

# SIDELIGHTS OF AMERICAN PHARMACOLOGY

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Before anyone gets any further into this dissertation, it is important that he be disabused as to the nature of its content. If the title of this chapter happened to be "Highlights of American Pharmacology," there would be little disagreement as to what it should attempt to cover. It should begin with John Leigh's "An Experimental Inquiry into the Properties of Opium and its Effects on Living Subjects," published in 1786, which may be regarded as the first piece of experimental pharmacology done in America. There would be mention of the discovery of ether anesthesia and of other anesthetics subsequently, of the discovery of many hormones such as epinephrine and insulin, of the isolation of many active principles from plants such as ephedrine, and so on. There would be brief biographical sketches of the pioneers in American Pharmacology such as Horatio Wood, John Jacob Abel, Reid Hunt, Torald Sollmann, A. N. Richards, Yandell Henderson, and many others.

Merely hinting, as I have, as to what a chapter on The Highlights of American Pharmacology should include, demonstrates that such a title would warrant a volume rather than a chapter. My assignment is much more modest. It is to preface a volume of serious work without being overly serious itself. It is to call attention to some of the minor attributes of pharmacology and pharmacologists. It is to reminisce, reflect, and, perchance, amuse, as one contemplates the evolution of this discipline in America.

The first pharmacologist that I became acquainted with was S. A. Mathews. I heard about him before I entered medical school and it was an amusing story. He had been downtown to a meeting of the Institute of Medicine of Chicago. He returned to the Midway via the elevated railroad, getting off at 55th Street to walk diagonally across Washington Park, as was then customary. Before continuing with the story, I should explain that Mathews had a number of eccentricities. Besides being quite absent-minded, he talked out loud to himself and had a peculiar festinating gait. He leaned so far forward, that, to catch up with his center of gravity, he had to intersperse a number of trotting steps between periods of walking ones. He had been inspired by some of the discussion at the meeting, and, as he crossed the park, he was thinking of two dogs upon which he had been conducting some studies. "Yes sir," he said, "I think I'll kill those two and examine their livers for glycogen."

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As it happened, there were two young girls directly ahead of him, who overheard him and turned around to see a snaggle-toothed old man trotting after them. Alarmed that they were the intended victims of some maniac, they raced across the park to the police station. There were then some embarrassing hours before Mathews' colleagues at the University could assure the girls and the officers as to this pharmacologist's identity and harmlessness.

There is an additional story about Mathews that needs to be told in order to illuminate the reference to him as a "snaggle-toothed old man." When the great influenza pandemic appeared during World War I, it soon became evident that one of the major complications of this disease was the development of a pleural empyema. There then arose a great controversy as to the relative merits of draining this pus by means of a rib resection, which would necessitate a collapse of the lung on that side, or of draining it by means of a closed system of suction which did not. Dean Lewis, a professor of surgery on the Rush Medical College faculty, proposed to study this problem by some controlled experiments on dogs. He arranged to work with Mathews, and they secured a variety of organisms from the bacteriology laboratory with which to inoculate the chest cavities of a number of dogs. But none of the cultures induced a dependable empyema in their animals. Contemplating this problem one day, and, no doubt influenced by the fetid odor coming from Mathews' mouth (which had been innocent for many years of any acquaintance with dentist or toothbrush), Lewis suggested that Mathews should spit into the dogs' chest cavities. According to the story, this produced an empyema which no method of treatment could mitigate.

I tell this story about Mathews for a definite purpose. At the time of this story, almost none of the medical schools in America provided laboratories for experimental work on animals in the various clinical departments. It was necessary for a clinician to arrange a liaison with some one of the preclinical departments, usually physiology or pharmacology, in order to conduct some animal experiments. Consequently, in reviewing the bibliographies of many of our earlier pharmacologists, one will find many titles of a strictly clinical character.

One of the important sidelights of American Pharmacology has to do with the textbooks on this subject. Until the recent rapid expansion in the number of pharmacologists working for industry, government, or research institute, the overwhelming majority of pharmacologists were teachers in medical schools, dental schools, pharmacy schools, and nursing schools. Correspondingly, the texts available for their use presented an important consideration. When I first became acquainted with pharmacology at the University of Chicago, the texts used there were those of A. R. Cushny and of Meyer & Gottlieb. While Cushny did serve for a short period at the University of Michigan, and it was Yandell Henderson's translation of the

Meyer & Gottlieb text that was used, neither book could be called American. How different it is now. There are a dozen or more excellent American texts of which we can be justly proud, and a number of these are being used in other countries.

Since it is virtually the only one of its kind, I would like to mention Jackson's book on experimental pharmacology by name. Having been a teacher during the depression era, when the budgets for equipment were conspicuous for their anemia, I found Jackson's book to be an invaluable guide to the mechanic, technician, and the do-it-yourself teacher.

An important sidelight of American Pharmacology deals with the United States Pharmacopeia, which is the oldest national pharmacopeia of a modern type in the world. Founded by physicians under the leadership of Dr. Lyman Spalding in 1820, it has been supported by the leaders of the medical and pharmaceutical professions ever since. When men from the various professions came to devote themselves to those aspects of drugs and their actions which earned them the designation of pharmacologists, they were frequently drafted for service in the preparation and revision of this important work. And, when the Food and Drug Act was passed in 1906, adopting the standards of the United States Pharmacopeia as standards to be enforced under the Act, the importance of this work was greatly enhanced. The impetus which this gave to the study of many important pharmacological problems such as biological assay, etc., cannot be overemphasized, since there was now the possibility that some of these pharmacological procedures might be challenged in the courts.

Accepting the risk of omitting some names which deserve to be included, I would like to list Horatio Wood, Reid Hunt, Charles Edmunds, Cary Eggleston, Walter Bastedo, Arthur DeGraff, John Krantz, Walter Modell, Erwin Nelson, Soma Weiss, William Salter, E. K. Marshall, Henry Barbour, M. S. Dooley, Harry Gold, Windsor Cutting, Arthur Grollman, Ewart Swinyard, Joseph Jerome, and Lloyd Miller as being individuals who have given much service to this task. I hope that those I have neglected to mention are aware of the dimming of the memory which characterizes the aging process. Having served for 25 years on the Revision Committee, I can testify to the valuable experience such service provides, as well as to the valued friendships which it has nourished.

A somewhat similar sidelight on American Pharmacology is provided by the Council on Drugs of the American Medical Association, which began its career as the Council on Pharmacy and Chemistry. The Council, consisting of physicians, pharmacologists, and allied scientists, by its regular publication of *New and Nonofficial Remedies*, *Useful Drugs*, *New Drugs*, adverse drug reaction reports, and numerous related reports as to new drugs or new findings with respect to old drugs, has performed an extremely valuable service to the medical and allied professions. The Council was under the guidance of Torald Sollmann for so many years, that, de-

spite its varied composition, American Pharmacology can claim a major share of the credit rightly coming to this agency.

Additional sidelights on American Pharmacology are provided by the establishment of Poison Control centers, the Commission on Drug Safety, the Pharmacology Study Section of the National Institutes of Health, and many other agencies which utilize the services of pharmacologists in a more or less specialized manner. But there seems no need to call the entire roll to validate the claim that American Pharmacology, although a junior discipline in years, has worked hard to earn the respect of its colleagues.

An important sidelight on American Pharmacology is the story of the relationship between academic pharmacologists and those employed by industry. When the American Society for Pharmacology and Experimental Therapeutics was first founded (as a sort of stepchild of the American Physiological Society), those regularly employed by industry were specifically barred from membership. They were thus branded as unclean, as being scientists with ulterior motives and feet of clay, as having sold their integrity for a mess of pottage. They could belong to the American Physiological Society and thus attend the meetings of the Federation Societies. Consequently, there were occasions when some of the most important papers in pharmacology were presented before the other Federation Societies. This was an embarrassment. In the 1930's an effort was made to rewrite the Constitution, making provision for "Associate Members," but this was violently opposed by some of the more prominent members as permitting these outcasts to "get one foot in the door."

The policy of excluding employees of industry may have had some apparent justification at its inception, but it soon became clear to many that it was a shortsighted and selfdefeating policy. Although Gruber's efforts to revise the Constitution failed at the time, they paved the way for later efforts. There is reason to believe that A. N. Richards may have been most instrumental in the reversal of the Society's position. When he announced that he was serving as official consultant to Merck, and when he was instrumental in bringing Hans Molitor over from Meyer's laboratory to take charge of the Merck pharmacology department, he succeeded in overcoming the fears and scruples of most of the members. As there were already "commercial" men of such unquestioned ability and unimpeachable integrity as K. K. Chen to point to, the bylaws were soon amended to permit membership to all qualified pharmacologists. Thus, this chapter in American Pharmacology has a happy ending. For my part, I am pleased to record that I have had many pleasant and rewarding contacts with the pharmacologists employed by industry, and am very grateful to those who gave me much valuable assistance while I was at Northwestern University.

I now come to a different category of sidelights with respect to American Pharmacology. Nearly all of the pharmacologists I came to know, admire, and respect, had a wonderful sense of humor. It may well be a pejor-

ative aspect to my task, but it would be shirking my responsibilities if I neglected this area of discussion.

For example, a sidelight of American Pharmacology consists of the witticisms and bon mots contributed by its members to the service of those who must lecture and teach on this subject. I now refer to unpublished items, and thus rely upon an unreliable memory for a record of these gems. I have forgotten completely all the "barbarisms" of Henry Barbour, and while the pungent profundities of Chauncey Leake which have been published are familiar, the unpublished ones have leaked away. Even "Moe" Seevers' graphic descriptions of his morphine-addicted monkeys grow dim. But I still recall how Paul Hanzlik concluded his presentation of the evidence for the prophylactic efficacy of bismuth against syphilis by stating that he had established a sound basis for that well-known aphorism "Bismuth before Pleasure"; and how Charles Edmunds concluded that gold could not be considered completely inert pharmacologically, because there was overwhelming evidence that it had a healing effect upon the itching palm. I have forgotten who the pharmacologist was who stated that a lecture on the pharmacology of alcohol would be one sort of treatise if the opening statement read: "Alcohol is an ethyl hydroxylated hydrocarbon which boils at 78.5 degrees C and freezes at -117.3 degrees C," and quite another sort if the opening statement were: "Alcohol is the distilled essence of ripened grain, born of soil mated with sunshine, flavored with the secrets of the flowers, and softened by the hand of time." I am inclined to accuse David Macht because he wrote such a fine treatise dealing with the pharmacology of alcohol as depicted in the Hebrew Bible, but I recognize a certain Omar Khayyam flavor also. I have but vague memories of Ross McIntyre's lecture on curare in which he described Claude Bernard's journey through the Amazon jungle with a retinue of retainers dragging a depolarized polar bear and even more vague memories of many other scintillating discourses. It is my belief that some of these gems would be remembered more readily if they were phrased in a catchy rhyme or set to a catchy tune. That is why I wrote my rhyme on Histamine, and many friends have told me that they were grateful to Kipling's pattern of versification for its assistance to the memory process.

In addition to the witticisms which have flavored pharmacology so well, there are assorted histrionics which have illuminated the scene. I am told that Carl Pfeiffer's demonstrations of the explosive hazards of various anesthetics cannot be excelled. Theodore Koppanyi's demonstration of postural apnea in the duck is a masterpiece not to be forgotten. Harvey Haag's performance of nailing his cigar to the lecture desk before turning to write something on the blackboard so that his students would not seize it and pass it around for all to enjoy, is not in the same category of course, but it deserves mention because it was a regular performance whenever he lectured about nicotine and tobacco. The graphic picture of "Pete" Geiling wad-

ing in his boots into a whale's carcass in order to chop out the pituitary glands should never be forgotten.

The death of homeopathy may be considered as a sidelight of American Pharmacology which does not reflect much credit upon professional pharmacologists. As may be recalled, homeopathy was a doctrinal discipline based upon two major doctrines. The first was *Similia Similibus Curantur* (like cures like) and will be considered no further. The second was to the effect that the therapeutic efficacy of a drug increased progressively as the dose was progressively decreased by dilution. In spite of the fact that the study of the dose-effect relationship of a drug is a major task for the pharmacologist, and that there was therefore a vast amount of well-controlled data with which to impugn this esoteric concept, there is little evidence that its death was materially hastened by the labors of the pharmacologist. There is, on the contrary, reason to believe that President Abraham Lincoln was more effective in this connection. The story goes that Lincoln, when considering an application from a homeopathic physician for a commission in the medical department of the army, and after having had homeopathy explained to him, said: "Well, I may not know much about medicine, but I know enough about farming to know that you cannot fertilize a farm with flatus. The application is denied."

There is another amusing example of an episode in American history bearing upon this pharmacological problem of dose-effect relationship. During the 1920's the United States undertook the great experiment of prohibition. This fostered considerable interest in the study of the pharmacology of alcohol since, as A. J. Carlson phrased it, the government had made the physician the only legal bootlegger by authorizing him to prescribe it for medicinal purposes. The upshot of these studies was that doctors were prescribing whiskey to stimulate gastric secretion, to cure anorexia, to relieve chronic bronchitis, to act as a sedative to the nervous system, and a vasodilator to the circulatory system and so on. But, and this is the intriguing pharmacological question, it was always prescribed in 16-ounce quantities because this was what the law permitted.

If it can be said that a highlight of American Pharmacology is a piece of research that has been conducted and published, perhaps it can be considered as a sidelight to mention some that have been conducted but not published. I am informed by one of my colleagues that an anatomist was greatly intrigued by the fact that, while there were occasional instances of dextrocardia and even situs inversus, the heart was almost always located on the left side. When he learned that epinephrine, which seemed to him to be the body's dominant hormone, was a levorotatory compound, he immediately jumped to the conclusion that this was the explanation. He asked his pharmacology consultant for some potent dextrorotatory compound in order to test his theory. Dextroamphetamine was made available. Some weeks later, the anatomist reported to the pharmacologist that he had injected a pregnant bitch daily throughout her pregnancy with dextroamph-

tamine, but that the bitch had finally delivered seven puppies, none of which had dextrocardia. "Ah," the pharmacologist rejoined, "but you're left-handed, and this influence, although subtle, could well vitiate the result. You should repeat the experiment with a right-handed assistant and, furthermore, it would be well also to administer some monoamine oxidizing agent which inhibits levorotatory compounds." To my knowledge, this more sophisticated experiment has not been conducted. There are wonderful things yet to be done!

I close this *mélange* on a more somber note. About the same time that I received the invitation to write something as to the sidelights of American Pharmacology, I received another letter. It was from a faculty committee assigned to make recommendations with respect to their pharmacology department. The department chairman was retiring and the question at issue was, should the names of some potential successors be presented, or should they recommend that the department of pharmacology be discontinued, its teaching and other functions being allocated to the junior staff men in physiology and biochemistry? Thus, at the same time that I was asked to consider the sidelights of American Pharmacology as a whole, I was also asked to contemplate the twilight of a pharmacology department at one of our major universities, which could well presage the twilight of American Pharmacology.

I shall not bother with my rather explosive rejoinder. The American Society for Pharmacology was formed as a sort of stepchild to the American Physiological Society and, to a considerable degree, American pharmacologists have been accorded the courtesies traditionally reserved for stepchildren. Since they use the same instruments and techniques common to the other biological scientists, there is no badge for the pharmacologist in the way that a microscope is a badge for a histologist. By the same token, a number of important contributions to pharmacology come from investigators who are not primarily pharmacologists. Consider, for example, du Vigneaud's work on the relationships between the chemical functional groups and the biological activities of the pituitary hormones for which he received the Nobel Prize.

The ill-defined zone of what comprises pharmacology is thus partially responsible for this stepchild situation. I would add other reasons. The chemist who isolates or synthesizes a new compound, and the clinician who first observes that it does something apparently useful, are placed in the role of brave and successful explorers. They also become promoters with respect to it. Even though they may have no financial interest at stake, there is an *ipso facto* stake as to credit and glory. The pharmacologist, on the other hand, often appears in the role of critic and skeptical judge. His labors as to its mechanism of action, fate in the body, factor of safety, and so on, frequently put him in the position of a jealous rival seeking to demean and degrade the discovery.

There is another reason. It is only recently that we have established

The John J. Abel Prize in Pharmacology and The Torald Sollmann Award in Pharmacology to recognize outstanding contributions in our area of study. There should be several more of these kinds of awards to help in this task of identification. It would not matter whether they took the form of walking canes, dinner plates, or loving cups, such as some of our sister societies favor, or amulets with some sort of cryptic significance to the healing arts. They would help to identify the type of "pharming" we are concerned with.

Thus I conclude with the hope that this portrayal of some of the sidelights of American Pharmacology (considered of course in conjunction with its more important "Highlights"), may help postpone the day when we are asked to contemplate its twilight.



# CONTENTS

SIDELIGHTS OF AMERICAN PHARMACOLOGY, <i>Carl A. Dragstedt</i> . . .	1
AZTEC PHARMACOLOGY, <i>E. C. del Pozo</i> . . . . .	9
RELATIONSHIPS BETWEEN CHEMICAL STRUCTURE AND BIOLOGICAL ACTIVITY, <i>Alfred Burger and Anilkumar P. Parulkar</i> . . . . .	19
CARDIOVASCULAR PHARMACOLOGY, <i>Francis J. Haddy and Jerry B. Scott</i> . . . . .	49
ELECTROLYTE AND MINERAL METABOLISM, <i>L. G. Welt, J. R. Sachs, and H. J. Gitelman</i> . . . . .	77
THROMBOLYTIC AGENTS, <i>Anthony P. Fletcher and Sol Sherry</i> . . .	89
AUTONOMIC NERVOUS SYSTEM: NEWER MECHANISMS OF ADRENERGIC BLOCKADE, <i>E. Muscholl</i> . . . . .	107
EFFECT OF DRUGS ON SMOOTH MUSCLE, <i>G. Burnstock and M. E. Holman</i> . . . . .	129
NONSTEROID ANTI-INFLAMMATORY AGENTS, <i>Charles A. Winter</i> . .	157
COMPARATIVE PHARMACOLOGY, <i>William G. Van der Kloot</i> . . . .	175
PERINATAL PHARMACOLOGY, <i>Alan K. Done</i> . . . . .	189
ANTIBACTERIAL CHEMOTHERAPY, <i>I. M. Rollo</i> . . . . .	209
ANTIVIRAL CHEMOTHERAPY, <i>Hans J. Eggers and Igor Tamm</i> . . .	231
DRUGS AND ATHEROSCLEROSIS, <i>Karoly G. Pinter and Theodore B. Van Itallie</i> . . . . .	251
RENAL PHARMACOLOGY, <i>John E. Baer and Karl H. Beyer</i> . . . .	261
TOXICOLOGY, <i>L. I. Medved and Ju. S. Kagan</i> . . . . .	293
ANTIBODIES OF ATOPY AND SERUM DISEASE IN MAN, <i>Mary Hewitt Loveless</i> . . . . .	309
DRUGS AND RESPIRATION, <i>Christian J. Lambertsen</i> . . . . .	327
ANESTHESIA, <i>Leroy D. Vandam</i> . . . . .	379
ON THE MODE OF ACTION OF LOCAL ANESTHETICS, <i>J. M. Ritchie and Paul Greengard</i> . . . . .	405
REVIEW OF REVIEWS, <i>Chauncey D. Leake</i> . . . . .	431
INDEXES . . . . .	445
AUTHOR INDEX . . . . .	445
SUBJECT INDEX . . . . .	471
CUMULATIVE INDEX OF CONTRIBUTING AUTHORS, VOLUMES 2 TO 6 .	492
CUMULATIVE INDEX OF CHAPTER TITLES, VOLUMES 2 TO 6 . . .	493