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SECOND W.D.M. PATON MEMORIAL LECTURE

The evolution of experimental pharmacology as a biological science: the pioneering work of Buchheim and Schmiedeberg[1]

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Introduction

The term 'pharmacology' as we understand it today seems to have been defined for the first time in 1791 by the German chemist and physician Friedrich Albrecht Karl Gren (1760-1798) when he distinguished between 'pharmacology as the science of the action of drugs' and 'materia medica as the description and collection of drugs'. His contemporary and friend, Johann Christian Reil (1759-1813), Professor of Medicine at Halle University, believed not only that drugs affected the body but, conversely, that the body altered the composition of drugs, an idea which anticipated the present term 'drug metabolism'. Reil also established some rules on how to perform trials on the efficacy of drugs, namely, using patients with a defined diagnosis, standardizing the experimental test conditions, describing symptoms by special technical terms, and repeating an individual experiment. However, these considerations were not followed by application in drug trials which he performed. Rather, Reil seems only to have analyzed the empirical work carried out by others, putting forward a *theory* of drug testing (*Beitrag zu den Prinzipien für jede künftige Pharmakologie*, i.e. Contribution to the principles of a future pharmacology, *1799*). The most impressive examples of scientific trials of therapeutic measures known at that time were the studies of James Lind on the effect of lemons in scurvy (publication 1753), of William Withering on the foxglove (1785), and of Edward Jenner on vaccination against smallpox (1798).

To mention just one of these studies, James Lind (1716-1794), a Scotsman, had carried out a trial in 1747 aboard HMS *Salisbury* on twelve sailors suffering from scurvy. He tried six different treatments that had been recommended previously and found the only one effective against scurvy was two oranges and a lemon given daily. Despite the success of Lind's 1753 publication *A Treatise of the Scurvy* (three editions and translations into French and German) the preventive measure of a daily ration of lemon juice was recommended for the Royal Navy only 42 years later (1795) and officially made compulsory in 1799, at the instigation of Lind's disciples, Sir Gilbert Blane and Thomas Trotter.

In the same year as Reil's study, German physician, Adolph Friedrich Nolde (1764-1813), Professor of Medicine at Rostock, published a treatise on the principles of drug evaluation. Surpassing Reil he demanded experiments on both healthy and sick human subjects as well as on animals. He discussed possible problems which the investigator might encounter, such as faking of symptoms by the patient, interfering effects of a diet changed during the course of the study, possible impurity of the drug, and non-compliance of the patient in taking the drug as prescribed. Nolde even advised the investigator to conceal expected drug effects from the patient, in order to have his unbiased opinion. Furthermore, Nolde established several ethical rules that are compulsory in drug trials on humans. Thus, at the beginning of the 19th century there was enough theoretical knowledge to start experimental and clinical pharmacology on an empirical basis but the drugs available at that time were poorly defined chemically, and the body functions could not be measured by objective means, perhaps with the exception of body temperature and the pulse rate.

Early animal experimentation with drugs and poisons

A breakthrough came about 10 years later when François Magendie (1783-1855), physician at the Hôtel-Dieu and from 1831, Professor of Medicine at the Collège de France, started to investigate drugs in animal experiments and in patients. Magendie who nowadays is best remembered as a great physiologist outspokenly 'distrusted theory and had only firm faith in experiment'. His principles can be summarized as follows: He planned animal experiments irrespective of current theories or the taking for granted of results of previous workers; he developed unprecedented skills in surgical operations and dissections; he used drugs purified by himself or by others; he observed precisely all possible functions in the animals; and he applied drugs therapeutically to patients guided by the possible beneficial effects to be expected from the actions he had noticed in animal experiments. Thus, Magendie has rightly been regarded as having established experimental pharmacology in a modern way. His book of 1821, *Formulaire pour la préparation et l'emploi de plusieurs nouveaux médicamens, tels que la noix vomique, la morphine, l'acide prussique, la strychnine, la vératrine, les alcalis des quinquinas, l'iode, etc.* was based mainly on his own observations in the laboratory or at the bedside. It was widely circulated and went through 9 editions.

Magendie found a congenial pupil in Claude Bernard (1813-1878) who later became his successor in Paris. Bernard, like his teacher, was both an eminent physiologist and pharmacologist. In the present context I would like to mention two of his major contributions which have stood the test of time and are still textbook issues. First, the analysis of the action of curare on the motor nerve-voluntary muscle junction, the endplate, and second the finding that carbon monoxide is bound to haemoglobin in a rather firm manner resulting in failure of this combination to carry oxygen from lung to tissues. Bernard also realized that parameters such as absorption, distribution, binding to blood, and elimination determined the kinetics of drug or effects of poison in the body. Finally, he seems to have been the first to state that poisons are useful experimental tools for the physiologist in unravelling biological mechanisms of organ functions.

Poisons were studied thoroughly for quite different reasons by the Spaniard, Mateo José Buenaventura Orfila (1787-1853) who came to Paris as a postgraduate and remained there, achieving high academic positions. He was the first to demand chemical analysis for proof of a lethal intoxication, and for

[1] Based on a lecture, delivered at the BPS Meeting in Brighton, 15th December, 1994.

mainly forensic reasons carried out a vast number of animal experiments. Orfila can be regarded as the creator of toxicology as a scientific discipline.

Rudolf Buchheim, years of apprenticeship

Up to now we have seen that pharmacological or toxicological experiments were carried out mainly for the purpose of finding new drug treatments, with the intention also of employing discriminatory tools in physiological experiments and for solving forensic questions. The first scientist who set up a real laboratory, and later on, an institute of pharmacology was Rudolf Buchheim (1820–1879). He was born in Bautzen in the Kingdom of Saxonia, the son of a physician. While he was still a medical student in Leipzig he began research as an assistant to the famous physiologist, Ernst Heinrich Weber (1795–1878). His supervisor, the physiological chemist, Karl Gotthelf Lehmann (1812–1863), introduced him to the chemical aspects of medicine which remained his lifelong area of interest. Buchheim had lost his parents at an early age and had few resources; he earned his living by literary work. Thus, he edited a pharmaceutical periodical and wrote articles on physiological chemistry for *Schmidt's Jahrbücher der Medicin*. His most renowned work was the translation into German and critical adaptation of the then popular book by Jonathan Pereira *The Elements of Materia Medica and Therapeutics*. Buchheim revised its contents, omitted various drugs which he considered to be ineffective, replaced them by others, and tried to give a rationale for therapy. For instance, he supplemented the original by adding a new passage to each drug chapter, and named it: 'Mode of Action' in which he summarized the experimental pharmacological data known. This task took him four years but endowed him with a broad knowledge; 75 years later, Buchheim's pupil and successor Schmiedeberg commented on this unusual start to a scientific career, writing: 'This was a kind of pharmacological apprenticeship, for Buchheim had no teacher except his books'. Buchheim's name became known, and as early as 1847 he accepted the chair of Materia Medica, Dietetics and History and Encyclopaedia of Medicine at the University of Dorpat.

Figure 1 Rudolf Buchheim (1820–1879). Photograph courtesy of the *Archiv der DGPT*.

The importance of Dorpat University in the 19th century

Dorpat was a small town in Estonia, near Lake Peipus. The present Estonian name is Tartu. In Buchheim's time Dorpat belonged to Russia but the majority of inhabitants spoke German and this was also the administrative and teaching language in the University. Actually, the University was founded in 1632 when Dorpat was Swedish, by King Gustavus II Adolphus, shortly before his death in the battle of Lützen. Like many other European universities, Dorpat did not flourish in the 18th century. However, in 1802 Tzar Alexander I reopened Dorpat University, funding it generously. In the middle of the 19th century the Faculty of Medicine had acquired a high reputation among the German-language universities and there was a constant exchange of professors between Dorpat and central or east European universities. Thus, Buchheim was no exception when he went from Germany to Dorpat. He had been chosen on the strong recommendation of the physiologist Friedrich Bidder (1810–1894) who at that time was Dean of the Faculty.

In the second half of the last century, the list of staff of Dorpat University contained many people who are notable for their scientific achievements even nowadays. For example, Georg Dragendorff (1836–1898) was the Professor of Pharmacy who, interestingly enough, belonged to the Faculty of Medicine. His name is familiar to students of pharmacy as he invented a sensitive reagent for alkaloids which is still used. Karl Kupffer (1829–1902), an anatomist who finally went to Munich, described the liver cells which now bear his name. Alexander Schmidt (1831–1894) was the physiologist who discovered thrombin as the major clotting factor. Emil Kraepelin (1856–1926) is regarded as the founder of clinical psychiatry. He established the modern classification of mental disorders and introduced the clinical concepts of dementia praecox and manic-depressive illness. He rejected psychoanalysis as a method of procedure and believed that experimental psychology, as he had learned it as a pupil of Wundt (1832–1920), was the basis of psychiatry. In 1891 Kraepelin went to Heidelberg and published the first scholarly account of the effects of drugs on mental function.

Buchheim in Dorpat

During the first years of his tenure at Dorpat Buchheim organized the pharmacological laboratory in the basement of his own house; he also had to carry the financial burden himself. The faculty appreciated Buchheim's personal efforts and in 1860 he moved into a newly erected and spacious *Pharmakologisches Institut* which was sufficient for the needs of his many pupils, and also for his successors, Schmiedeberg (1867), Boehm (1872), Meyer (1882) and Kobert (1886).

Buchheim attracted numerous co-workers. As a rule, these were young physicians who worked for at least one year in the department to prepare an experimental thesis under his guidance. Finally, the title 'Dr. medicinae' was conferred after an oral examination. The standards were comparatively high, but for the successful candidate the efforts paid in terms of better promotion in the Russian civil and military services. During his twenty years at Dorpat Buchheim had 90 candidates; their results were partly published in journals and partly summarized in the books which Buchheim wrote.

In the beginning of his professorship at Dorpat Buchheim

had to justify why he definitely turned from materia medica in the old fashion to a new discipline of experimental pharmacology as a full-time occupation and a curricular teaching topic for under-graduates. In 1849 he wrote:

> 'The investigation of drugs is a task for the pharmacologist and not for a chemist or pharmacist, who until now have been expected to do this. We have to be acquainted with the tools which we use. The appearance of *Senna* leaves is a matter of indifference to the pharmacologist, just as it is unimportant for the surgeon what the box looks like from which he selects the scalpels for an operation. However, it is important which constituents determine the action of *Senna* leaves, and what are their properties; likewise, it cannot be irrelevant whether the box contains instruments suitable for dissection or not, and where the backs and the cutting edges of the knives are. Fortunately for the patient, the surgeon cuts his own fingers when he uses the wrong side of the scalpel; if the same happened in the case of drugs they would have been examined most carefully a long time ago . . .'

Biographical accounts of pupils and successors contain anecdotes of how Buchheim tricked the authorities into providing him with the unprecedented laboratory space he wanted. He pretended to have to enlarge the pharmacognostic collection for teaching the numerous students Dorpat University expected to attract, but in fact he turned the rooms into laboratories when he got them. He also moved into new rooms immediately after they had been painted but before they were completely finished, just to show that his needs were extremely urgent. This caused some concern because the University had planned an inaugural ceremony for the new department, and Buchheim had to answer an official inquiry about the 'occupation of rooms' as the authorities termed it.

Buchheim received calls to Breslau and Bonn which he declined, despite his intention to settle finally in Germany because of the education of his children. The reason was that pharmacology earned little recognition at Prussian universities at that time, where the subject had been dropped from the final medical examination. This was not the case in the Grand Duchy of Hesse, and Buchheim hopefully accepted the chair of Pharmacology at Giessen in 1867. However, again he had to carry out experiments in a laboratory which was part of his private rooms. A spacious department was promised but it took so many years to build that Buchheim, whose health deteriorated, did not live to see its completion. He died in 1879.

To present an outline of Buchheim's scientific achievements: he thought that the roots of modern pharmacology were in physiology and pathology. The methods have to be adopted from these disciplines as the pharmacologist has no genuine ones. However, the pharmacologist is distinguished by the uniqueness of the scientific questions he formulates: what is the mechanism of action of a particular drug? It is important to know the results of previous investigators and to scrutinize them under refined conditions. Physiochemical reasoning has to guide the investigator when he tries to explain biological effects since Buchheim was convinced that all functions of the organism are governed by chemical processes. These ideas were laid down in a textbook on pharmacology which was well received by scientists but aroused little enthusiasm among medical practitioners. Buchheim's critical attitude towards drugs used in empirical medicine appeared to offend the practitioner who, of course, knew better. This experience is not uncommon to textbook authors even today. Buchheim classified drugs according to a new system, namely, similar actions on organ functions as the main principle, rather than common botanical origin, or chemical class. The name of Buchheim is not connected with a single great discovery but with the systematic exploration of experimental methods leading to improvement of pharmacological knowledge, covering all areas relevant in those days.

Oswald Schmiedeberg

While it was Buchheim who established the basic principles of pharmacology, it was Oswald Schmiedeberg (1838–1921) who brought world-wide recognition to this discipline. In the words of Holmstedt & Liljestrand (1963) who have written an authoritative account of the history of pharmacology and toxicology, 'Schmiedeberg was undoubtedly the most prominent pharmacologist of his time'. He had numerous pupils, about 120, from twenty different countries. He helped many of them to acquire good positions because his advice to faculties was highly esteemed. It has been estimated that his pupils occupied forty pharmacology chairs throughout the world.

Schmiedeberg was born to German parents in a small place in Courland, one of the Baltic provinces of Russia. He studied medicine in Dorpat and wrote his thesis under Buchheim in 1866, on the determination and fate of chloroform in the blood. When Buchheim moved to Giessen, Schmiedeberg became his successor in Dorpat. During his tenure he took a one year leave and worked with the famous physiologist Carl Ludwig (1816–1895) at Leipzig. There he learned methods which Buchheim could not have taught, met Rudolf Boehm (1844–1926), his life-long friend and later a professor at Leipzig, and Henry Pickering Bowditch (1840–1911) who had just finished his study on the 'treppe' ('staircase') phenomenon. With Koppe he published the classical work on muscarine in 1869, showing that its effect on the heart is indistinguishable from that of vagus stimulation, and that both actions are antagonized by atropine. For the first time, a specific antidote against an intoxication had been evaluated in animal experiments which was suitable for clinical application. Schmiedeberg stayed in Dorpat only a few years. When in 1872 the newly erected 'Imperial University' at Strasbourg required a Professor of Pharmacology, Schmiedeberg was chosen on the recommendation of Ludwig.

The Schmiedeberg School

Schmiedeberg did excellent and original research work, executed at the highest professional standard. For brevity I will list only a few examples of drug classes and actions evaluated in Schmiedeberg's department: hypnotic effects of urea derivatives and of paraldehyde; the primary action of digitalis on the heart muscle; nicotine as blocker of cardiac vagal ganglia; central and peripheral actions of caffeine and other purine compounds; toxic actions of heavy metals and their organic complexes; formation of hippuric acid in the kidney and of urea in the liver; and detoxication of various organic compounds by coupling to glucuronic acid. In 1873 Schmiedeberg, together with the pathologist Klebs (Prague) and the clinician Naunyn (Königsberg, formerly of Dorpat and Bern), founded the *Archiv für experimentelle Pathologie und Pharmakologie* which he edited until his death in 1921. When Naunyn died in 1925, the periodical was named *Naunyn-Schmiedeberg's Archiv*, from volume 110 onwards. In 1969 the designation 'experimental pathology' was dropped, since nearly all papers submitted for some time past had dealt with pharmacology.

On the occasion of Schmiedeberg's 70th birthday in 1908 many of his previous pupils assembled at Strasbourg and a group picture was taken which has been published repeatedly (e.g. by Holmstedt & Liljestrand, 1963; Koch-Weser & Schechter, 1978; Stille 1994). Referring to this birthday party provides a good opportunity to mention at least a selection of co-workers of Schmiedeberg. Apart from German pharmacologists and clinicians many nationalities are represented: The professors of Pharmacology, Cloetta (Zürich), Wallace (New York), Lindemann (Kiev); Herlant (toxicologist at Brussels), Cervello (Palermo), Hofmeister (Prague), Kobert (Dorpat and Rostock), Cushny (at that time in London); Heubner (at that time in Göttingen, later in Heidelberg and Berlin), Hans Horst Meyer (Vienna) and the professor of Medicine in Breslau, Oscar Minkowski who in Naunyn's

Figure 2 Oswald Schmiedeberg (1838–1921) and his pupils in 1905. Photograph courtesy of the *Archiv der DGPT*.

clinic at Strasbourg had done the famous experiments on dogs, showing that diabetes is produced by removal of the pancreas.

Of Schmiedeberg's pupils, perhaps Hans Horst Meyer (1853–1939) had the greatest impact on pharmacology. He came from Insterburg, East Prussia, got his first chair in Dorpat, went to Marburg and finally to Vienna where he stayed until his death. We still instruct students about the Meyer-Overton theory of narcosis. As a pharmacologist, Meyer holds an outstanding record. Four of his pupils won the Nobel Prize: George Hoyt Whipple (1934), Otto Loewi (1936), Corneille Heymans (1938), and Carl Ferdinand Cori (1947). Loewi (1873–1961) spent eleven years with Meyer, seven in Marburg and another four in Vienna, before he accepted the chair at Graz University. Meyer was also the most prominent founder member of the German Pharmacological Society in 1920.

Arthur Robertson Cushny (1866–1926) was born at Fochabers near Elgin, Morayshire, and received his medical education in Aberdeen. With a Thompson Fellowship he went to Bern for a year in order to be trained in physiology by Kronecker (1839–1914). Then he entered Schmiedeberg's department who, after only one year, conferred on him one of his precious assistant positions. Cushny worked on digitalis, a subject he pursued during his whole life. After three years in Strasbourg and on Schmiedeberg's recommendation he obtained the pharmacology chair at Ann Arbor, University of Michigan, as successor of Abel. After twelve years in America, Cushny returned to Britain to occupy the newly created chair at University College, London, and in 1920 he went to Edinburgh. He is known for his digitalis studies and for his equally famous work on kidney functions. Cushny also wrote an extremely successful *Textbook of Pharmacology* which, after eight editions in his lifetime, was continued under later editors.

Next to Schmiedeberg, the second most important breeder of pharmacologists was Rudolf Boehm whom I have mentioned already and who succeeded Schmiedeberg in Dorpat. Subsequently, Boehm was professor in Marburg and later in Leipzig. He had not as many pupils as Schmiedeberg, but among them were Arthur Heffter (1859–1925), the first editor of the *Handbook of Experimental Pharmacology*, and Walter Straub (1874–1944) who created a large school himself. Paul Trendelenburg (1884–1931), known for his work on hormones, was one of Straub's pupils, as was Heinz Otto Schild (1906–1984) who will be remembered by many.

Why did experimental pharmacology, as a full-time occupation for prestigious scientists, emanate from Germany in that particular era? Looking back, the following reasons appear to be significant. In the medical curriculum at German universities, physiology and pathological anatomy were important teaching subjects and, therefore, also research topics, due to the interest of clinicians and the international reputation of men like Johannes Müller (1801–1858) and Rudolf Virchow (1821–1902). There was also much competition between different universities and motivation for the authorities to search for the best candidate when a chair was open. A leading figure was Carl Ludwig who was mentioned above. Ludwig invented several kinds of apparatus which proved to be indispensible for both physiology and classical pharmacology: for example the kymograph (1846) and the heart perfusion apparatus (1866). He had the astonishing number of 200 pupils, among them the pharmacologists, Schmiedeberg, Boehm and Meyer, and the physiologists, Edward Sharpey-Schafer, Henry P. Bowditch, Walter H. Gaskell and Ivan P. Pavlov.

Thomas Lauder Brunton (1844–1916) an M.D. of Edinburgh was another of Ludwig's pupils. He had worked for some years in different continental departments of physiology. In Leipzig, Brunton analysed the action of amyl nitrite and discovered that it dilated the blood vessels by a direct action.

He obtained a lectureship at Bart's in London and introduced amyl nitrite as a remedy for angina pectoris in 1867. Very influential was his *Textbook of Pharmacology, Therapeutics and Materia Medica* (1885) which was translated into German as a competitor to Schmiedeberg's textbook and was dedicated to 'lieber Meister (dear master) Carl Ludwig'. Interestingly, in the German edition it is called 'Handbook' which appears justified as it contains many references to original papers and detailed explanations of experimental procedures.

A scientist who spent seven years in Germany to round off his education was John Jacob Abel (1857–1938), a native of Ohio and pupil of Ludwig, Boehm and Schmiedeberg. On his return to America in 1891 he was the first Professor of Pharmacology at Ann Arbor (University of Michigan), needless to say, on the recommendation of Schmiedeberg. He moved to Johns Hopkins two years later. He has been called the 'father of American pharmacology'. Abel had an enormous spectrum of methodological experience which he conferred on his pupils; he also worked in the laboratory until the age of eighty. His work on the purification of adrenaline, pituitary hormones and insulin is universally known.

Thus, the main reason for the rise of pharmacology at the end of the last century seems to rest upon the high standards which physiology had achieved shortly before. The early pharmacologists had inherited the appropriate methods and used them busily to study effects of newly-discovered chemicals or highly-purified old drugs on the whole animal and, at an increasing rate, on isolated organs. The latter methods enabled them to elucidate complicated mechanisms of drug actions more easily. However, when we ask the question, why did all that start mainly from Strasbourg, two other reasons must be considered.

The University of Strasbourg provided a unique possibility when it was re-opened in 1872 as an 'Imperial University' immediately after the German-French War and the incorporation of Alsace into the German Empire. It was well-equipped with financial means. The young Faculty of Medicine had the choice of appointing, within a year or two, the most promising scientists of the time and in fact recruited them from all German-speaking parts of Europe. Finally, Schmiedeberg, as a strong personality and eminent scientist, played a decisive role in the establishment of pharmacology as a biological science within the academic world. In that respect, Schmiedeberg was not surpassed by any of his contemporaries

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