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TWO PHARMACOLOGICAL TRADITIONS: NOTES FROM EXPERIENCE

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I was born at the end of the Manchu Dynasty, a period of national decay. The Empress Dowager had usurped the power of the government and, with money appropriated to build a navy for China, she constructed a luxurious summer palace. Japan and western nations took advantage of Chinese weakness by establishing wide interests for themselves in China. Desirous of expelling foreign influence, the Empress Dowager encouraged a group of civilians to murder foreign diplomats and Christians, later known as the Boxer Rebellion of 1900.

When I was 5 years old, my parents hired a tutor for me to memorize and pronounce individual characters written on sheets of paper about two inches square. It was merely for recognition of the words, not their meaning. After about one hundred characters were committed to memory, I was given a book of surnames (about one hundred in number). This was followed by four books and five classics. Slowly I was taught the meaning of sentences, starting with a collection of Confucius's teachings. I began to learn writing and composition with the hope of passing literary examinations, which unfortunately were abolished in 1908. This led me to enter an organized public school, reading elementary books of history, geography, and arithmetic. In 1916 I graduated from a middle school, and by competitive examination, was accepted to the third year class of Tsing Hua College of Peking. This school had been established by the United States in 1908 with a portion of the "Boxer Indemnity." Most of the faculty members were American scholars. They prepared Chinese boys to continue their

education in American universities. I was thus exposed to the English language for the first time. I graduated in 1918 and joined the junior class at the University of Wisconsin.

It took me a short time to appreciate the generosity and kindness of my teachers and schoolmates. One of my classmates tried to help me improve my English by introducing me to a debating society (Hesperia), which also helped me gain confidence in speaking before an audience. To encourage my interest in Chinese materia medica, Edward Kremers had me steam distill 300 pounds of leaves and 200 pounds of twigs of *Cinnamomum cassia* that were imported from China. He asked me to obtain the cassia oils, but he published the paper entirely under my name (1). After I received a BS in pharmacy, I transferred to the School of Medicine. For personal reasons I completed only the first two years of medicine. Then I earned a PhD after graduate studies with Harold C. Bradley and Walter J. Meek in biochemistry and physiology.

In 1923 I returned to China, and through Bradley's recommendation to Carl F. Schmidt, I became a member of the pharmacology department of Peking Union Medical College (PUMC) and its hospital. This school was financially supported by the China Medical Board of the Rockefeller Foundation. In addition to teaching, I continued my study of Chinese herbal medicine. My uncle Zao-Nan Chou told me of the important properties of Ma Huang as recorded in Chinese dispensaries. Without a literature search, I purchased a sample of Ma Huang from a Chinese drug shop, and applied the phytochemical techniques I learned from Kremers' laboratory at Wisconsin. By use of immiscible solvents, I succeeded in isolating an alkaloid in crystalline form within a short time. Fortunately I found an early reference of Nagajosi Nagai (2, 3) in which he had named the base *ephedrine* in 1887. Stapf (4) of Kew Gardens gave the Linnean name of *Ephedra sinica* to Ma Huang.

Carl F. Schmidt directed the pharmacological investigation of ephedrine with his elegant techniques, and revised the manuscript we were preparing repeatedly, but refused to accept senior authorship (5-7). Our results were analogous to those of sympathomimetic amines of Barger & Dale (8). As compared with epinephrine, ephedrine has the advantage of oral effectiveness and long duration of action. Thus, clinically ephedrine is useful in allergic diseases, bronchial asthma, and hay fever and in spinal anesthesia, where it prevents the fall of blood pressure. Its mechanism of action has been thoroughly reviewed by Aviado (9). It has both α - and β -adrenergic effects. Its protracted pressor action is due to the inhibition of monoamine oxidase, and its tachyphylaxis following repeated injections of small doses may be the result of the depletion of norepinephrine storage.

C. F. Schmidt was my tutor for only one year because he had to return to the University of Pennsylvania to continue teaching and research in the Department of Pharmacology. My contract with PUMC was completed after the second year, when our Chairman, Bernard E. Read, returned from Yale University. At that time, in 1925, Arthur S. Loevenhart invited me to become an associate of his Department of Pharmacology at the University of Wisconsin. This year turned out to be a busy period: I completed credits for the third year of medical school; W. J. Meek assisted me in working on circulatory effects of ephedrine; William S. Middleton allowed me to serve as an intern while doing clinical work on ephedrine; and Loevenhart arranged through John J. Abel for me to finish my fourth year of medicine at Johns Hopkins University School of Medicine. After all the credits were approved in the Dean's Office, I was fortunate to graduate in 1927. Upon Eugene M. K. Geiling's recommendation Abel appointed me as an associate for two years. My teaching duties were light, for lectures were divided among the staff members, and the laboratory periods were assigned to few of us. Our contact with Abel was best at lunch hour in the laboratory because his wide knowledge often led to discussion of various subjects which benefited us all.

In 1912 Abel & Macht (10) obtained two crystalline substances, bufagin and epinephrine, from the skin secretion of a tropical toad *Bufo aqua*. It was my good fortune to discuss with him my intention to study a Chinese toad venom, Ch'an Su, used in Chinese materia medica. With a grant from the American Medical Association, I purchased 1729 kg from a Chinese drugstore in Peking. This commercial preparation of toad venom comes in round, hard black discs, 7 to 8.6 cm in diameter. Hans Jensen in the same laboratory joined me in the chemical investigation. We succeeded in isolating epinephrine, cholesterol, and two digitalis-like products later known as cinobufagin and cinobufotoxin (11).

In 1929 Eli Lilly and Co. wrote to Abel offering me Directorship of Pharmacologic Research. J. K. Lilly, Sr., and Eli Lilly, father and son, told me in an interview in Indianapolis that they would give me complete freedom of research, particularly in Chinese materia medica by buying crude herbs through their Shanghai Branch. Abel and I both realized the disadvantage of accepting the offer, which was that permanent employees of drug firms were not allowed membership in the American Society for Pharmacology and Experimental Therapeutics (ASPET). I had been elected a member of ASPET in 1925, and with a heavy heart, I resigned from membership in 1929. Abel again came to my rescue by nominating me to the American Physiological Society (APS) in 1929. By so doing, I could request transferring my paper to ASPET in its annual meetings. Indeed I

presented a paper to ASPET every year. No rejection was exercised by either society in those days. It was not until 1942 that my membership was reinstated.

Upon my arrival in Indianapolis in 1929, I took full advantage of the opportunities at Eli Lilly and Co. to investigate Chinese materia medica. My work on the Chinese toad venom was continued and extended to 16 species of toads (*Bufo*) (12) collected from different parts of the world. By elegant methods of isolation as employed by T. Reichstein of the Institute of Organic Chemistry and K. Meyer of the Pharmaceutical Institute of the University of Basle, Switzerland, a single toad such as *B. gargarizans* can yield 25 derivatives of bufadienolide and cardenolide. We determined their potencies, each in 8–10 etherized cats. Some of the members, arenobufagin and bufotalidin, are even more potent than ouabain. In our work we expressed the “parotid” glands of 13,800 live toads. We found that the cat is the most sensitive laboratory animal to assess the digitalis-like activity of each pure compound. As with mammalian epinephrine, one can detect a trace of norepinephrine, 2–4% (13) from the Chinese toad epinephrine. While each *Bufo* species biosynthesizes its own bufadienolides and occasionally cardenolides, the larva of North American monarch butterfly and a North African grasshopper consume a glycoside, calactin, of a species of milkweed family, Asclepiadaceae (14).

With the collaboration of T. Reichstein of Basle, R. C. Elderfield of Ann Arbor, and several other organic chemists, we extended our investigation to many natural glycosides, aglycones, synthetic esters and glycosides, and Erythrophleum alkaloids—a total of 463 principles. In order to assay their cardiotonic activity we used 5100 cats. We concentrated on structure-activity relationships. Our clinical work on cinobufagin, thevetin, and acetylstrophanthidin was focused on their possible utility. Toward the end of 30 years, Harry Gold became interested in comparing a few of our compounds with digitoxin, ouabain, and digoxin. Economically, the last three glycosides can easily compete with the galenic preparations.

In my 34 years at Eli Lilly and Co., the list of Chinese herbs I selected was generously secured by the administration. γ -Dichroine, having a Q value of 148 (15) against *Plasmodium lophurae* in ducklings, almost became an important antimalarial drug. Unfortunately, it causes vomiting and hydropic degeneration in the liver of experimental animals. It seems very difficult to develop a superior product from Chinese herbs—much like Henry Wagner’s recent experience (16), “Screening these herbal medicines is a little like drilling for oil.” More successful results may be often achieved by collaborating with organic chemists and other specialists (17). Much aid was received from my wife. For example, she thought of using isopropyl alcohol to increase the yield of crystalline thevetin. No wonder Kahn (18)

mentioned her contributions in the laboratory on the eve of our Golden Anniversary.

In 1937 I was invited by Indiana University School of Medicine to attend Friday evening seminars, give a few lectures in Pharmacology, and occupy space for research, particularly after my retirement at Lilly Laboratories. I surely appreciate the privilege of sharing the finest facilities in the large University now covering seven campuses in addition to the Indianapolis and Bloomington Centers.

In 1947 I was elected Treasurer of the ASPET. After five years of service ASPET nominated me President-Elect. Automatically, I became President next year and by rotation I served as the Federation President in 1953–1954. Being stimulated by the confidence of ASPET Council and Membership, I attempted to initiate certain projects for the good of the Society and the Federation.

The first item was the annual J. J. Abel Award offered by Eli Lilly and Co. to a young pharmacologist not older than 36 years of age, entirely administered by ASPET. At the spring meeting of 1980 the thirty-fourth candidate received this award.

At the Federation Meeting I asked Milton O. Lee, the Executive Secretary, for duties other than presiding at board meetings and arrangement of the Tuesday evening program. He lost no time in saying the Federation needed a permanent headquarters. He and I surveyed the Washington DC area and were attracted to a large private property, Hawley Estate, in Bethesda, near the National Institutes of Health and the National Naval Research Institute. The house and land have been thoroughly described by Lee (19). William F. Hamilton and Lee named it Beaumont House, after the US Army Medical Surgeon (20). To accelerate the interest payments, two thirds of the land was sold off. A new building named after Milton O. Lee was completed and dedicated on October 12, 1962.

Another assignment was the publication of the first volume of ASPET History (21). W. DeB MacNider was our first historian, but resigned because of illness in 1951. E. M. K. Geiling immediately succeeded him, but as a perfectionist he could not finish the work in 16 years. Harold C. Hodge, then President of ASPET, appointed me as the third historian in 1967. It was with the assistance of Allan D. Bass, Ellsworth B. Cook, Robert M. Featherstone, Maurice H. Seevers, and access to the minutes of all society secretaries that the volume was published in two years.

In my humble life, I am grateful for the recognition I have received for my contributions. The China Foundation Prize came from the Mainland in 1927. An honorary ScD was conferred on me by Philadelphia College of Pharmacy (1946), University of Wisconsin (1952), and Indiana-Purdue University (1971). The Remington Honor Medal, 1965; honorary member-

ship in Finnish Pharmacological Society, 1975; and honorary presidency of International Union of Pharmacology, 1972, were all received with appreciation. I have been assigned some government responsibilities, such as preparing Panel Report to the President (22) and serving as State Department Delegate to the First General Assembly of International Union of Physiological Sciences at Brussels, 1956.

The past five decades in the pharmaceutical and chemical industries have seen tremendous gains in the development of effective research products. I am happy to have had a chance to contribute to these advances.

ACKNOWLEDGMENTS

I thank Professor Henry R. Besch, Jr. for his editorial assistance and Ms. Betty Rode, secretary, for her careful typing.

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