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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.