



Rudolf Buchheim
1820—1879

RUDOLF BUCHHEIM AND THE BEGINNING OF PHARMACOLOGY AS A SCIENCE

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Birthday celebrations, academic plaudits, and obituary notices comprise, with regularity, a sequence of ornamenting attributes. The top award that an investigator can receive is to be honored as the founder of a new science or at least of a new branch of science. However, as always in history, since the number of praiseworthy researchers by far outweighs the maximal number of individual fields of science, it has proven unavoidable that more than one person has been credited with founding "their" science. Pharmacology is no exception. The mindful, regular reader of *Annual Review of Pharmacology* may find many examples from introductory chapters containing personal, historical, or regional backgrounds of various people.

My view of science and history is different. Research and researchers are embedded in the sociological conditions of their respective times. Scientific growth needs well-prepared soil. The seed that is first to find a favorable environment will overgrow the others. In this sense, scientific greatness is a kind of not earned but "inborn merit" (Goethe).

1. BIOGRAPHICAL DATA

Origin and Development

Reference is made mainly to the descriptions given by Buchheim's student and successor Schmiedeberg (1), to the obituary notices of his colleague Rossbach (2) and his friend Hirsch (3), and to information collected by Oelssner (4) and myself (11).

Rudolf Buchheim was born on March 1, 1820 in Bautzen, which at that time was part of the kingdom of Saxony. His father, Christian Friedrich Buchheim, was a physician and a district medical officer there. Rudolf Buchheim lost his parents early. His father died when he was 4, and his mother when he was 14 years of age (10). In 1838 he left the high school (Gymnasium) in Bautzen to enroll in the

Medical Academy (Chirurgisch-Medizinische Akademie) in Dresden, the capital of Saxony. Three years later, in the fall of 1841, he continued his studies at the University of Leipzig, where, as a student, he started scientific work. He became an assistant in the "Anatomisch-Physiologische Anstalt" under E. H. Weber. Here a physiological chemist introduced him to the chemical aspects of medicine, which profoundly influenced his later activities. On January 7, 1845, he took his doctor's degree with an inaugural dissertation on the behavior of egg white, pepsin, and mucin against various reagents, and the resorption and elimination of ferrous sulfate when mixed with protein.

Publicistic Activities

It is doubtful that Buchheim's subsequent activities from 1845 to 1847 resulted from genuine interest only. As a "Privatgelehrter in Leipzig" he had to earn his and his family's livelihood. In 1845 he had married Minna Peschek, daughter of a minister in Zittau. They had six children.

From 1845 to 1847 Buchheim edited the *Pharmazeutisches Zentralblatt*. The journal covered a much more extensive area of chemistry than its title indicated. Later on, it was transformed into the still existing *Chemisches Zentralblatt*. In addition, Buchheim wrote the sections on physiological chemistry for Schmidt's *Jahrbücher der Medizin*. His third and most important task was the edition and adaptation of Jonathan Pereira's *The Elements of Materia Medica*. The book, translated into German, was widely distributed. The first volume of Buchheim's edition with 844 pages appeared in 1846 and the second with 929 pages in 1848. Thus, before having done any specific laboratory research himself, Buchheim tried to evaluate critically the bulk of pharmacological knowledge and views of his time. Today, this sequence is occasionally reversed. The importance of his publicistic activities can hardly be overestimated. In his editions of *Elements of Materia Medica* he dealt with the mode of drug action. By that, he at least intended to replace the descriptive, empirical *Materia Medica* by a science based on logical connections. Schmiedeberg (1) believed that Buchheim's "literary period" was the time of his apprenticeship. Under such circumstances, Buchheim had no other teacher than himself.

His Best Time at Dorpat

More than a century later, the Buchheim of 1847 appears to us as an especially active, talented young man. His exceptional and somewhat dominating personality had not yet become apparent. However, the young Buchheim must already have impressed university administrators as having one of the best brains available in his field. Less than one year after he had received his doctor's degree, he was offered the position of professor ("Außerordentlicher Professor für Arzneimittellehre, Diätetik, Geschichte und Enzyklopädie der Medizin") at the University of Dorpat (Esthonia). He accepted this position in 1847. In 1849 he was promoted to full professor ("Ordentlicher Professor"), after having had to declare that "he did not belong to a freemason's lodge, nor to a secret society neither within or outside the empire, nor intend to join such an organization in the future" (10). At that time (up

to 1891), the lectures at the University of Dorpat were given in German, although Dorpat was under Russian administration. The university, despite being located in a cultural fringeland, attracted many outstanding individuals in science and medicine, including Friedrich Bidder and Carl Schmidt. Buchheim completed the triumvirate.

Carl Schmidt, at this time, was able to demonstrate free hydrochloric acid in gastric secretions, and the unequal distribution of potassium and sodium between blood plasma and erythrocytes. Later, also in Dorpat, Alexander Schmidt described thrombin as the principal factor of blood coagulation. Thus, his 20 years in Dorpat brought Buchheim into the main stream of the rapidly developing fields of science and medicine and became his most productive period. He also gained the confidence of his faculty, which twice elected him dean. Shortly after his establishment, he converted part of his home into a laboratory for pharmacological work and financed the scientific endeavors himself. As Schmiedeberg expressed it, "Buchheim was the promoter of the first pharmacological laboratory, and he kept that glory for an unusually long time." The spirit and the equipment of this laboratory were well known to Schmiedeberg, who worked in it for his doctoral thesis in medicine: "Über die quantitative Bestimmung des Chloroforms im Blut und sein Verhalten gegen dasselbe." He noted and reported the relatively high standards to be met by the doctoral candidates: At least one year was devoted to research which could only be done after graduation from medical school. In addition a rigorous examination had to be passed before the doctor's degree was finally awarded. Graduates with such doctoral degrees enjoyed considerable esteem and financial benefit. Over the years, enough qualified people were interested in doing research in pharmacology for their thesis to keep the laboratory active. Buchheim often participated in the laboratory investigations himself. Some self-experiments were reported, which resulted in self-intoxications. A total of almost 100 papers appeared during that time, most of them written in Latin as doctoral theses, and only a few published in journals.

Until 1851 the pharmacological laboratory remained in Buchheim's home. It is not known where it was located between 1851 and 1860, but from 1856 to 1860 a pharmacological institute was founded as part of the "Alte Anatomieum." Impatiently, Buchheim moved into it before it was finished, and this caused some difficulties. The main laboratory of the institute had at least one bench for the professor and two benches for independent co-workers (10).

Dissatisfaction and Death at Giessen

Even the very favorable working conditions—for that time—did not keep Buchheim at Dorpat. He wished to return to Central Europe, especially because of his children, whom he wanted to educate in Germany. Nevertheless, in 1863 he refused a position at the University of Breslau, because the working conditions there were not satisfactory. At the end of 1866 he received simultaneous offers from the medical faculties in the Hessian Giessen and the Prussian Bonn. Buchheim went to Giessen, because Hesse, not Prussia, prescribed a thorough examination of therapeutics. Schmiedeberg became Buchheim's successor at Dorpat and stayed there until 1872, when he went to Strassbourg to establish his famous laboratory.

For Buchheim, facilities and contacts with congenial friends were significantly fewer in Giessen than they had been in Dorpat. There were only a few rooms which his predecessor in Giessen, Philipp Phoebus, had considered a pharmacological institute. In reality, there was merely a collection of illustrative, often curious material for teaching *materia medica*. However, students liked those rooms very much, especially during the winter. This was evident from warnings written by Phoebus to restrain the vandalism of his pupils, who apparently cleaned their long pipes there. Laboratory rooms were in a distant future. So Buchheim set up working facilities in his home again. It seemed, however, that he won only a few co-workers, not more than four of whom are known by name. As at the beginning of Buchheim's scientific career, literary activity prevailed at its end. After 1874, he became progressively ill. A retinal disease confined him to darkened rooms for long periods of time during the winter of 1874–1875. On June 30, 1879 a stroke paralyzed him. He did not recover from a second stroke and died on December 25, 1879, survived by his wife. The pharmacological institute he had designed was still not completed.

2. HIS CONTRIBUTION TO THE DEVELOPMENT OF PHARMACOLOGY AS A SCIENCE

Rudolf Buchheim was born into a time that could be called the “Gründerzeit” of medicine. Appreciation of scientific methods and thinking replaced the speculative medicine of the Romanticism. During those few decades, the fundamentals of modern medicine were established: Pasteur opened the ways to microbiology; Darwin developed the theory of descent; Virchow published the cellular pathology; two physicians, Helmholtz and Mayer, formulated the law of conservation of energy; many diseases of man were morphologically and functionally defined. Chemistry and physiology advanced rapidly. The time was ripe also for the scientific foundation of therapeutics. Buchheim introduced two principles, which appear self-evident to us. Each alone would have had a considerable bearing on our field, but both were interdependent, and Buchheim's greatness rests upon their combination.

The Natural System of Drugs

The first and most important achievement was the concept of a “natural system” for the classification of drugs, based on their mode of action. This concept must have been quite revolutionary at that time, as a considerable nonacceptance of it indicated. Until then the *materia medica* was a collection of therapeutic material in the word's narrowest sense. Its classification was cursory, for example, by origin or by chemistry. No wonder critical physicians questioned whether such museal knowledge should be transmitted to students. The “Oudenotheapie” of the Vienna school expressed the complete rejection of *materia medica*: Since causally acting drugs were not available anyway, physicians could only confine themselves to descriptive nosology, as the botanist registers growth and withering of a plant.

Buchheim's concept pointed in another direction. The mode of action should be elucidated by scientific means: this, once achieved, should eventually lead to a more

rational therapy. He wanted pharmacology to be “a theoretical, i.e., elucidating science, which should provide all the information on drugs necessary for the precise understanding of their therapeutic values.” On the basis of this postulate he arranged the contents of his *Lehrbuch der Arzneimittellehre* (6), the first edition of which appeared between 1853–1856. Of course, not many drugs of that time would have survived when subjected to Buchheim’s postulates. The same would apply to many of today’s drugs too. The understanding of the mode of action of drugs is like the truth in general: it is the asymptote of cognition. Buchheim’s critique at least opened the eyes of his contemporaries. They became aware of the scantiness of their pharmacological knowledge and of their crude therapeutic empiricism. Buchheim postulated a new science, and did not hesitate to project its ultimate goal when he wrote (5):

If we translate our often obscure ideas about drug actions into an exact physiological language, this should, without doubt, be a considerable achievement. However, scientific cognition of the action of a given drug would imply our ability to deduce each of its actions from its chemical formula.

This incredibly bold statement was written at a time when chemical formulation was at its very beginning. It is to be remembered that the benzol nucleus had just been introduced by Kékulé. Buchheim also drew attention to the relevance of statistical methods and to metabolism for understanding drug effects (6). He formulated pharmacology as an independent science, both from its philosophy and from its methodological approach (7):

The new era of pharmacology will bear its date not from the discovery of chloral hydrate, but from that time when pharmacology will cease to ornate itself by the waste of other disciplines; when pharmacology with its own area and aided by related sciences, will become equivalent to its sisters, chemistry and physiology.

When Buchheim tried to classify drugs according to their mode of action, many “white areas” became apparent. He realized how insufficient present knowledge was for his task, and he fully understood the preliminary character of his system. In a paper on irritant substances, he wrote:

We are used to deleting drugs from the series of irritants, as soon as we have gained some insight into their mode of action. Therefore, it is to be expected that, with increasing knowledge, the number of irritants will decrease until the term will fade eventually from pharmacology.

Towards an Experimental Pharmacology

For those reasons, the institution of experimental pharmacology appeared inevitable to him. Of course, the action of drugs had already been studied in man and animals, but mostly in a physiological or a biochemical connection, seldom to achieve a rational therapy (9). Buchheim may have been inspired by the great French physiologist Francois Magendie (1783–1855), whose work was undoubtedly known to him (9). Buchheim’s determination carried him on. As soon as he had a firm footing

in Dorpat or in Giessen, he founded pharmacological laboratories and trained co-workers. He conducted his investigations under considerable financial sacrifice without much government support.

What about Buchheim's own achievements in the experimental sector? Before answering this question, it must be stated that Buchheim published astonishingly few papers presenting experimental material. Most results were buried in dissertations, often written in Latin. Sometimes, when he tried to disprove a supposedly wrong hypothesis given in the literature, he just reverted to his Fort Knox of facts.

Buchheim preferred the chemical and physicochemical way of thinking. The mode of action of drugs could not yet be analyzed with complicated substrates, for instance, the central nervous system, whose function and structure were still obscure. Simple biological systems were needed, approximated as far as possible to chemical or physical models. It may be more than a merely historical parallel that the molecular biology of today has taken the same successful path. Buchheim made use of the possibilities of the just-emerging organic chemistry by purifying and characterizing active ingredients of drugs and by studying their metabolic fate. While working with chloral hydrate, Buchheim detected its hypnotic effects for the first time. He was convinced—as at that time everyone was—of its metabolic transformation into chloroform and formic acid, although he realized that the body is a physiological-chemical, not a chemical laboratory. Nevertheless, he tried to introduce acid equivalents into the body in that manner. He regarded the sleep-promoting action as a side effect, and omitted publishing this finding, as he often did. A few years later, Liebreich started from the same wrong assumption of chloral hydrate metabolism and introduced it into therapy as the first hypnotic. Buchheim was too late when, pushed to a reply, he mentioned his Dorpat protocols.

His preference for physicochemical explanations became apparent when he tried to elucidate the mechanism of acidification of gastric juice and the changes in urinary pH values. He asked the modern question for transport processes and believed, in this respect, in a specific reaction between ions and proteins. He studied water movements in the damaged web of the frog and related them to diffusion and water binding capacities of the surrounding media. For model experiments *in vitro*, he made use of the collodium membrane. He devoted much effort, though with varying success, to the analysis of the structure and mode of action of laxants.

The multiplicity of the problems dealt with in Buchheim's laboratories can be grouped roughly as follows (1):

- I. Diffusion; endosmosis; mode of action of laxant salts; resorption and elimination of alkali and earth alkali ions and acids.
- II. Heavy metals, arsenic, phosphorus, potassium iodide.
- III. Anthelmintics, organic laxants, irritants.
- IV. Fate of various organic substances in the body.
- V. Drugs and digestion, nutrition and metabolism.
- VI. Pharmacology and chemistry of alkaloids.
- VII. Ethanol, chloroform and blood gases.

I cannot help concluding that no great discovery was connected specifically with Buchheim's name. However, he introduced into pharmacology the methods that were essential for later achievements.

3. RESIGNATION AND POSTHUMOUS FAME

During the last years of his life, resignation grew within him to a considerable degree. It is true that pharmacological departments were erected at most German universities during the 1870s. But in an essay written in 1876, dealing with the task and the significance of pharmacology within German universities, Buchheim deplored many drawbacks. Medical students had only a minimal interest in pharmacological facts. Drugs were often used irrationally. There was no bedside pharmacology. The field was in low esteem by clinicians, for instance by the great surgeon Billroth. Some of Buchheim's remarks on the academic career should be underlined today:

Not seldom the duties of a professor of pharmacology were conferred to a lecturer who had been omitted on other occasions, and who was, after long perseverance, designed to sail into the port of the faculty under that flag. Therefore, the position of the pharmacologist was mainly taken by a home-made man and endowed with the lowest salary. The duties of the pharmacologist were admittedly not too difficult. At first, he bought a textbook of chemistry and one of botany and told his audience what was written in those books about preparation and properties of chemicals or about geography, genealogy and botanical properties of drugs. Then the diseases were enumerated, against which single remedies had been tried at any time. . . . Excellent chemists or physiologists, needed for the development of pharmacology, will be offered much better opportunities in their own fields. Which goal can be reached by a man having devoted himself with all his abilities and efforts to pharmacological research? A professorship with a minimum salary and an empty auditorium! (8)

One hundred and fifty years now have passed since Buchheim's birth. Each honor bestowed on him during his lifetime would have appeared to his clearheaded, calm character, as inadequate; the modest number of posthumous honors would not have annoyed him. His home in Giessen, which had served also as his laboratory, survived the war nearly undamaged, while the city was destroyed. About 50 years ago, a memorial tablet was installed in it—by whom and on what occasion cannot be ascertained. His birthplace in Bautzen was marked by a similar tablet, on the occasion of the ninth annual meeting of the *Pharmakologische Gesellschaft der DDR*. I shall not forget the scene at the romantic "Schloßstrasse" in Bautzen where a small group of pharmacologists, tired from the meeting and feeling chilly in the December air, honored their grand man before his native house while the present inhabitants watched with the curtains pulled aside. The street in Giessen, where the *Pharmakologisches Institut* was located, bears his name and medical students risk being examined about the main features of Buchheim's work.

However, the most affectionate and instructive memory stems from his sole congenial follower, Oswald Schmiedeberg. Without the biography and bibliography

from his pen (1), many details would have been forgotten. It was also Schmiedeberg who introduced Buchheim's thoughts and working methods, which were conceived in the more provincial university cities of Dorpat and Giessen, into pharmacological research all over the world. In this way, Buchheim became indeed one of the founders of pharmacology as a science.

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