Ann. Rev. Pharmacol. Toxicol. 1985. 25:1–26

REMINISCENCES IN PHARMACOLOGY: AULD ACQUAINTANCE NE'ER FORGOT[1]

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INTRODUCTION

Avoidance of personal pronouns in reminiscences is difficult; nevertheless, the main theme of this memoir will relate insofar as possible to its subtitle (with apologies to Robert Burns). Of necessity, this peripatetic writer has interacted with a great many colleagues during a period of over half a century. Marcia Davenport, in her autobiography (1), wrote beautifully, "I look back across the years and know of course that the real substance of my life, as of all lives, is the men and women with and through whom I have lived." And so it has been with me.

ORIGINS

My life began (7 November 1908) in a small New Hampshire town to which my parents had moved, after illnesses and business reverses, from Lynn, Massachusetts (where we were to return when I was eight). Of my ancestors, many of whom had settled in these areas in the seventeenth century, only the Reverend Stephen Bachiler seems particularly memorable (he even possessed a coat of arms!): he founded the first church in Lynn and then left hurriedly to

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launch the town of Hampton, New Hampshire. The Reverend Stephen left a great many descendants, both in the colonies and in England (where he returned in his nineties); one of these, my maternal grandfather, was Colonel Joseph DeMerritt Batchelder (a colonel of what I have not discovered). Although at least doubly descended from Stephen, I had from 500 to 2000 lineal ancestors in the seventeenth century, of whom he was one; of the other 99.9% but little is known: par for the course in the USA. The original Welch in the colonies also derived from England, but the term *Welch* originally meant foreigner (a term appropriately applied to the vexatious Celts of Wales); hence, the surname Welch does not certify a Welshman. I especially regret that I cannot safely claim descent from the illustrious William Henry (Popsy) Welch, one of the founding fathers of The Johns Hopkins Medical School: Popsy died a bachelor. My sometimes mildly annoying middle name, DeMerritt, presumably was once de Mérite; this name, shared with my grandfather, was derived from his mother's family and now belongs to one of my grandsons (he is not yet old enough to regret its other connotations).

EDUCATION (THROUGH 1931)

My education began in the home, where my stern father's demands engendered little mutual affection. When I was seven he began, rather unsuccessfully, to expose me to French and Spanish; nevertheless, I am now grateful for his teaching, because my interests in linguistics, etymology, and grammar resulted (which perhaps contributed to my alleged editorial talents and to my being dubbed a *which*-hunter). The death of my mother when I was thirteen devastated me and adversely affected my scholastic performance. Fortunately, two years later my father retired to Florida, where I had a wonderful science teacher who encouraged my scholarship and devotion to chemistry. [This led to my eventual membership in the *23 Club* (in the Federated Societies *2* stands for biochemistry and *3* for pharmacology); for the older pharmacologists, however, such membership was a kiss of death. Times indeed have changed; otherwise, an invitation to write this prefatory chapter surely could not have been extended.]

My entrance into the University of Florida was helped by my successful competition for a scholarship, which so surprised my father and a bachelor uncle that I received more financial and moral support than I had expected; nevertheless, I always had at least one job while at the university. In spite of such distractions, I attained certain honors, such as Phi Beta Kappa, Phi Kappa Phi, and even Blue Key. In my fifth year, I began my studies in pharmacology; my first paper, with B. V. Christensen, appeared in 1932 in the *Journal of Pharmacology and Experimental Therapeutics*. My initial textbooks were those of Sollmann (whom I was to succeed at Western Reserve University in 1944) and of Meyer & Gottlieb as translated by Velyien E. Henderson (who

was to guide my research to a PhD in 1934 at the University of Toronto). I was pleased in 1973 to receive the DSc (hc) from Florida thanks to my good friend Tom Maren.

Before moving to Toronto, I spent a pre-fellowship summer session in physiological chemistry at the University of Minnesota. The then chairman was not inspiring, but the professor of pharmacology at Minnesota, Arthur Hirschfelder, gave me friendship, lab space, and an introduction to toxicology. A belated offer from Toronto's Henderson afforded me, then a lowly MS, the monetary equivalent of a post-doctoral teaching fellowship (then $1500). In those terrible depression years, such a fellowship was manna from heaven. My release from the anticipated fellowship in P-chem made it available to a friend from the University of Florida, Earle Arnow. A few years after finishing his PhD and MD, Arnow joined Sharp & Dohme as director of biochemical research. He succeeded me as director of research in 1944 and went on to an outstanding career at Merck, Sharp & Dohme and later at Warner-Lambert.

Here I must note the almost incredible effects on human lives that the apparently inconsequential act of a single individual can have. Henderson's belated offer to me, which had resulted only from the last-moment defection of a young MD unknown to me, had great impact on my life, on that of Arnow, on those of several thousand of our medical and graduate students, post-docs, and almost innumerable colleagues.

TORONTO YEARS (1931–1935)

The years in Toronto were eventful and sometimes chilling, both literally and figuratively. My initial course in physiology, presented by Best & Taylor before their classic textbook was first published, was stimulating. In Toronto I formed a deep and lifelong friendship with Tom Jukes (we even shared digs[1] for two years before he went off, as Dr. T. H. Jukes, to Berkeley as a post-doc). Both Charlie Best and Fred Banting befriended us; from them I learned a bit about the real story of insulin. I learned much more from Brock, the chief "diener" in pharmacology, a good friend of mine as well as of Sir Frederick-to-be. How Banting handled another of the four main scientific participants at Toronto when Collip refused to disclose his method for partial purification of the pancreatic principle is not to be found in most sources, but perhaps can be surmised. Henderson supported Banting when McLeod, with whom Banting was forced to share the Nobel Award, was unable to find funds for him. Although Best, a medical student, did not share the honor of the prize, Banting

[1]My first experiment in clinical pharmacology resulted from Tom's and my discovery that our lonely bottle of medicinal Scotch was being mysteriously emptied. Suspecting the nephew of our motherly landlady, I carefully calculated the necessary (but non-lethal) amount of emetine and added it to the residual spirit. The culprit identified himself very audibly and further problems were avoided without retaliation.

promptly gave him half of his share of the money, which shamed McLeod into doing likewise for Collip, while McLeod was offered a Scottish chair. Best had earned his MD by 1925; then, shortly after a few years with Dale in London (under whom he earned a DSc), he was appointed chairman of physiology at Toronto at the age of thirty. Thus, when I first met Best in 1931 he was only ten years older than I.

I grew very intolerant of the apparent complacency of many pharmacologists, who had neither the training for nor any interest in probing molecularly into drug actions. Certainly the idea that new drugs would some day be designed was yet to come (2). Classical pharmacologists regarded biochemistry with anathema rather than anticipation. Henderson, although he sometimes took a rather dim view of my biochemical leanings, was very tolerant, all things considered. It was Best, however, who encouraged my initial delvings into structure-activity relationships, especially among analogs of choline (later I continued these studies with Tom Jukes). Best and others had already shown choline to be required by depancreatized dogs maintained with insulin, and he encouraged my further studies of mechanisms with Huntsman.

New approaches to mechanistic studies of drug action had been initiated by the splendid book by A. J. Clark, poorly titled *Applied Pharmacology,* which introduced much biophysical analysis, but it was the work of Otto Loewi in Graz in 1920 that began the biochemical revolution. Vagal neurotransmission was shown to involve a biochemically labile entity [later identified as acetylcholine (ACh)] that was enzymically inactivated. Indeed, Loewi demonstrated that one of the most classical of drugs, eserine or physostigmine, exerts its powerful actions by inhibiting the inactivating enzyme. (Henderson moved promptly into this area and carried out his important studies on the chorda tympani nerve, ACh, and the submaxillary gland; however, it was his paper on the mechanism of erection that prompted many requests for reprints!) Loewi also probed the sympathetic neurotransmitters, which had been anticipated by Elliott and by Langley, although their studies had had little impact. The structure-activity studies of congeners of adrenaline by Dale and his associates Barger and Dudley offered clues not fully recognized at first. Nevertheless, the work of the brilliant Dale, by then Sir Henry (who had noted in 1914 that synthetic ACh mimicked the effects of parasympathetic nerve stimulation and that ACh was quickly inactivated by a tissue extract), led to the Nobel Prize for him and Loewi in 1936.[2]

[2]Had I had the courage of my convictions (a dated notebook outlines my reasoning), as well as the necessary experience and encouragement, I might have identified L-noradrenaline (the synthetic DL-form was then termed arterenol) as the sympathin E postulated by Cannon. Indeed, I obtained arterenol as well as D- and L-acids for its possible resolution, but other pressures prevailed. Hence, it remained for U. S. von Euler over ten years later to establish that L-noradrenaline is indeed the excitatory sympathetic neurotransmitter. As one wag recently stated, "You lose some and you lose some."

During my graduate years the adrenal medulla fascinated me, especially the claim by Kendall (of later cortisone fame) that the remarkable stability of adrenaline in the gland, compared with that of the pure compound, was attributable to its conjugation with lactic acid. With post-doc Don Heard, I perfused fresh bovine glands; we reported that gland-derived ascorbate in the perfusate prevented the oxidative inactivation of the catecholamines. This and another report on the mechanisms of oxidation and stabilization of adrenaline caught the attention of the Coris, who then used ascorbate to protect minute amounts of adrenaline during their studies on glycogenolysis. This fortunate circumstance led to correspondence, a meeting, a job and an MD degree for me.

Martin Roepke and I studied ACh as a cation and showed, with a model system, that it possibly was attached to an anionic receptor in or on cells. This led to my conviction that the quaternary N of ACh might be replaceable (so to speak) by quaternary P or As and that such synthetic compounds might behave qualitatively like ACh. Indeed they did, perfectly, although the P-analog exhibited 10–20% of the activity of ACh, while the As-analog had 1–2% of its activity. We also prepared the planar molecule: $(CH_3)_2S^+$-CH_2-CH_2-O-CO-CH_3 (Cl^-). This too was highly active and, like the other analogs, was inactivated by choline esterases, potentiated by eserine, and blocked by the classical drug atropine.[3]

Despite (or because of) these often exciting days, the Chief finally put his foot down and gave me some new alkaloids to study, saying that it would be good for me to learn some neuropharmacology. Perhaps the *real* reason was that these compounds had come from the Canadian National Research Council and had to be studied and I was the rather unwilling victim. The most interesting of these hydrastine-like alkaloids, bicuculline, was a powerful convulsant. Who could have guessed that nearly forty years later, when bicuculline had become a valuable tool in the study of GABA, I would be introduced by Professor Curtis in Canberra as the father of bicuculline? Indeed, Henderson was the father and I only an illegitimate son. The visit in Australia gave me then, as has occurred many times later, an opportunity to renew my warm friendship with Adrien Albert, the author of a real classic, *Selective Toxicity,* new editions of which continue to be in demand.

Henderson lectured to medical students cloaked in a decrepit baccalaureate gown. He always began by peering over his pince-nez with a somewhat

[3]In the synthesis of the S-analog of ACh, we were too impatient to wait for $(CH_3)_2S$ to be delivered and chose to synthesize it; fortunately, this was on a Saturday, because our attention wandered for a few moments and exothermia took over. Stinking $(CH_3)_2S$ shot out of the reflux condenser; the mess was cleaned up and the stench, to our relief, was abated by Monday. Had the disaster occurred on a weekday, the medical building would have been evacuated and our own evacuation could well have been permanent.

sardonic grin. After saying, in a very British manner, "In my lawwst lect-chaw," he would continue in the speech of Upper Canada. The students loved it, although as individuals they were terrified of him, not without reason. The only other staff member, George Lucas, PhD, who was perhaps appropriately listed on the departmental letterhead as Ass. Prof., did not lecture. Henderson regularly took Tom Jukes, the post-docs, and me for an hour or two on Saturday mornings to drill us in scientific German. He even certified (doubtless with his fingers crossed) that Tom and I were qualified for our language requirements in French and German. May this very kindly scholar, who hid behind a mask of acerbity, rest in peace, as I wrote most sincerely in an obituary after his sudden death.

ST. LOUIS YEARS (1935–1940)

Under Carl Cori in St. Louis I became for a second time a scientific great-grandson of the reputed father of pharmacology, Schmiedeberg (actually a pupil of Bucheim in Dorpat). One of Schmiedeberg's pupils was H. H. Meyer; Henderson, in turn, had worked with Meyer in Marburg, and Cori also had worked with Meyer in Vienna and with Loewi in Graz. Cori's pharmacological credentials were as good as or better than those of certain classical pharmacologists who regarded Cori as an unsuitable occupant of the chair of pharmacology at Washington University, where the Coris had moved from Buffalo; their MD degrees had been earned in 1920 from the German University of Prague. Observed in Vienna by a Dr. Gaylord of the New York State Institute for the Study of Malignant Diseases (later to become the Roswell Park Memorial Institute), Carl and Gerty Cori were recruited in 1922; they were world-famous for their work in carbohydrate metabolism by 1931 (hence, a disgrace to pharmacology!). Carl Cori's thoughtful kindness to me was displayed immediately upon my arrival in St. Louis, albeit he mandated that I must obtain medical qualifications. This he made possible by wangling free tuition (as well as advanced standing) and by raising (somehow) my initial stipend from $600 to $800 (per year, not per month!). My wife, Mary, became an assistant mainly to the Coris; however, we also published two choline papers together. I published only once with Cori, a review on adrenaline; all other Cori-Welch papers are by Mary Welch. Initially, I had expected to be an assistant to the Coris, but Carl suggested that I prepare three research proposals; of these, he might approve one for my independent investigation (one was found approvable); otherwise, I would be his assistant. How many times have I wondered what would have have happened had I worked with the Coris rather than independently? Note what happened to Earl Sutherland, who later worked with Cori and then independently on what proved to be cyclic AMP; he succeeded

me at Western Reserve in 1953 and won the Nobel Prize, as the Coris had in 1947.[4]

Cori approved my proposal to study arsenocholine as a labeled form of choline (in those days carbon-14 was not yet available, and the mass spectrometer for work with nitrogen-15 was not dreamed of). I hoped that arsenocholine not only would be nontoxic, but also would serve as a metabolic mimic of choline. The resynthesis of arsenocholine (not a job for one man) was made possible with the help of Sidney Colowick, then a new technician Cori loaned me.[5]

Arsenocholine worked like a charm as a lipotropic agent. It was converted to some extent by the liver to the arsenic analog of betaine [$(CH_3)_3As^+$-CH_2COO^-]. Clearly, the analog had to be synthesized, because betaine [$(CH_3)_3N^+$-CH_2COO^-] had been found to be lipotropically active (transmethylation not yet having been discovered, it was thought that betaine might be reduced to choline); however, synthetic arsenobetaine proved not to be lipotropically active. Surprisingly, my S-analog of choline was too toxic to detect lipotropic activity (instability?); sulfobetaine [$(CH_3)_2S^+$-CH_2-COO^-], however, was very effective as a lipotropic agent. It was likely, therefore, that sulfobetaine and betaine were donating one or more of their methyl groups for the biosynthesis of choline. Before this hypothesis could be tested and transmethylation established, duVigneaud, who knew of my work, renamed sulfobetaine dimethylthetine and hastened to publish without appropriate reference to my studies. Even some gods have feet of clay!

During my first post-MD year (1939–1940), Richard Landau, then a fourth-year medical student, did his BSc (Med) with me (Landau for many years has been a professor of medicine at Chicago and the distinguished editor of *Perspectives in Biology and Medicine*). We found great pleasure in working together then and in the friendship that has continued. The gold salts of choline-fractions derived from lecithin isolated from rats fed arsenocholine analyzed correctly with respect to the ratios of N:As:Au; thus, these fractions

[4]In competition for my attention with heavy teaching and research was an uninspiring course in anatomy. The professor (Terry) cared little for function and even less for holders of the PhD. When the female pelvis was dissected, I was attending the Federation meetings; hence, I was given an incomplete and told to report in June. I did, albeit reluctantly, as the speed and poor quality of my dissection displayed. Terry descended upon Cori (who also disliked anatomy and, I suspect, Terry as well) to complain about my performance. In no uncertain terms, Cori told me to get with it and do a perfect dissection. I did one so well that Terry found no hiatuses in my knowledge, but he barely passed me. I take some pride in the fact that, in spite of the magnanimous Terry, I graduated three years later (cum laude) with membership in Alpha Omega Alpha.

[5]Shortly after he had returned to Cori, Colowick, a chemical engineer then without experience with the tools of biochemistry, allowed the ungreased top of a desiccator to crash on the concrete floor directly in front of Cori's office. Cori emerged in horror (how short funds were in those days!) and said in essence, "This guy has gotta go." I like to believe that without my pleading this first of Cori's PhD students might have been lost to science and to his great career in biochemistry.

represented a mixture of choline and arsenocholine, the latter having functionally replaced much of the choline (3).

The days in St. Louis were exciting: the discovery and synthesis of the "Cori-ester" (glucose-1-phosphate); my close friendships with Carl and Gerty, Helen Graham, Gerhard Schmidt, F. O. Schmitt, my late brother-in-law Gordon H. Scott, Evarts Graham, the great surgeon, who offered me a career in anesthesiology, and many others of my colleagues; even those in my own medical class (dear friends still) who had to suffer my lectures and my grading of their papers. The offer to head a new research department of pharmacology at Sharp & Dohme (before its merger with Merck) came in 1940, at a time when I had no intention of ever leaving Cori. One sour note had been heard, however; the dean, despite Cori's urging, refused to promote me unless I did some "proper pharmacology," i.e. work on new sulfonamides. In my "spare time" I had already written (1937) the very first review of the "sulfa" drugs at the request of the *Journal of Pediatrics* (as I recall, it contained less than 40 references!). The mandate of the dean I found intolerable; thus, despite the belated offer of a promotion, an increase in salary from $2500 to $3500 per year, and a technician, I reluctantly parted from my dear friends, although I almost returned as Cori's successor in pharmacology only six years later. I had been elected to membership in ASPET in 1937 at age 28; however, when I became director of pharmacological research at Sharp & Dohme my membership was canceled, as the bylaws then required. Accordingly, the directory indicates that my membership dates from 1942, when, bylaw reform having occurred, I was reelected.

SHARP & DOHME (S & D) YEARS (1940–1944)

William A. Feirer (MD and DSc from The Johns Hopkins University), who had recruited me as director of pharmacological research, had just become director of research of S & D. We remained very close friends until he died only a few years ago. In view of my rejection of the sulfa drugs at Washington University, it was ironical, to say the least, that important discoveries of new sulfonamides by Jim Sprague and M. L. (Mel) Moore made study in this area mandatory for me while I was building a new department of pharmacology at S & D, the first of four. The small initial group included Paul A. Mattis, DSc, a most helpful colleague who later joined me in Cleveland, Albert Latven, a super technician, the animal man, and myself; however, the group grew rapidly to some twenty-five or thirty. The first of the new sulfonamides to show promise was a sulfamethylpyrimidine, which appeared superior to sulfapyrimidine, i.e. sulfadiazine; indeed, equal dosages gave much higher blood levels of the new drug, termed sulfamerazine. The latter was much better absorbed than sulfadiazine after oral administration, while renal clearance took twice as long; hence, equal

blood levels of the chemotherapeutically equivalent drugs could be maintained by half as much sulfamerazine given at eight-hour, rather than four-hour, intervals. It seemed that we had a winner.

Feirer proposed that our findings be reviewed with E. K. Marshall at The Johns Hopkins, then the panjandrum of sulfa drugs. The discourse had hardly begun when Marshall stopped me, saying, "Welch, you are a damned fool! Don't you know that sulfamethylthiazole causes peripheral neuropathy and that sulfamethylpyrimidine will do the same? It also causes renal damage; look at the holes in this kidney section!" I asked him why a methyl group should be toxic when substituted on a pyrimidine ring compared with a thiazole ring; it seemed to me a non sequitur. He inquired whether I had heard of CH_3OH! No chemist, Marshall apparently really believed that the methyl group per se is potentially toxic; he suggested that we start over with a sulfaethylpyrimidine! The holes in the kidneys reflected hydronephrosis, of course; they resulted from crystal deposition due to overdosage. I stated that no renal differences would be found with equal blood levels of the two drugs. Marshall remained unconvinced and Feirer was nonplussed, to say the least. To make a very long story short, chicks were used to show that the peripheral neuropathy, readily caused in that species by sulfamethylthiazole, was of minor degree and equal with sulfadiazine and sulfamerazine. Extended studies of many phenomena made clear that the earlier contentions had been correct. With a massive paper ready for publication, we went again to Baltimore. Marshall, really a great man, at last was completely convinced and congratulated us. A very long paper was published in 1943 in the *Journal of Pharmacology and Experimental Therapeutics* without any changes; I suspect that one referee of that manuscript can be identified! Why then did the no-more-costly sulfamerazine not completely displace sulfadiazine, with half the dose given half as often? The reasons were entirely economic. S & D, then a relatively small company, could not afford to out-advertise the developers of sulfadiazine, which by then was so well established that few physicians were interested in altering their memory patterns. Science versus the marketplace!

My career appeared to benefit, at least temporarily, from promotion to assistant director of research (but now with seven departments to supervise), while shortly thereafter Feirer became vice president and I became director of research at age 34. I tried to spend half-time in pharmacology but failed. The then assistant director of the department, Karl Beyer, was given full responsibility for research and went on to a brilliant career. Only my studies that led to folic acid (see below) were continued, then with Lem Wright. At the same time several academic posts became available and in 1944 I decided to move to Western Reserve University, where Torald Sollmann was retiring. Solly had been dean at Western Reserve for fifteen years; the Department of Pharmacology was spatially large but almost without equipment, and with the departure of

the last assistant professor, the staff was zero, while my new salary, $7500 per year, now seems inconceivably small.

In addition to my lasting friendships with Bill and Jeanne Feirer, I left S & D with great respect for my many scientific colleagues and for the ethics of the company, then led by John Zinsser. [Incidentally, I began my first major review at S & D; it was the first on the design and use of antimetabolites (4).]

WESTERN RESERVE (WRU) YEARS (1944–1953)

I moved to Cleveland in 1944 during the war. A medical officer in the Army Reserve Corps, I had been rejected for active duty: cardiac hypertrophy, diagnosed erroneously. Two of the men who first moved to the department at Western Reserve were Lawrence (Lawrie) Peters, PhD (now deceased), who had worked with me at S & D for two years (I helped him earn his MD), and Ernest Bueding, MD, who had come from New York University. With army support, we promptly undertook chemotherapeutic studies of filariasis, which the military expected to be a major problem in the South Pacific (it proved not to be). Peters and I were soon chasing vicious wild cotton rats naturally infested with the only practicable source of a filariasis resembling that of man. We had to learn that *Litomosoides carinii* in the pleural cavity of these animals responds differently to drugs than *Wuchereria bancrofti* in the lymphatic system of man. We studied new classes of compounds and found activity among a group of cyanine dyes with resonating systems of bonding. We selected a compound with acceptable toxicity that could kill all adult filarial worms in the cotton rats; however, the microfilaria in the blood-stream (infectious for the vector, a mite) were not directly killed. After extensive studies of toxicity in many animal species, we conducted clinical pharmacological investigations in human volunteers with inoperable neoplastic diseases. We carried out clinical trials in Puerto Rico; these were disappointing. The adult worms in the human lymphatics were not killed, although the *microfilaria* were sensitive; they returned in due course, as might be expected. We developed derivatives, however, for the chemotherapy of other nematodal infestations. In the meantime, the army asked us to study schistosomiasis. Bueding, while studying the mechanism of action of the cyanine dyes, began investigations in mice, using a snail colony to produce the miracidia of *Schistosoma mansoni*. In this and related fields, Bueding is today the world's authority.

Other prominent members of the Department of Pharmacology at Western Reserve included George Bidder, MD, Giulio Cantoni, MD, and Harold Chase, MD, about whom space restrictions preclude discussions.

A major dilemma arose in 1946: I was offered the chairmanship of the Department of Pharmacology at Washington University; Carl Cori had moved to the chair of biological chemistry. Despite my nostalgia for Washington

University, I decided to remain in Cleveland; I wanted to follow up on the two years of hard work I had expended in building something out of almost nothing. In addition, my studies leading to folic acid, begun at S & D, had been reinitiated and were moving forward rapidly.

Lem Wright and I had added poorly absorbed succinylsulfathiazole together with the then-known vitamins to highly purified diets of rats. We hoped to learn whether intestinal microorganisms produce essential nutritional factors that might be disclosed in this way. Elvehjem and his associates had similar ideas using sulfaguanidine and they first identified a factor, not then an entity, termed folic acid. To conserve space, the reader is referred to other articles for the history of this research (5–7).

Much of the work on folic acid, and later on vitamin B_{12}, was done in collaboration with Bob Heinle of the Department of Medicine at Western Reserve. He was a superb colleague who was very even-tempered—always mad. Trained with W. B. (Bill) Castle at the Thorndike in Boston, Heinle was an expert hematologist and internist; we worked effectively together for seven years. After Jack Pritchard, MD, joined us, we fed piglets a purified diet containing succinylsulfathiazole and a crude antagonist of folic acid (supplied by Tom Jukes, by then at Lederle); the piglets became relatively huge swine, so strong that only Jack could successfully wrestle them. Eventually they developed striking bone marrow changes and a macrocytic anemia; their marrow became indistinguishable from that of human pernicious anemia in relapse. This condition responded initially to folic acid, but gradually became insensitive to folate unless we injected purified liver extract, as was used in the treatment of pernicious anemia (later replaced by vitamin B_{12}). Combined system disease did not develop in the deficient animals, but sudden deaths occurred eventually unless liver extract (later vitamin B_{12}) was injected. During subsequent army service, Pritchard became involved in obstetrics and gynecology and has been head of that department at Dallas for many years.

Our studies with swine, coupled with evidence that the purified liver extracts contained no folic acid, led me to suggest that the extrinsic factor, utilized orally by pernicious anemic patients only when administered with Castle's intrinsic factor (i.e. normal human gastric juice), could be identical with the parenterally active antipernicious anemia factor of liver. This was established in 1948 in collaboration with Castle and associates, and was extended to pure vitamin B_{12}, which had just then become available (8). Also in 1948, in collaboration with Stokstad, Jukes, and others (9), we demonstrated the antipernicious anemia efficacy of the microbially produced animal protein factor, given parenterally. This was probably the first reported use of a material derived from a source other than liver for the parenteral treatment of pernicious anemia in relapse.

In 1949, two superb post-docs, C. A. (Chuck) Nichol and W. H. (Bill) Prusoff, joined the group. With the latter, I initiated a program to concentrate the intrinsic factor using desiccated pig stomach as a source, while with Nichol I began studies of the effect of rat liver slices on folic acid. Using *Leuconostoc citrovorum,* which requires for its growth reduced forms of folate, e.g. leucovorin, we soon obtained evidence for a folate reductase. From the standpoint of chemotherapy, it was exciting to find that aminopterin, the forerunner of methotrexate, almost irreversibly inhibits the reductase (10–12), because this was the first clue to the mechanism of action of this invaluable antileukemic agent. Warwick Sakami and I showed the involvement of folate derivatives in the biosynthesis of labile methyl groups (of betaine, methionine, etc) (13).

Some comments concerning the rather ghastly years of anguishing debates about teaching are necessary, because these led to the nearly total (and rather famous) revision of the curriculum of WRU Medical School. Initially, I had inveighed against the examination system that prevailed (frequent regurgitation after memorization), but I knew not whereof I wrought. Major funds were raised by the dean, Joe Wearn (a man with whom I had great personal rapport and who nominated me for membership in the Association of American Physicians); Hale Ham came from Harvard to coordinate the program, and eventually teaching by committees resulted. One participation I will proudly acknowledge: the multidisciplinary student laboratories. Otherwise, I became essentially antipathetic. I believed then, as I do now, that good instruction comes from within; it is a product of knowledgeable individuals who love to stimulate and debate with willing recipients. No committee can do this—or legislate it—only earnest and dedicated individuals. My departure for Yale in 1953 introduced me to a very different teaching system: no examinations except by the National Board. It was a joy to have real rapport with medical students, who studied without built-in fear of their instructors (in most schools then, teachers also were potential executioners). By mid-1952, however, I was able to accept an invitation from Professor J. H. (Josh) Burn to recover at Oxford University.

Other dear old friends at WRU included Normand Hoerr, John Dingle, and Carl Wiggers (deceased) and Harland Wood and Lester Krampitz.

OXFORD DAYS (1952–JANUARY 1953)

Oxford was an unforgettable experience for me; it was a Mecca for pharmacologists, with such stars as Burn, Edith Bülbring, Hugh Blaschko, and many, many others. Initially Burn and I worked together, but discussions with Blaschko soon led us to attempt to determine (again without the possibility of using isotopes) whether dopa and dopamine were converted to noradrenaline

and adrenaline by the adrenal medulla. A fresh homogenate was cold-dialyzed against a very small volume of buffered saline suspension of mushroom catechol oxidase to pump out the pressor amines, forming insoluble melanins, by creating a concentration gradient while minimizing the loss of possible cofactors; O_2 was bubbled through the external compartment and N_2 through the homogenate. The level of the pressor amines (as assayed on the blood pressure of the pithed cat) fell rapidly; however, an asymptote was soon reached at 75–80% of the initial concentration in the homogenate. What was causing retention? Could the amines be held within particles? Using Florey's high-speed refrigerated centrifuge, we found the pressor amines in vesicles that sedimented with the mitochondria; from these particles the catecholamines could be readily released. A new field was opened (14) and lasting friendships were made.

Progress toward the end of these experiments was slowed by my hospitalization for a lumbar disc (after a previous laminectomy, I had not anticipated this); during my return to the States from England on the Queen Mary, I was encased in plaster. On an earlier visit to Yale University at the invitation of Joe Fruton I had met the dean-to-be, Vernon Lippard (not yet moved from Charlottesville), and eventually I accepted an offer from Yale. At the same time, 1953, Peters became chairman of pharmacology at Tulane and moved to Kansas two years later, and Cantoni moved to head a lab at the National Institutes of Health. In 1954, Bueding became chairman of pharmacology at Louisiana State University and moved to The Johns Hopkins six years later.

YALE YEARS (1953–1967)

After the death of the previous chairman, Salter, the Department of Pharmacology at Yale had deteriorated somewhat. When I arrived with several colleagues from Western Reserve [e.g. Charles (Nick) Carter, an assistant professor of medicine strongly grounded in biochemistry, Chuck Nichol, Bill Prusoff, Bill Holmes, and Sheldon Greenbaum, as well as several post-docs, including Bernard Langley, and even two graduate students], only two of the former Yale staff members (and too many graduate students) remained. Desmond Bonnycastle, an associate professor, departed when his five-year term-appointment expired. Nicholas (Nick) Giarman, an assistant professor, proved to be an exceptional teacher and a very competent neuropharmacologist; we urged him to remain. Indeed, at the invitation of J. H. Gaddum, Giarman exchanged positions with Henry Adam for a year (to keep it simple, the two men exchanged jobs, salaries, cars, and homes; everything except wives!). Giarman returned as associate professor. In 1963 he succeeded me as American editor of

Biochemical Pharmacology. He died in 1968, a great loss for Yale, science, and his many friends.[6]

In 1953–1954, Blaschko spent six months with us at Yale and work on the adrenal granules resumed, in collaboration with Joe Demis, and later with Paul Hagen. We obtained proof of the precursory role of ^{14}C-dopa in the formation of the pressor amines, and continued studies of the extraordinarily high levels of ATP in the vesicles.

One outstanding recruit of the pharmacology department at Yale was John Vane, D Phil, whom I had known as a graduate student at Oxford. Vane came to Yale as an instructor and was soon promoted. Eventually, however, the tug of his home country became too great and he joined the Department of Pharmacology of the Royal College of Surgeons. Later, he became group research and development director of the Wellcome Laboratories. It is pertinent to mention here, although out of context, that prior to Vane's joining Wellcome he was a very great help to us at Squibb as the senior consultant in pharmacology. For his brilliant work on the prostaglandins and prostacyclin, as well as the mechanism of action of aspirin, Vane shared a Nobel Prize in 1982; he was knighted in 1984 and became a foreign member of the National Academy of Science of the United States. In December 1982 my wife and I were greatly honored by an official invitation, through Vane, of course, to attend the Nobel ceremonies in Stockholm, one of the most memorable experiences of our lives.

The great strengths of the Department of Pharmacology at Yale, which gained worldwide recognition, lay in the many outstanding young scientists who came to work there, either as young faculty members or as post-doctoral fellows. We were able to secure the funds to retain many of these men and women, and gave them encouragement and help in full measure to develop their ideas and intellectual growth. Over the years, many of that group received various honors and special appointments, e.g. Career Development Awards, Scholars in Cancer Research awards, Markle and Burroughs-Wellcome Scholar awards, as well as career professorships. In addition, I shared in memberships and chairmanships of study sections of the NIH and advisory committees of the NSF, the NRC, and the American Cancer Society. The department grew rapidly and in addition to research gained a deserved reputation for good

[6]Prior to Giarman's American editorship of *Biochemical Pharmacology*, I (and others) had helped Sir Rudolph Peters in the founding in 1958 of that soon rather prestigious journal. As American editor my initial roles were demanding ones. High standards were set and were maintained by Giarman, while I became a vice chairman of the International Board of Editors. Subsequently, Alan Sartorelli carried the standards of the journal to even greater heights (despite his having much to do with the issue in 1979 that commemorated my seventieth birthday). Subsequent to the death of Sir Rudolph, I became chairman of the editorial board, at the time of a symposium in Oxford (1983) that celebrated the twenty-fifth anniversary of the founding of *Biochemical Pharmacology*.

teaching of medical students (much in small discussion groups), as well as of graduate students, while offering an excellent atmosphere for post-doctoral training. Much of the early financial help came in the form of no-strings grants from either the Squibb Institute for Medical Research or the Upjohn Company, where I was a consultant for about eight years. As research and training grants became more readily available (prior to recent years), funds were relatively easy to obtain. Among the many members of the group were such outstanding men as Bob Handschumacher, a scholar in cancer research and a career professor of the American Cancer Society, who was chairman of the Yale department from 1974 to 1977; Van Canellakis, a career NIH professor; Henry Mautner, chairman of biochemistry and pharmacology at Tufts. Jack Cooper was promoted to professor and remained at Yale, while Julian Jaffe was attracted to the University of Vermont, where he is a professor of pharmacology. Chuck Nichol became head of experimental therapeutics at the Roswell Park Memorial Institute and later director of medicinal biochemistry at the Wellcome Research Laboratories (USA). Another man of distinction who moved to Yale from WRU, Bill Prusoff, became a professor and remained at Yale. Nick Carter returned to WRU as chairman of pharmacology and is now scientific director of NIEHS (NIH). After two years at Cornell, Jack Green became chairman of pharmacology at Mt. Sinai Medical School. Paul Hagen moved to Harvard for three years prior to becoming chairman of biochemistry at Manitoba; he is now dean of graduate studies at the University of Ottawa. Glenn Fischer, after eleven years at Yale, transferred to Brown as a professor of biochemical pharmacology.

Alan C. Sartorelli joined the department as an assistant professor and became a professor in 1967; he was a very distinguished chairman of the department from 1977 to 1984 and is now director of the Yale Comprehensive Cancer Center. Since 1968 the American editor of *Biochemical Pharmacology*, Sartorelli is also the executive editor of *Pharmacology and Therapeutics*. Joe Bertino joined the department (and internal medicine) as assistant professor and later became an American Cancer Society professor. Paul Calabresi left Yale in 1968 for the chairmanship of the Department of Medicine at Brown, but he deserves very special mention because of his various contributions to Yale and to his many co-workers there, including myself; he headed the first section on clinical pharmacology at Yale and was a Burroughs-Wellcome Scholar in that field. Dave Johns, a member of the department for seven years, became chief of two laboratories (medicinal chemistry and biology and chemical pharmacology) at the National Cancer Institute. The two-volume monograph edited by Sartorelli & Johns on antineoplastic and immunosuppressive agents remains a classic in these fields after nearly ten years.

Space does not permit other than brief mention of many other friends and important workers in the department between 1953 and 1967 and subsequently;

these certainly include Pauline Chang, Dave Ludlum, Joe Demis, Bob Levine, Maire Hakala, Zygmunt Zakrzewski, Ming Chu and S.-H. Chu, Arnold Eisenfeld, Richard Schindler, Ron Morris, Norm Gillis, Zoe Canellakis, Bill Creasey, John Perkins, John McCormack, Bill Macmillan, Malcolm Mitchell, Bob Roth, Jack Cramer, Morris Zedeck, Karel Raška, and Ed Coleman, who later joined me at Squibb. A dear friend from Germany, Helmuth Vorherr, with whom I studied the selective embryolethality of 6-azauridine and later, with his wife, Ute, that of N-(phosphonacetyl)-L-aspartate (PALA), is now professor of pharmacology and gynecology at the University of New Mexico. Other dear friends from abroad who worked at Yale included Laszlo Lajtha, until recently director of the MRC unit in the Paterson Labs of the University of Manchester; Ronald Girdwood, professor of therapeutics at the University of Edinburgh; Peter Reichard of the Karolinska Institutet; Tony Mathias; Hamish Keir; Charles Pasternak; Margaret Day; and Margaret and Brian Fox. Warm friends in other departments included Paul Beeson, Joe Fruton and his wife, Sofia Simmonds, Aaron Lerner, Sam Hellman, Dan Freedman, Bob McCollum, Bill Gardner, and Nick Greene. Unintentional omissions of other Yale colleagues I hope will be forgiven.

To discuss the investigations of all these exceptional scientists would require an entire volume. Many of my own studies through early 1966 were summarized in part in my Sollmann oration (15), presented at the time of my Torald Sollmann Award from ASPET; these studies involved many of the fine colleagues referred to above. They and other co-workers enabled me to participate in research and contributed greatly to our efforts to build a strong department that continued to prosper. As I said at the time of the dedication of a newly remodeled wing donated jointly to Yale by the Wellcome Trust and the National Cancer Institute, when I announced my imminent departure for the Squibb Institute for Medical Research, "There is nothing that succeeds like *successors!*" At that time also, my old friend George Hitchings, vice president for research at Burroughs Wellcome, presented me with a most appropriate gift: two large bottles of Empirin Compound, which he correctly predicted I would very soon be needing for my new headaches.

If space permitted, I could present much interesting information concerning the remarkably successful oral therapy of severe psoriasis with azaribine (triacetyl-6-azauridine) initiated by Paul Calabresi, Charlie McDonald, and colleagues. The NDA was approved in 1975 but was withdrawn fifteen months later because of the approximately 4% incidence of thromboses, some intra-arterial. Evidence now suggests that in a few susceptible individuals a deficiency of pyridoxal phosphate may be induced, with resultant homocystinemia (in rabbits, these are prevented by pyridoxine). At present, azaribine is an orphan drug and psoriasis is an orphan disease! The remarkable efficacy of azaribine, not only in psoriasis but also in mycosis fungoides, choriocarcinoma, polycyt-

hemia vera, and perhaps as an embryolethal agent, may now be studied in other countries but not in the USA.

After Squibb's initial production of 6-azauridine for us (~700 g) with the aid of a contract from the National Cancer Institute (NCI), the NCI contracted with Calbiochem to manufacture the substance. Handschumacher and I helped that company to initiate production, using 6-azauracil incubated with *E. coli,* a method devised by our friends in Prague, Jan Škoda et al. Thus, Bob, Jan, and I became close friends of Dr. William (Bill) Drell, then president of Calbiochem. These deep mutual friendships have survived time, distances, and the devastating effect of the loss of azaribine on Calbiochem, now a subsidiary of Hoechst. Handschumacher and I went to Prague to conduct studies with Škoda and Šorm, with each of whom, and with Helena Rašková, warm friendships developed. Toward the end of my second sabbatical, in Frankfurt at the Institut f. Therapeutische Biochemie,[7] where I developed friendships with Helmut Maske, Jürgen Drews, and Bill Pratt, Škoda and I began studies in Prague in March 1965; these were extended in July-August of that year.

This second sabbatical leave (1964–1965) was precipitated by a fall while I was skiing with Tom Jukes in Badger Pass in Yosemite; result: a broken fibula and the man who came to dinner. Later complications of the original break were debilitating, and finally a change in scenery was deemed essential. I must comment that one of the finest personal letters I have ever received had been written by Van Canellakis, who felt I was headed for disaster (presumably attributed to premature aging and overwork [?]); hence, I should slow down and rest on my laurels (i.e. contemplate my navel and admire the wonderful department at Yale that the many great colleagues, he, and I had built). My reactions to these concerns were (*a*) to go to Germany in 1964 to work in the laboratory and write a paper (without coauthors) for the Proceedings of the National Academy of Sciences on the selective inhibition of an enzyme induction; (*b*) to go to Prague in 1965 to work with Škoda; (*c*) to end years of unhappiness through divorce; (*d*) to go to India to study the chemotherapy of smallpox with 5-iododeoxyuridine, (*e*) above all, to be most happily married in Prague in 1966 to Erika (Peter) Martinková; and (*f*) to leave Yale in 1967 to head research and development at Squibb, involving about 1000 scientific

[7]While working in Frankfurt, I was invited by my old friends Gustav Born and Sir Alex Haddow to dine with them and Sir Henry Dale, Vane, and several others after a lecture in London. Dale was delighted to learn that I had visited the laboratory of Paul Ehrlich, with whom Dale had worked before I was born. Sir Henry then began to reminisce most fascinatingly about his days with Ehrlich, but in German! Born gently reminded Dale of the German limitations of many of his table companions. Sir Henry commented that if Born, who speaks perfect German, was having difficulty, perhaps he (Dale) should speak English. Within a moment, however, when the old gentleman continued his wonderful anecdotes, he spoke again in German! What I would have given then (as well as on other great occasions) for a tape recorder!

colleagues. Now twenty years later and still working, signs of disintegration have not yet become evident.

5-Iododeoxyuridine (IUdR) was first synthesized by Prusoff and studied by him, others, and me; it was the first specific antiviral drug to be used in man. Its efficacy against corneal keratitis caused by herpes simplex virus had led to studies of other DNA virus–induced diseases. The remarkable efficacy in rabbits of parenteral therapy with IUdR on advanced dermal lesions caused by vaccinia virus led to attempts to treat supposedly terminal human smallpox infections in India. Only three moribund patients became available during an entire year (1965–1966) of observation by David Fedson, then a post-doctoral fellow of Calabresi and mine; by a curious coincidence these patients were admitted during my visit to Madras. Intravenous infusions with IUdR were initiated immediately; result: two of the three patients survived (not reported as a 67% cure rate!). Since the disease probably has now disappeared, it is unlikely that the possible value of IUdR in smallpox therapy will ever be known.

During the last eight of my Yale years, I was a research advisor to Upjohn. There the many good scientists and friends are too numerous to name here, with the exception of Earl Burbidge, one of my closest friends in medical school, Bob Heinle (both died several years ago), and Dave Weisblat, then director of research and development. About Charles G. (Chuck) Smith, Upjohn's then director of biochemical research, much more will be said below.

Only three times prior to 1967 did I even consider offers of positions other than that at Yale: two medical deanships (one also a vice-presidency)[8] and one as vice-president for research and development at a pharmaceutical company other than Squibb. None of these appealed to me, however.

SQUIBB YEARS (1967–1974)

As indicated previously, throughout the years at Yale I had had many contacts with scientists at Squibb, and they had supported Yale's Squibb Fellows for fourteen years.

During the years subsequent to the discovery and development of the fluorocorticoids by Gus Fried and other Squibb scientists, however, Squibb had

[8]A memorable incident occurred during an interview for one of these positions: A rather distinguished surgical specialist on the search committee asked, "Dr. Welch, where do you think cardiovascular surgery is going in the next ten years?" My reply, as Paul Calabresi reminded me, was, "That's for you to tell me, and, should I accept this position, for me to help you get there." After a brief pause, I continued, "And if you cannot conceive where it should be, it will soon be time for me to appoint a new Chief of Cardiovascular Surgery." According to Paul, this philosophy, which he had observed during our years at Yale, has become a modus operandi for him and others of my colleagues.

made few contributions to drug discovery. Furthermore, with devastating impact on both morale and productivity, E. R. Squibb & Sons, Inc. had been acquired by the Mathieson Chemical Company, and the latter in turn by the Olin Corporation. In 1967 Squibb research and development was floundering. Then, thanks to the genius of a vice president of Olin then in charge of the E. R. Squibb Division, Richard Furlaud, real vision was introduced to the company. When first approached by Mr. Furlaud, I had no desire to leave Yale; in fact, with an endowed chair (the Eugene Higgins Professorship), it had been agreed at last that after fourteen years I would relinquish the chairmanship and return to my laboratory full-time. Nevertheless, with Mr. Furlaud's assurance that Squibb would shortly be a separate entity again (as indeed it became by a complicated separation from Olin), the challenge to try something very different became irresistible. Accordingly, in 1967 I became vice president for research and development and the director of the Squibb Institute for Medical Research. My first major act was to recruit Chuck Smith from Upjohn, initially as associate director. In 1970 he became a vice president. In 1969, another exceptional man, Dennis Fill, became president of E. R. Squibb & Sons, and Mr. Furlaud took on higher responsibilities. My second major act was to accept the resignation of the then head of pharmacology. John Vane became a senior consultant in pharmacology (three one-week visits annually). In due course, Zola Horovitz was promoted from within to head the department of pharmacology; later he became an associate director and a vice president.

Turning research around was not exactly an easy job for us. Company earnings then did not permit any major new research programs to be launched, except when ongoing programs were terminated. Initially, despite the very complex problems involved in increasing the yield of penicillin, further reducing its cost, and seeking better semi-synthetic derivatives of it, we had few other projects. Great improvements in producing penicillin were accomplished, and a valuable cyclohexadiene derivative of penicillin was developed. With great difficultics we entered the cephalosporin field and developed a new drug, cephradine. Effective new corticosteroids were created to replace those soon to be lost by the expiration of patents. These developments had salutary effects on earnings and therefore on the research and development budget. In addition, we made major efforts in the field of β blockers (β-adrenergic receptor-blocking agents), despite the then antipathy of the Food and Drug Administration toward such valuable drugs. As a result, a major entry into the field was later developed.

At last, however, the long-awaited hot lead appeared and we began research that could genuinely be termed basic. Earlier studies by Professor Rocha e Silva in Brazil had shown that the venom of a poisonous local snake, *Bothrops jararaca,* incubated with plasma led to the formation of a vasodilator polypeptide, bradykinin. Another Brazilian worker, Sergio Ferreira, observed

that the venom also contained a factor that potentiated the effects of bradykinin; this was later shown to be the result of inhibition of an enzyme that rapidly inactivates bradykinin. Vane had suspected that this bradykininase might be the same enzyme that activates the polypeptide angiotensin I. (The latter substance, then suspected to be involved in renal hypertension, causes no effect on blood pressure until it is enzymically converted to angiotensin II, the most powerful vasoconstrictor known.) In Vane's lab, Mick Bakhle found that the peptide in the snake venom that inhibited bradykininase was also a powerful inhibitor of the angiotensin-converting enzyme (ACE). ACE catalyzes the removal of two terminal amino acids from both bradykinin and angiotensin I; it was later obtained in a homogeneous state by another good friend, Ervin Erdös, at the University of Texas, Dallas. The inhibitor isolated from the venom by Ferreira and Greene was a pentapeptide, while another potent inhibitory peptide, isolated at Squibb, was a nonapeptide. Management's lack of enthusiasm for research in this area was understandable, when one considers that the peptide inhibitors of course were impracticable as drugs. Indeed, it had not even been firmly established that so-called renal hypertension could be explained entirely by the release of the enzyme renin from hypoxic kidneys, with the final hypertensive state being caused by angiotensin II. To validate this concept required a major gamble. Despite the cost and the difficulties of synthesizing the inhibitory peptide in gram-quantities, I decided to go ahead despite a reluctant management; hence, Dr. Miguel Ondetti, an excellent protein chemist, and Dr. David Cushman, an enzymologist and pharmacologist, continued their now well-known studies. To make a very long story short, their colleagues established that the parenterally administered synthetic nonapeptide could prevent a rise in blood pressure from being caused by the intravenous injection of angiotensin I. Furthermore, studies in patients with malignant hypertension showed that the nonapeptide given intravenously could lead to a normotensive state, without evidence that accumulations of angiotensin I or the plasma precursor or renin in themselves were deleterious. Whereas I had reacted with enthusiasm to the potential for new drug discovery, the then president of the Squibb Corporation (neither Dennis Fill nor Richard Furlaud) could only understand the impracticality of the nonapeptide as a drug. The entire program was regarded as a costly exercise in futility. He ridiculed the idea that the concept of the renin cascade had indeed been validated, and rejected the potential importance, if hypertension was to be attacked rationally, of a key enzyme to inhibit having been identified. Indeed, I was told that the major effort to develop a new and practicable inhibitor of the converting enzyme should be terminated. This, I must state, I refused to do—termination of Welch would have to come first! Fortunately for what was to come, that did not happen. The brilliant work of Ondetti & Cushman continued; they eventually determined the essential inhibitory features and synthesized a modified

dipeptide with oral activity! By this time, however, my mandatory retirement at 65 (actually 65.98 years) had occurred. In due course, the then president also left the corporation for reasons other than age and the outstanding Mr. Fill was persuaded by the chairman to become president of the entire Squibb Corporation.

In the meantime, angiotensin II had been shown to be much more than a vasoconstrictor; e.g. it stimulates the secretion of aldosterone and thus affects the retention of both sodium ions and fluid. The ultimate drug, termed captopril and now marketed world-wide, is a modified dipeptide of L-cysteine (free SH) and L-proline. A methyl group adjacent to the imid-linkage renders the compound insusceptible to attack by peptidases; hence, it is orally active. It is used not only in the control of malignant, but also essential, hypertension. In addition, captopril is efficacious (for reasons not yet fully understood) in the therapy of congestive heart failure, while other potential activities (as well as promising new ACE inhibitors), are under investigation, not only by Squibb, but also by other companies.

I like to believe that my approximately 7.5 years as director (or president) of the Squibb Institute for Medical Research did help to turn the company upward. In addition to challenges, headaches, and some successes, Squibb gave me wonderful opportunities for scientific edification as well as for travel. Often my wife was able to accompany me. Frequent trips to the research laboratories of Squibb-Germany (Regensburg) were essential, as were trips to London and Liverpool for pharmaceutical research and to Ireland for production, while for other reasons I traveled to Australia, Austria, Belgium, China, Czechoslovakia, Denmark, Finland, France, Greece, Hawaii, Holland, Hong Kong, Hungary, Italy, Japan, Mexico, Nigeria, Sardinia, Sweden, and Switzerland. These and personal trips to Alaska, the Bahamas, Brazil, East Germany, Egypt, India, Portugal, Puerto Rico, Russia, and Spain bestowed insights that could not have been gained in any other way.

Late in 1974, Chuck Smith, a fine executive and innovative scientist who remains our close friend (as does his wife, Angie), also found the previous president intolerable, and six weeks after Smith's promotion to the presidency of the Squibb Institute for Medical Research, he left the corporation. Chuck is now an executive vice president of Revlon with responsibilities for research and development in such component health-care companies as USV Pharmaceuticals, Armour, and many other subsidiaries. Among my other colleagues at Squibb were also many good friends (some now deceased). I think particularly of Oskar Wintersteiner, Helmut Cords, Naomi Taylor, George Donat, Peter Koerber, Fred Wiselogle, Jack Bernstein, Pat Diassi, Jim Knill, Frank Weisenborn, Bill Brown, Zola Horovitz, Miguel Ondetti, and many others.

Now, ten years later, the Squibb Institute is a very different organization than

it was and I know but little about it. A period of my life, which in a great many ways was both exciting and memorable, regretfully came to an end. I am "gone, but not forgotten," or forgotten—I know not which.

ST. JUDE YEARS (1975–1983)

Retirement not being an attractive prospect, I accepted an offer from an outstanding institution, St. Jude Children's Research Hospital in Memphis, on whose board of scientific advisors I had served for three earlier years. My goal was to organize a new Division of Biochemical and Clinical Pharmacology. Many things had changed since my last visit in 1972: a new director, Alvin M. Mauer, MD, had replaced Don Pinkel, of whom I had been fond; a new seven-story building was due to open within three months (the new division was to occupy most of the third floor), while an important change for me was a return to cancer research, none having been possible at Squibb. Indeed, a three-month period in early 1975 offered an excellent opportunity to bore into the two then new superb monographs edited by Alan Sartorelli and David Johns. These massive handbooks, which I had actually commissioned as a senior editor of the handbook series, could not have appeared at a more appropriate time if I had designed it that way. I could afford time for planning as well as for recruiting, particularly in the area of medicinal organic chemistry, which I regarded as a mandatory development for the new division. In this area, I was joined as a full member by an outstanding man, Josef Nemec, whom I lured from the Squibb Institute for Medical Research, where I had known him well. Another chemist joined us, T. L. Chwang, who had worked for several years with Charles Heidelberger, while Bill Beck, who had done his post-doctoral work with Van Canellakis at Yale, came from the University of Southern California. Nahed Ahmed became my research associate; her post-doctoral training with Nicholas Bachur at the Baltimore branch of the NCI had qualified her highly. I began studies of the activity of uridine-cytidine kinase in human colorectal adenocarcinomas. Other studies of this enzyme led to the discovery, with Alan Paterson and colleagues at Alberta, that despite the apparent deletion of this kinase activity from certain 3-deazauridine-resistant mutants of a human B-lymphoblast, their proliferation in culture remained quite sensitive to inhibition by either 6-azauridine or 5-azacytidine (16). We suggested that another nucleoside-phosphorylating enzyme is present in such mutants; my assistants and I have now confirmed and extended this hypothesis (17) using a new method for quantifying acidic nucleosides (18). Judith Belt, a post-doctoral trainee of Efraim Racker, and I found that only the undissociated portion of 6-azauridine (pKa ~6.7), at pH 7.4, is transported by the process of facilitated diffusion (19).

Two post-doctoral fellows from the Chester Beatty, Drs. Janet and Peter Houghton, came to St. Jude after we helped them to immigrate. This was

done with almost incredible difficulties, which were finally resolved only with the help of Senator Baker. In addition to those named, four scientists already at St. Jude continued as effective members of the division. These were DeWayne Roberts, a biochemical pharmacologist; Thomas L. Avery, an experienced experimental chemotherapist and colleague with whom I worked very closely and with much friendship; Arnold Fridland, a very competent enzymologist; and Thomas Brent, a specialist in the mechanisms of DNA damage and its enzymic repair.

In 1980, my five-year appointment as member and chairman of the Division of Biochemical and Clinical Pharmacology was extended for a year to enable a search committee and the director to select Raymond L. Blakley to succeed me as chairman. Blakley formerly was professor of biochemistry in the University of Iowa School of Medicine. I became member-emeritus and once again a bench scientist at 72. The subsequent two years were among the happiest of my life, although fifty-hour weeks in the laboratory with two splendid assistants, Jim Panahi, BS, and Glen Germain, MS, gave me little time for my personal life or to write papers.

During my continued studies of resistance to 3-deazauridine in both B- and T-human lymphoblastoid cells, I made the unexpected observation that the cytosolic uridine-cytidine kinase activity is not deleted in CEM(T) cells; indeed, in the parent cells that enzyme has no affinity for the cytotoxic nucleoside. Thus was uncovered a hitherto unrecognized enzyme associated with the nuclei of these (and other) cells that catalyzes the phosphorylation of 3-deazauridine and the activity of which is greatly diminished in the drug-resistant mutants. This enzyme activity can either complement or supplant that of the classical cytosolic enzyme.

At this stage (1983), however, I was approached by three government agencies (the EPA, the FDA, and the NCI), and I decided to accept an offer from the National Cancer Institute. We moved from a lovely home in Memphis to a condominium in Chevy Chase, a suburb of Washington, DC, so that I could start still another career just prior to turning 75.

Before leaving the subject of Memphis and St. Jude, I want to present a few impressions of our eight and a half years there. Memphis provided a rather different atmosphere from those of New Haven and Princeton, particularly for Erika, whose almost unaccented British English, acquired in Prague, had already been transformed to American, although not mid-South American. This new learning period was helped greatly by her linguistic talents (she was formerly a scientific translator). The people of Memphis were warm and friendly, and the city progressed remarkably during our stay there. Today, any individual can and should be able to live happily in Memphis, as we did (with the aid of air-conditioning and a swimming pool!). We have left many dear friends there.

St. Jude Hospital only opened in 1962, and in 1975 it was almost incredible

to see what had happened there in only thirteen years. In fact, from our arrival until our departure, the continued growth of the hospital was evident. It is a splendid children's hospital, which provides superb (and completely free) medical care to children with all forms of neoplastic disease. I have only the highest praise for the Board of Governors and Danny Thomas for their dedication and their steadily more efficient fund-raising, especially for the clinical activities at the hospital. St. Jude is now as much the pride of Memphis as is the home of Elvis Presley.

The clinical research accomplishments of St. Jude, e.g. the introduction of cranio-spinal irradiation, which increased the apparent cures in acute lymphoblastic leukemia by tenfold (to now more than 50% of the patients), was a major breakthrough. This occurred during the tenure of Dr. Donald Pinkel, the first medical director, in collaboration with Dr. Joseph Simone. The second director, who departed in 1983, was a dedicated pediatric hematologist and oncologist who made every effort to help St. Jude grow and burnish its image brightly. He had little ability to communicate scientifically, however, or to understand the importance of molecular developments. Thus he could not fully appreciate the reasonable needs for the encouragement and financial support of basic scientists, who are developing many new methods for the treatment of cancer.

St. Jude needs many improvements, and the new director, Joseph Simone, a very experienced oncologist and pediatrician, could institute them with strong advisors in basic areas and with the support of the Board of Governors. The basic science divisions not only need to be more strongly supported financially, they also need to be better oriented toward goals more sensible in terms of modern chemotherapy and immunotherapy (for example, the roles of oncogenes and the great promise of monoclonal antibodies). I am and will continue to be an ardent supporter of the institution, and of the best scientists within it. Finally, I am personally very grateful, despite the very difficult and traumatic struggles we experienced at times, for the many courtesies my colleagues there extended to me. In addition to those in our own division, already mentioned, such splendid colleagues as Charles Pratt, George Cheung, the discoverer of calmodulin, Dave Kingsbury, George Marten, Gaston Rivera, and their respective wives, as well as Dolores Anderson, are among those whom I won't forget as are other wonderful Memphians, especially Dr. Gordon and Nancy Mathes, Dr. Eric and Marie Louise Muirhead, and Dr. Henry and Rosalie Rudner.

One other memorable group in Memphis is the Memphis Medical Seminar, of which I was a member (and once the president). It is largely composed of investigative clinicians, for example, Hall Tacket, our splendid internist; Eric Muirhead, an outstanding investigator and pathologist; and Irv Fleming, a dedicated surgeon. These and all the other members are friends whom I will always remember.

NATIONAL CANCER INSTITUTE (NCI) (1983–)

In October 1983, I joined the NCI and assumed the rather remarkable title of cancer expert, attached initially to the Office of the Chief of the Drug Evaluation Branch (Dr. John Venditti), Developmental Therapeutics Program, Division of Cancer Treatment. The director of this division, Bruce A. Chabner, MD, is a splendid basic scientist and clinical oncologist as well as a fine administrator. My initial responsibility became the coordination of those National Cooperative Drug Discovery Groups (NCDDG) that were launched in mid-1984. These groups include cooperating academic institutions and in some cases industrial organizations. The admirable and I hope attainable goal of these groups is the discovery and development of essentially new approaches to the treatment of human neoplastic diseases, including new entities and new techniques. For the NCDDG, I function as an intellectual participant and facilitator, not as a director. In the meantime, I have become the acting deputy director of the Division of Cancer Treatment, a relatively huge organization whose total budget, intramural and extramural, is about $318,000,000.

During a long series of careers spanning forty-four years of involvements with the administration of four departments of pharmacology and the research and development activities of two pharmaceutical organizations, inevitably I have gained considerable experience and I hope some wisdom and judgment. If so, my presumably terminal contributions may be of value in the multifaceted areas of research and development of the Division of Cancer Treatment in the fields of biochemical pharmacology, chemotherapy, and drug development, the fields with which I have been deeply concerned for so many years.

Certainly, I am now making many new acquaintances who also will be ne'er forgot as long as the gods see fit to help me, not only to be useful, but also to continue to have a time for remembering.

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