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# WHY AN ANNUAL REVIEW OF PHARMACOLOGY?

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My sincere thanks to the Editorial Committee for the opportunity to write a Bon Voyage! to the new *Review* as it sets out on its journey of adventure. "Annual," of course, only in the sense that it will be published every year, not that it will confine itself to what has been published in the current year. I trust that it will have a much broader base; that it will aim to review present tendencies in the light of their development.

And why do we need such a review of pharmacology? Let us start with fundamentals: What is "Pharmacology"? There are those who consider it the use of drugs, against disease and in poisoning. I prefer a broader definition: The reactions of living substance to chemical changes in the environment. That is surely broad enough. It covers large sections of biology, microbiology, physiology, biochemistry, biophysics, and probably all the "bios" that the future can and will devise; even anatomy in its modern conceptions, if you please. Why not say "all science," while we are about it? All can be viewed as ancillary to pharmacology—and vice versa. Even those who, for simplicity, would prefer the pragmatic concept of "Drugs and Poisons," cannot go very far without invading and infringing on these various disciplines. The boundaries between them are artificial and arbitrary, like the boundaries between the nations of a continent. But these have different customs, different governments—all arbitrary and subject to change. Ah, but the nations have different languages, which are not intelligible to the others without interpreters or special training, which is one reason why we need reviews. Another reason for such a broad concept is that it takes away the feeling of poaching, when the work of the investigator tagged with one of the arbitrary disciplines "transgresses" into the domain of another "department." In short, the pharmacologist is interested in all these fields, needs them, and, therefore, works with and in them. All the better.

But there are difficulties in this extension: difficulties of multiplicity, and of technicality. As to multiplicity, pharmacology, even in the restricted sense, has grown with the years in geometric progression, far exceeding the fertility of our best guinea pigs and rabbits, and so have the cognate sciences. Long ago Faraday wrote that if he tried to read all that was published in his field, he would have no time for other research, and it is this other research that makes progress. We are faced with the same problem, only vastly more gigantic.

Then we are faced with another specter, Technique. No longer do we work with cork, sealing wax and string, smoked drum, mercury manometer and Marey tambours, and the simple compound microscope. Modern concepts, modern apparatus require special engineering training beyond the

understanding of the profane. And language yet! For the nonspecialist much of that, often the most essential, is esoteric. He does not know the grammar, the words, even the alphabet. Most of the technicality is a necessary price of growth. We may rejoice in this growth—indeed we may, and we may groan—and indeed we do, but we have to do something more about it than rejoice and groan. To that there is only one answer: Divide and conquer! Leave it to one specialist to dig into one subject, another into another. Let them serve as interpreters in the first place, and then as guides who may show us glimpses of the landscape, and then maybe as leaders who give us an outline map of the territory and point to where we may go from there. With such an outline map before us, we may choose our path intelligently and push forward with some confidence. They may also guide us from uselessly exploring territory that has been virtually exhausted; although we may be sure that even the best worked mine may still contain nuggets of gold that previous explorers, with their eyes on their special objectives, have overlooked. Following even a well-beaten path, you are fairly certain to come upon something new—if you have the nose for it, but there is also a fatal chance of getting bogged in trivialities.

This holds especially for pharmacology. There are incalculably many chemicals that may change the environment of living substance, and in so many cases their study adds nothing substantially new. So many are practically the same thing, but they hold the temptation of playing them up as something new, something better; at least the same thing; or, anyhow, no worse.

Half a century ago, some of us had the idea that there already were too many drugs to be studied thoroughly and used well, and that it would be a gain if the less useful were dropped and attention concentrated on the more useful. The fundamental idea was right, but it should not militate against the everlasting search for new drugs that are valuable. And what valuable new drugs have been found that were beyond the dreams of those days! Some have been discovered by a keen scent, by luck, by trying many things and holding on to the best; the second-best will eventually sink. As an old philosopher remarked: If you wish to develop a good flute player, you must have a nation of flute players, most of them not so good. If only we adhere strictly to the facts, to truth, things will find their own level.

But in the meanwhile, all the more need for these specialists whose reviews may guide us through the labyrinth to the facts, to the truth. Since it is not possible for any of us to read all that is being published on every subject, we must make a practical compromise. Let us be thankful that there are guides who will interpret for us the topics in which they feel competent.

Here I am impelled to indulge in a personal nostalgic note: I was elected to the Physiological Society in 1902, and had the privilege of helping in founding the Biochemical and the Pharmacological Societies. The three usually met at the same place and time, with mutual contacts, and no conflicts of space—we were only a handful that any lecture room could

hold with room to spare. And incredible as it may seem, everyone could understand what everyone was saying, and talk about it freely. The meetings were really friendly affairs, almost a *Kaffee Klatsch*. You came away refreshed. Now there are sections innumerable, and you go away exhausted.

But that is the way it had to be; indeed, it was the way we all wanted and still want it to be. And when we do not understand, we trust that the *Annual Review* will tell us what is said and written. Let them come, and we shall follow them the best we can. More power to them! And so, may this *Review* strive to be what we all need, and thrive accordingly.

#### POSTSCRIPT

I thought I had finished, but Dr. Cutting insisted that I must add some autobiographical reminiscences of those early nostalgic days when I entered on the scene of pharmacology. The readers may pardon the personal note. It was his idea, not mine. So here goes!

I was born, as is self-evident; I still live, as is equally evident. I worked, *tant bien que mal*, or I tried to. *Voilà tout l'histoire*. But Dr. Cutting insists on detail.

My birth was on February 10, 1874. It was in Coburg, one of those picturesque towns, like Weimar, which is located in a small ducal German state, with the renaissance architecture of Rothenburg, a medieval castle on a hill (like the Wartburg), parks, fields and forests, and a shallow little river—the Itz(istula). My father had been a schoolteacher—as some eight generations of his forbears before him. Now he held the office of *Stadt-kirchner*—registrar of the protestant diocese and curator of the great medieval church, the Moritzkirche, in whose shadow—or light—we lived. The office took only part of his time, but he was naturally a worker and a naturalist with a scope ranging from microscopy to fossils. He published a monograph on edible mushrooms, another on the tongue of snails, on the sting of bees, on the sex life of trichina. He took a daily walk into the woods and fields; and by his side, or before or after, trotted his little son, as soon as he had learned to trot, and absorbed some of his lore, his love of nature, his love of knowledge; and before the boy had reached his tenth year, he had decided on his career; he would be a *Naturforscher*, a searcher into Nature. This was confirmed by his dislike for the formal grammar studies when he progressed to the gymnasium. It was a good gymnasium, dating back to the Reformation, and had the honor of graduating Goethe's father. I liked it, liked my schoolmates, liked my teachers, and got along well enough; but I preferred the great outdoors; and besides, I had other plans. My two older brothers had emigrated to "Amerika," that glorious land of opportunities, and gone into business. The oldest had married and owned a drug and bookstore in a small Ohio town, and he had plans for me. I must become a doctor! When I had the grounding of three or four years of Gymnasium, I must join him as an apprentice in America, and he would see to the rest of my education himself. Here was a prospect, a dream, sure to entrance a boy of 13 with an adventurous mind. America—maybe

Indians!—and study of facts instead of declensions and conjugations. Not a moment's doubt as to my decision. My parents consented, and so at the age of 13½ I formally cancelled my obligations to the Kaiser, and vice versa, and took ship with my brother, who was traveling in Europe, and High-ho on the bouncing main—and bounce it did indeed.

The drugstore experience was good for me, and in a few years I passed the Stateboard in pharmacy. Meanwhile my brother directed my studies, including botany, for the real goal was still before us. My brother decided that the next step toward this should be analytical chemistry, and with my informal educational background, he decided on Paris. To Paris I went and had the good luck to be accepted as special student at the chemical laboratory of the Military Hospital of Val de Grace, and at Paris I completed my premedical education—and learned more besides.

A small-town youth of 19 on his own in Paris!—in any cosmopolitan center for that matter, but Paris especially. The contrast between the restricted opportunities of a small, American town and the innumerable opportunities of the metropolis of France: the galleries and museums and open lectures; the new intellectual world in the making; the fellow students and other friends, from all over the world; the intimate talks in the cafés; the long walks through the boulevards, through humble streets packed with old apartment houses packed with people, living their complex lives; walks through trim parks with neat children and uniformed nurses; walks along the *quais* of the Seine, browsing through the bookstalls. It was enchantment, the Arabian Tales of the West.

That lasted a year and a half; then a tour through much of Europe, much of it on foot, knapsack on back, like a wandering scholar of old. Then, the boat to New York, the train to Ohio, and the medical school—where I entered in the fall of '94, and spent the next 50 years, the rest of my working days. This was indeed a lucky stroke, if not a special providence. In those days, medical teaching was generally an avocation of clinical practitioners. Few medical schools had funds to "hire" full-time trained teachers, but Western Reserve School of Medicine had recently received a liberal endowment to make the mare step more lively and was just engaging young men in the medical sciences to teach and do research. As the year opened, there arrived George N. Stewart in physiology (including histology and physiological chemistry, according to the English system), trained at Edinburgh under Rutherford, at Berlin under Du Bois-Reymond, at Strassburg, Manchester, Harvard. William T. Howard in pathology and bacteriology, trained at Hopkins under William Welch. Charles F. Hoover in clinical diagnosis, trained in Munich, Berlin, and Vienna. Carl A. Hamann, in anatomy, had arrived the year before from the University of Pennsylvania. Their common interest in scientific medicine drew them together in a congenial quartet. I was fascinated, attended their classes, besieged their laboratories. They soon adopted me into their circle, allowed me to share their interests and to join in their teaching; the Elysian fields spread out resplendant before me. Clinical classes may have been somewhat

neglected, but I managed to "pass"; work was a pleasure; days were long and nights were short; and the next year I was regularly launched as "demonstrator of physiology and histology" under Stewart's guidance. My fate was decided. I graduated and continued with Stewart, rising grade by grade, trusted with more and more responsibility.

Meanwhile Pharmacology was experiencing birth pains emerging from the womb of didactic "Materia Medica and Therapeutics." John G. Spencer, who studied under Schmiedeberg, was given funds to equip a teaching laboratory in an unused attic, but left for another school. After some rather abortive attempts, the faculty assigned it to me in the spring of '98, and I started a regular lab class, improvising the day's work as I went along. This succeeded so well that the faculty gave me a title in Pharmacology, relieved me of my duties in Physiology, and generously supplied me with funds to spend a semester or two at the Strassburg Pharmakologische Institut—the seedbed of pharmacologists—to find out what it was all about, to see how German institutes were run; above all, to meet some of the men who were making medical science and to see what made them move and tick. I carried a "project" or two with me as a back-log, picked up others that would give me some insight. When the University closed for summer vacation, I shouldered my knapsack, roamed through Germany and the Alps, took ship—and felt myself launched as a *Fachmann*, a pharmacologist by trade and profession.

And so, after many circuitous irrelevancies, we have at last arrived at the starting point of this Review—the Status of Pharmacology at the Turn of the Century. Actually, so far as I know, nothing relevant to pharmacology occurred at midnight of 1899, except the degradation of an uncertain amount of  $C_2H_5OH$  to  $CO_2$ , and of this only a relatively small, but not negligible, proportion by pharmacologists. Modern scientific pharmacology took its birth as an offshoot of experimental physiology a century earlier with Claude Bernard and was formally recognized, about a half a century later, by the foundation of an *Institut* at Dorpat under Buchheim, followed by the Schmiedeberg Institut at Strassburg. These are notable landmarks in a vista that stretches back beyond antiquity to Paracelsus, the Arabs, the Greeks; to the wise women or witches; to the magicians, wizards, and shamans. Indeed its driving spirit, curiosity, extends even to lowest animals—perhaps to the plants, the atoms, the electrons, the *Urstoff* itself. But where does that get us? To the Infinite, the Endless. A paper in the Review must have an end as well as an aim. Where were we when we got lost? Oh, at the turn of the century—only that, a mere sixty years ago when Pharmacology was struggling for official recognition in this country, and people asked (as some do still), "Pharmacology?—is that a new name for Pharmacy?" In Europe, thanks largely to Schmiedeberg and his Institut, and the Naunyn-Schmiedeberg Archives, this question of status had been officially and practically settled ("implemented," we would say now). In this country the subject had struck root through Abel and Cushny and their pupils, and (modestly) here at Western Reserve, and was sending

vigorous cuttings (no pun intended, *honi soit*) through the land. All searching, and teaching, and searching, ever-searching: What do drugs do, and how do they do it? First, the *what*, then the *why*, and the *how*, and many a rub, rub-a-dub-dub between. There were plenty of drugs in the pharmacopeia; plenty more in the drug shops; plenty had been written about them, was being written about them. But what did they do really? Clinical experience was always an incomplete and sometimes a false guide—it could not be controlled; the conditions could not be varied—until it was verified by the advancing methods of experimental physiology—respiration, circulation and intestines on rabbits, cats, and dogs; muscle, heart, capillary flow on frogs; lethal dose and chronic effects on guinea pigs, rats, and mice. No end of good work to be done, and at Woods Hole, the wealth of lower organisms from starfish ova to limulus. Each acquisition a steppingstone to the next; each problem answered posing other problems. Concepts and experimental techniques advancing day by day. Such was the exciting prospect, such the plodding practice, then as it is today.

New drugs, new active agents, came along; hormones, vitamins, synthetics. The *what* brought its rich harvest. The *how* too became clearer. Knowledge extended into depth as well as breadth. Abel, particularly, insisted that pharmacology rest on a chemical basis. As drug-apprentice, I had often wondered why strychnine should cause convulsions when quinine did not, why arsenic should be so much more fatal than salt. The discovery of enzymes, those leprachauns of the chemical world, later revealed glimpses into the *how*, if not yet into the *why*. Biological exploration of the endocrines brought the isolation of the hormones, the concept of their regulation of body functions, down to the transmission of the nerve impulse. Step by step we are still climbing the ladder, to where more and more of the *how* and of the *why* can be seen. In nutrition, the vitamins entered the field, each with its lantern.

Always, with better understanding of drugs—incomplete as it was—came new and better drugs. Organic synthesis was still an infant at the turn of the century, relatively small, but lustily growing, always growing. Ever more and more chemicals in need of pharmacological investigation. It is tempting to follow such topics as the evolution of antisyphilitic treatment, from mercury to arsphenamine to bismuth to penicillin, of suprarenal extract through to the latest corticoids, and so many more, but such may be the function of special articles in the *Annual Review*.

As we finally try to sum it up, the intellectual world of Pharmacology, at the turn of the century, was fundamentally what it is now, although so much has changed. We can read the great Book of Nature better with fluorescent lighting, than with the old kerosene lamps: chiefly and fundamentally, Light is Light; we must strive for *Mehr Licht*, and to this the *Annual Review of Pharmacology* is dedicated.

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