucky. After three years I received my BS degree. I spent an additional year at Western Kentucky taking the graduate courses offered in both zoology and chemistry while teaching in both departments and waiting for such an opportunity as the WARF scholarship afforded.

At Wisconsin, it was possible to work toward the PhD and MD degrees concurrently as one did research and taught. Then, too, some courses, such as Dr. Karl Paul Link's famous Carbohydrate Chemistry (a source of entertainment as well as learning), were given at night. Somehow, one could get to other classes, like Advanced Colloid Chemistry across the street from the medical school in the vast chemistry department, if he was willing to make the effort. Credits and grades had long since become unimportant, and so was the structure of the university when it came to being helpful. If two courses were given at the same time, one got to enough lectures in each to piece together what he wanted to know by additional reading. Sometimes gaining new segments of knowledge was done more expeditiously by bringing specific research problems to the professors. In so doing, one could learn things like diazonium chemistry, which I needed for the colorimetric analysis of sympathomimetic amines; or the physical aspects of organic chemistry, which

helped to anticipate structure-activity relationships leading first to metaraminol (that I shall mention again); or the techniques and principles of enzymology, which were reflected in several papers on the metabolism of these compounds. One is tempted to pay tribute to the many people to whom he is indebted for such personal influence, but the list of names would be much too long. Even so, I shall always be grateful for his help to Dr. William B. Youmans who came from Western Kentucky two years before me, who shared his laboratory with me on my arrival, and who succeeded Dr. Meek as chairman of the Department of Physiology.

The purpose of this search for broad academic and research training was straightforward enough. I wanted to be able to synthesize compounds which (by chemical structure–biological activity relationships) seemed interesting, and then to have the capability for evaluating such agents as potential therapy in patients. The advantage of being based in physiology for this training and then moving to pharmacology (as the natural discipline in which to express that ambition) seemed to me that one could acquire the knowledge of the function and the integrative actions of tissues, organs, and systems of organs. One needed this background before trying to modulate such functions during their aberrations, which we call disease, by chemical compounds, which we refer to as drugs. This was to be the marriage of chemistry, which I came to love very early, with medicine, to which I had always been dedicated. This was my way to a career in pharmacology.

Without detailing my research during Wisconsin days, its publication was in journals as diverse as the *Journal of the American Chemical Society,* the *American Journal of Physiology,* or the *Journal of Pharmacology and Experimental Therapeutics,* the *Annals of Internal Medicine,* or *Surgery, Gynecology, and Obstetrics.* Mostly, the work had to do with the actions, metabolism, and elimination of sympathomimetic amines. A gratifying bit of serendipity was that later Dr. Julius Axelrod, by his famous research, successfully and substantially extended my exploratory study of ascorbic acid in the inactivation of sympathomimetic amines (1941),[1] according to personal conversation with him. Seven years at Wisconsin, 18 publications, several advanced degrees (PhM, MD, PhD), and a host of scientist friends later, I was ready for a career that combined these several fascinations in a dedication to the advancement of medicine, of therapeutics. (Later, my friends at Wisconsin added their own distinction, which I cherish, the honorary DSc degree.)

From my structure-activity work that began in 1936 with sympathomimetic amines and carried throughout the Wisconsin days and beyond, I gained a critically important insight that influenced the course of my life. It was the awareness that I would have to team up with capable chemists, biologists, and clinicians if I expected to accomplish as much as I wanted to. For example, the exciting experience of using fuming nitric acid to nitrate β-propiophenone in a physiology laboratory having no exhaust hood was fun and downright hazardous, but not a likely practice

[1]Dates in parentheses indicate a date of publication, marketing, etc. They do not indicate dates that concepts or projects were formulated or terminated.

for an extended career! (Actually, I blew some of the fumes out an open window with a cheap home fan.) The logical course then and now for one with my polyvalent inclinations toward research has been within the broad resources of the pharmaceutical industry. I was fortunate in my choice of such associates.

Incidentally, from the structure-activity studies on related chemicals mentioned above, the propiophenone derivative I had decided was worth making and studying (1943) was what we later called metaraminol (Aramine®). A search of the chemical literature revealed that the agent had been synthesized in this country by Dr. Walter H. Hartung, and also in Germany. Its biomedical significance had been overlooked previously, but the compound had the combination of potency and stability that I had anticipated. I called my interest in this agent to the attention of Sharp and Dohme when I joined the company. They marketed the levorotatory form in 1952. Some readers will know metaraminol as a vasopressor agent long used in anesthesiology and the management of hypotension attending shock. Others will recognize it from the literature on false neurotransmitters, a much more recent development to which this compound has contributed. I had synthesized one compound, one drug. A good start, I thought.

There seemed hardly a transition between my graduate and medical school days at Wisconsin and the beginning of research as assistant director of pharmacology at the (then) Sharp and Dohme Research Laboratories, May 1, 1943, except that I had access to more of everything than I knew how to use, at first. The following thirty years and three months, with all their excitement and challenge, never allowed time for looking back or changing course. At the outset of that association, I had intended to return to the academic life several years before I actually did. When I did choose to retire early, it was with immense satisfaction that I could commend to top management those who had worked closely with me in research. These were scientists like Dr. Clement A. Stone, identified with the early work on methyldopa (Aldomet®), and Dr. Ralph F. Hirschmann, who shared honors for the first synthesis of an enzyme, ribonuclease.

My retirement from Merck & Co., Inc. on July 31, 1973, some six weeks after having turned 59, was the termination of a first career. August 1, 1973, marked the beginning of a second.

Indeed, it was at a tremendous retirement party that my second career began to unfold. Dr. Allan D. Bass, long-time friend, chairman of the Department of Pharmacology and acting dean of the Medical School at Vanderbilt, had been asked by my associates to participate in the ceremonies at that affair. It was a surprise to all of us when Dr. Bass presented to me a formal invitation to be a visiting professor of pharmacology at Vanderbilt. I was delighted. On the same occasion, Dr. Elliot S. Vesell, professor and chairman of the Department of Pharmacology at The Milton S. Hershey Medical Center of the Pennsylvania State University, offered me a visiting professorship in his department as well. This seemed too good to be true. I accepted both, for I was familiar with the schools and their excellent faculties. Since Hershey, Pennsylvania, was only 27 minutes by plane into the beautiful foothills of the Appalachian Mountains, it was feasible for me to accept laboratory

space for research as well as the teaching responsibilities I had undertaken both there and at Vanderbilt. This has worked out very well.

Teaching at both institutions has been a source of great personal satisfaction—at both the graduate and the medical student level. The experience has not been entirely new, for I have held appointments at four of the Philadelphia medical schools for years. When relating to medical students, I have made it a practice to teach basic pharmacology as a clinical subject, not as molecular biology. The latter is more appropriate to graduate training in research, I think. At the graduate student level, I enjoy teaching the discovery, development, and delivery of new drugs—something about which most graduates in pharmacology know little. Actually, this is the title of a book I hope to finish while I am still intimately familiar with the details of such a complex subject.

Setting up a new laboratory, training personnel, and handling experiments at technical as well as conceptual levels have been as pleasurable in this second time 'round as was learning about such things when a graduate student years ago. Assuming responsibility for ongoing training at the PhD candidate level is new to me and is at least as serious as the responsibility for postdoctoral guidance. In the past, my role in this connection has been to choose from among men and women who have received such advanced training those whom we might help to reach their full potential within a (pharmaceutical) research environment that required the concerted effort and technical ability of many, much of the time. Now, I hope to be so favored by this present effort as to count toward accomplishment the training of useful students, in addition to the contributions to science, knowledge, and therapy with which I have been fortunate to be identified.

Undertaking the renal transport characterization of the quaternary ammonium compound amprolium (Amprol®), since setting up my new laboratory at Hershey, is reminiscent of the earlier days leading to the discovery of probenecid (Benemid®).

When I first joined Sharp and Dohme, I was sent to the laboratory of Dr. James A. Shannon where I learned the conventional renal clearance techniques. I had no prior experience with such concepts and procedures, and so it was fun to see whether I could adapt from a familiarity with sympathomimetic amines to this, for me, new line of research. That was in June and July of 1943. Altogether, about a month was spent in Dr. Shannon's laboratory among bright young men including David P. Earle, Bernard B. Brodie, Julius Axelrod, John E. Baer, Robert W. Berliner, Sidney Udenfriend, and others from that group whom I came to know later. Actually, the work done while at the Goldwater Memorial Hospital laboratories of Dr. Shannon and when I first set up the renal program in our laboratories was on the clearance of sulfonamides. The chemists there, with the guidance of their director, Dr. James M. Sprague, had synthesized sulfamerazine, succinylsulfathiazole, and phthalylsulfathiazole, which the company marketed. This sulfonamide chemistry was to serve us well for many years. The friendship that developed between Jim Sprague and me helped set a standard for personal cooperation between chemists and biologists that I think has contributed to the productivity of these scientists.

At the request of Dr. Homer W. Smith, the leading renal physiologist of his day, the company made available a useful formulation of *p*-aminohippuric acid (PAH) which he developed as a renal function test at that time, 1943–1944. Perhaps it was providential, at least it was thusly circumstantial, that we should be sensitive to the characteristics of renal tubular secretory mechanisms as set forth for PAH. [In retrospect it does not seem very profound, but not until we began to work with the carinamide (Statacin®) and probenecid analogues did we realize that compounds ultrafiltered at the glomeruli and secreted by the tubules could be reabsorbed by the nephron, actively or by back diffusion. A paper on this three-way pattern of transport was published later by us (1954) that also anticipated the primary renal characteristics of the thiazides.]

To the medical world penicillin was the exciting new chemotherapeutic agent in 1943. Short supply, poor absorption when administered orally, and rapid excretion plagued its early use. Indeed, its national distribution was measured out at that time by the renowned Dr. Chester S. Keefer, professor of medicine at Boston University. In the spring of 1944, by the time we had become used to renal clearance technology, an article that called attention once again to the rapid excretion of penicillin caught my attention at the right time. The availability and lack of toxicity of PAH together with some knowledge of enzymology suggested that PAH might inhibit competitively a transport mechanism for the rapid excretion of penicillin, if that took place by tubular secretion in addition to glomerular ultrafiltration. The practical objective of the project was to increase what we referred to as the physiological economy of the antibiotic agent by decreasing its excretion.

Having first exposed the concept to Dr. A. N. Richards, we took it to Dr. Keefer and procured our first 100,000 units of penicillin-G. The Sharp and Dohme bacteriologists, Dr. Willard F. Verwey, A. Katherine Miller, and Roland Woodward, devised a gadget for collecting urine aseptically from dogs. Their laboratory did the antibiotic assays, we in Pharmacology did the chemical analyses, and the organic chemists soon started synthesizing compounds to inhibit the renal tubular secretion of penicillin. I shall never forget the thrill of seeing those first penicillin clearance calculations. Clearly, the antibiotic was secreted by the renal tubules of the dogs. Just as clearly, PAH coadministered with penicillin depressed its clearance (1944).

A scientist is fortunate if there are even a few such moments of ecstasy in his career. We had applied a basic principle of enzymology to the purposeful advancement of medicine. The two drugs (penicillin-G and PAH) administered intravenously sustained the very high antibiotic plasma concentrations needed to treat effectively the then uniformly lethal subacute bacterial endocarditis. The treatment was about as impractical, though, as the disease was unmanageable otherwise. This deterrent was due to the large amount of PAH needed for its continuous venoclysis with penicillin, neither of which was absorbed very well when administered per os.

Out of this work on competitive inhibition of penicillin secretion came, first, carinamide (1947), then, probenecid (Benemid®, 1951). Probenecid was absorbed well when administered orally, the clinical dosage was practical as predicted from the laboratory data, it inhibited the excretion of other organic acids including uric acid, and it was too late to be a marketing success as a general adjunct to penicillin

therapy. Probenecid was the first really useful uricosuric agent for the management of gout. It has gained some popularity combined with penicillin in the one-dose therapy for the "hit-and-run" treatment of gonorrhea. The renal physiologist has found it a tool of many uses. Whereas PAH was first administered at an intravenous dose of some 200 g, the concept that made a practical oral (2 g) daily dose of probenecid seem possible was that the compound should be able to inhibit a definitive component of a transport system for penicillin, yet be refractory to secretion by that mechanism (1947). This concept turned out to lead us toward our objective, only to prove erroneous as a likely explanation of the way probenecid was handled by the kidney. Probenecid secretion was offset by a substantial pH-dependent back diffusion which was sufficient to give, for practical purposes, the same net effect as far as dosage is concerned as was anticipated had the concept been correct.

For all we knew at the time, carinamide, the forerunner of probenecid, inhibited all renal tubular secretion into the lumen—although this seemed unlikely. Therefore, at the First International Physiological Congress after World War II at Oxford in 1947, I was delighted to meet Dr. Ivar Sperber, a young scientist from Uppsala who reported the renal tubular secretion of N-methylnicotinamide by the goat. This was important to us, for if his observation could be generalized to man and other animals, it was evidence for still other secretory mechanisms that might not be affected by our compounds. We reported later that carinamide did not inhibit the renal tubular secretion of N-methylnicotinamide by the dog; neither did probenecid. Over the course of time, we reported the renal tubular secretion of other organic bases, mepiperphenidol (Darstine®), a quaternary anticholinergic agent (1953), and mecamylamine (Inversine®) a tertiary ganglionic blocking antihypertensive amine (1956), from among the therapeutic agents we have brought to the physician. Since retirement from the Merck Sharp & Dohme Research Laboratories, I have returned to this interest as we have undertaken fundamental studies on the transport of basic organic compounds (1974) at our new Hershey Medical Center laboratory.

Even before the probenecid work had been brought to a practical conclusion, we turned to the renal modulation of electrolyte balance. Incidentally, any third-year medical student can recognize gross edema. If he remembers his physiology, the various causes of edema and the forms it takes are comprehensible to him. However, in my student days, the teaching of electrolyte balance was as unconvincing as was respiratory physiology. What was clear, though, was that a good orally active, safe diuretic agent suitable for day-to-day usage would be a godsend. Moreover, if a low salt diet (salt restriction) was useful in the management of hypertension, then what we proposed to call a saluretic agent should be doubly important. It should get rid of excess extravascular fluid, edema. It should lower hypertensive blood pressure also, or so we thought. All this was set forth in a memorandum to management of the company when the program was initiated.

Since the chlorothiazide (Diuril®) story has been made to serve many purposes by many people not intimately associated with its discovery, a few words about this innovation in therapy seems justified in this context. This is my own favorite example of what I like to refer to as *Designed Discovery.* To be sure, the previous probenecid research was (*a*) conceived in terms of sound (enzymological) principles,

(*b*) adapted to a hypothetical expression of the nature of (penicillin) tubular secretion, (*c*) reduced to well-defined and controllable laboratory procedures, (*d*) precisely supportive of critical structure-activity studies, and (*e*) directed to an outcome that was translatable to a well-defined clinical objective. Actually, chlorothiazide could be substituted for probenecid in the foregoing resume and only the details would be different. In a way, the sentence is a pattern for Designed Discovery, but it is no guarantee of success. Moreover, the discovery of an interesting compound is only the beginning of product development, of the effort that goes into the tailoring of a new, useful, safe therapeutic agent.

Briefly, the way the research leading to chlorothiazide evolved, as expressed in this five-point formula for discovery, was as follows:

1. It was known, or rather believed at the time, that (*a*) the electrolyte and water content of extravascular-extracellular fluid was essentially the same as plasma; (*b*) the predominant matching of cation and anion in these extracellular fluids that needed to be sustained was sodium and chloride; and (*c*) in the passage of plasma water along the lumen of the proximal portion of the nephron, sodium was actively exchanged and its predominant reabsorption at that site was attended by mostly chloride and water. Thus, an effective diuretic had to inhibit sodium reabsorption and with it predominantly chloride if a proper electrolyte and water balance was to be maintained in the body. Hence, the term *saluretic* was selected to emphasize the importance of these relationships.
2. Theoretically, (*a*) organomercurial diuretic agents worked by inhibiting sulfhydryl-catalyzed enzyme systems involved in the exchange reabsorption of sodium (chloride) and water; (*b*) carbonic anhydrase inhibitors blocked the exchange of sodium for hydrogen from the cells, but at the time this work began the few such compounds that had been studied typically increased bicarbonate excretion along with sodium and water.
3. The conventional renal clearance techniques employed in well-trained dogs gave us precise control of acute changes in specific electrolyte and water balance suitable for quantifying and interpreting the comparative efficacy of even related compounds.
4. The structure-activity studies followed the lines of (*a*) chemistry that mimicked the sulfhydryl binding of mercurials. This led to the phenoxyacetic acid derivatives of which ethacrynic acid (Edecrin®) was a prototype; and (*b*) sulfanilamide analogues that were carbonic anhydrase inhibitors, some of which turned out to increase bicarbonate excretion predominantly, or chloride predominantly, or both bicarbonate and chloride along with sodium (some potassium) and water. For example, the simple substitution of a carboxyl group for the para amino group on sulfanilamide yielded a definite chloruresis (actually a saluretic effect). It was this lead into saluretic sulfonamides that caused the greater initial emphasis and effort by us in this type of chemistry that culminated in chlorothiazide (Diuril).
5. From the laboratory data, it was proposed that one to two grams a day would be an adequate, safe dose of chlorothiazide for an adult man for both diuretic and antihypertensive effects. It was. We marketed chlorothiazide in 1957.

This climaxed an exciting, exacting, cooperative project that will always be a source of the greatest satisfaction to those of us who were a part of it. At the time of the introduction of chlorothiazide, it was more important to recognize and accept the utility of this agent than to know exactly how or where these drugs were thought to act in the kidney. The structure-activity work leading to the thiazides made it clear that the balance of where the compounds acted along the nephron was as important as how they acted, but this was not emphasized at the time.

Likewise, a delicate aspect of the clinical trials was to get our friends in the management of hypertension to recognize that a diuretic, actually a saluretic agent, could be basic antihypertensive therapy. There are some wonderful stories about this. We did not assess the activity of chlorothiazide in hypertensive animals prior to clinical trial. At the time, that methodology seemed even less convincing than the literature on clinical response to dietary salt restriction.

Over the years, there were many who participated in this program to an important extent. Among the chemists, those who come particularly to mind are their director and my counterpart, James M. Sprague; Frederick C. Novello; Everett M. Schultz; Edward J. Cragoe, Jr.; and Carl Ziegler. Among the pharmacologists, Horace F. Russo, who was with me from the outset; John E. Baer; L. Sherman Watson; and George M. Fanelli. This same research team went on from chlorothiazide and hydrochlorothiazide (Hydrodiuril®, 1958) to discover the phenoxyacetic acid ethacrynic acid (Edecrin®) in 1964 which extended the scope of diuretic therapy beyond the capability of the thiazides, and an antikaliuretic agent, amiloride (Colectril®) 1967, used mainly as a potassium-sparing adjunct to saluretic therapy. The latter compound is marketed in the principal countries of the world except the USA. This renal program still makes important advances. Such a new compound (a saluretic-uricosuric indanone) was reported in the Abstracts of the Nephrology Society Meeting in Washington, DC, 1974. As I have moved away from a day-to-day association with the Merck Sharp & Dohme research program and have taken time to think about the more general aspects of transport mechanisms in the kidney and other organs, new questions are beginning to find expression in our research at Hershey.

While a member of the Merck Sharp & Dohme Research Laboratories, it was my privilege to help shepherd a number of interesting compounds to the status of useful drugs in various fields of application. Among these were the antidepressant, amitriptyline (Elavil®); the steroid and nonsteroid anti-inflammatory agents, dexamethasone (Decadron®) and indomethacin (Indocin®), respectively; the antihypertensives, mecamylamine (Inversine®) and methyldopa (Aldomet®); the anthelmintic and the coccidiostat, thiabendazole (Mintezol®) and amprolium (Amprol®), respectively; the unique antiserotonin-antihistamine, cyproheptadine (Periactin®), and a number of less well known drugs not mentioned in this text. Each new drug had its own ups and downs, its own story worth telling. Each brought me into close personal association with different scientists primarily identified with each product, different clinicians both in our laboratory and throughout the world who are better characterized by their publications than is possible here.

In turn, these numerous friends have done me the honor of letting me work for them as their director or counselor, as president of the American Society for Phar-

macology and Experimental Therapeutics, as president of the Federation of American Societies for Experimental Biology, as an original member of the National Academy of Sciences Drug Research Board, and in many other ways. My intuition many years ago was right. There is so much more that one can do by working with others.

All our research and the worthwhile therapeutic agents discovered and developed between 1943 and 1973 occurred while my associates and I were members of a pharmaceutical laboratory. It was a natural environment for turning today's theory into tomorrow's therapy. We have been accorded the satisfaction of recognition and respect that should go with reasonable accomplishment. I have been honored by my peers according to their individual expression of recognition throughout the world, and travel to their laboratories has contributed to my education immensely. To mention names and places here would be unseemly. My one regret about such travel is that frequently I have not been able to express my appreciation in the native tongue of my host and his confreres. Still, there are many things I have yet to do. Like the rueful comment of Professor S. V. Anichkov in his delightful 1975 prefatory chapter to the *Annual Review of Pharmacology* about his only trip to London, "I did not even go to the British Museum, putting my visit off to some next time." Having seen what the British left behind in many an exotic land, I have every intention of visiting that museum, some day. It would be pleasant if Professor Anichkov and I met again there!

In bringing this rumination to a close, I return to the basis for the introductory paragraph. When it became generally known that I planned to "retire," Dr. James Shannon—by this time the former "most remarkable" director of the National Institutes of Health and active more recently at The Rockefeller Institute—called to my attention the John E. Fogarty International Center for the Advanced Study of Medical Sciences, an affiliate of the National Institutes of Health. Being a scholar-in-residence on the NIH grounds would help to broaden my awareness of the current status of biomedical sciences while providing opportunity for reading and reflection. I was proposed for and accepted this distinction. On August 1, 1974, Mrs. Beyer and I took up residence at Stone House with the other Fogarty Scholars and their wives from lands abroad, the first stage of a wonderful experience. Having the plane at hand made it possible to take full advantage of this opportunity while supervising the research in my laboratory at Hershey, attending my personal affairs at home, lecturing and participating in the various commitments from which one derives a sense of being helpful.

That August morning flight to Hershey was the beginning of a beautiful and interesting day. I hope I shall be privileged to enjoy many additional productive days. On the other hand, there is a layman's concept of retirement that can wait until research and teaching lose their fascination, if ever. Perhaps then there will be time for things like painting, fishing, sailing, metal working, and music composition that I cannot seem to get to, yet.

One more bit of philosophy that occurs to me as I read these words more times than anyone else ever will—to be a reasonably successful idealist, opportunity needs be met realistically.