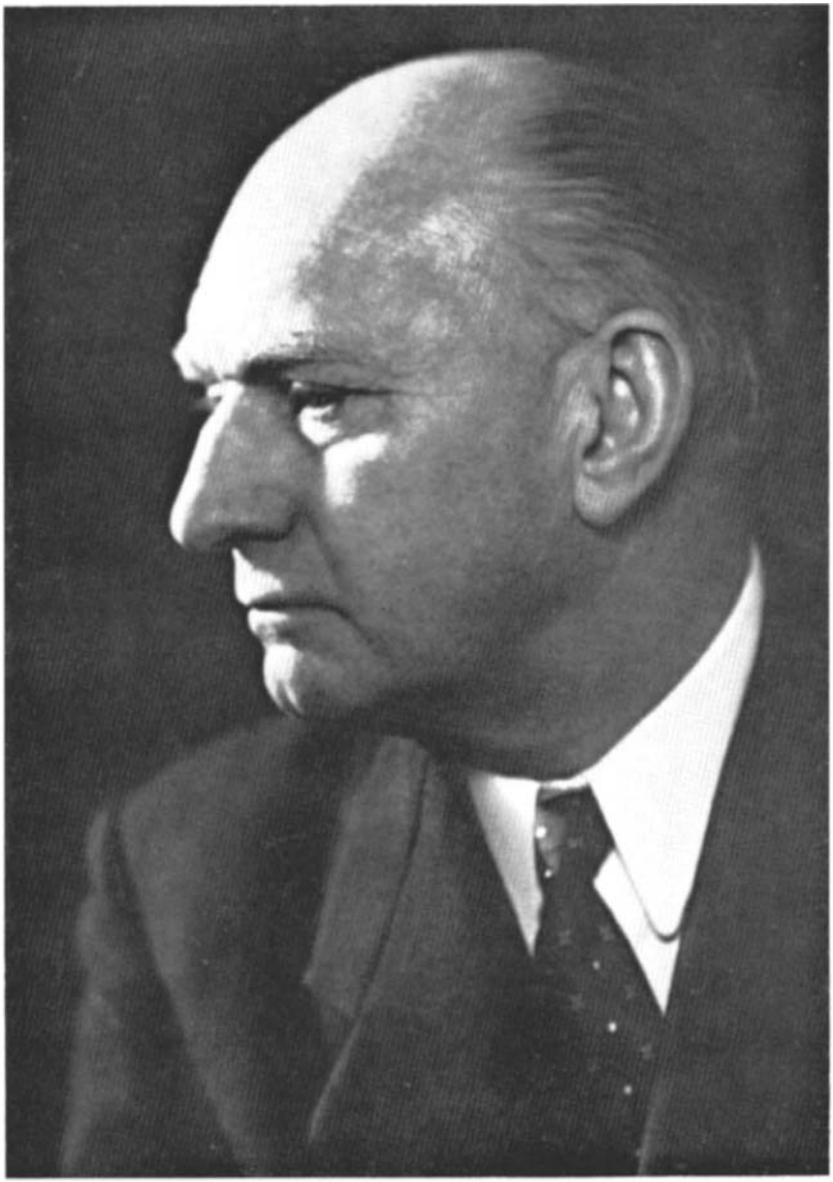

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PHARMACOLOGY IN OLD AND MODERN MEDICINE

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My acceptance of the kind invitation of the Editorial Board of the *Annual Review of Pharmacology* to write the prefatory chapter for this volume was rather a venture. I became, indeed, aware that it was a very difficult task to write a new chapter after the so excellent previous ones published by many distinguished colleagues. But during the preparation I thought that perhaps some ideas of a pharmacologist who has been, and still is, in the field for about fifty years, could be of some interest to the younger generation. As Winston Churchill stated so nicely: "The longer you can look back, the further you can look forward." This, I hope, may explain why I am committing some information and thoughts to paper.

The French writer and philosopher Auguste Comte stated that "to understand a science, one has to know its history and development." Let us, then, have a look at the origin and development of pharmacology.

Pharmacology, although a young branch of medical sciences, has a very old background. Indeed, as soon as man was conscious of diseases and suffering, he tried to find some means of protecting himself against these evils. Believing that nature provided the means to remove diseases and pain, man tried to find in nature, mainly in plants, minerals, and animals, remedies to help him. Numerous drugs were, thus, empirically collected in nature, mainly on the base of symbols. For example, iron therapy was used by the old Greek physicians against weakness and anemia, because the sword was, as it still is today, the symbol of strength and power. The therapeutic use of the leaves of digitalis against hydrops also started in a symbolic way and continued during the middle ages until Withering (1741–1799) introduced the agent as a more specific drug in heart diseases. Old Egyptian, Greek, Arabian, and Chinese physicians have been using, for many centuries, a large number of preparations, selected on such empiric and symbolic bases. Clinical observations sometimes showed favorable therapeutic results, while other preparations were withdrawn from medical use because they appeared to be inactive or dangerous. Today, modern pharmacology is using other symbols in order to prepare and discover new active drugs: the symbol of relationship between the chemical structure of natural or synthetic compounds and their possible pharmacological action. This symbol gives, of course, more useful results, but still keeps somewhat in the same line as primitive medicine and pharmacy.

At a very early stage in the development of medicine and pharmacy or materia medica, one tried to codify and standardize the remedies consisting

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of vegetable, animal, and mineral products. The first classification of drugs according to their therapeutic use was performed by Dioscorides, the surgeon of Nero. Dioscorides (1st century A.D.) was the first to emphasize the signs of the adulterated drugs. He indicated a method for the preparation of artificial calamine and recognized a surprising number of metallic oxides, sulfates, and sulfides. He was, thus, a real pioneer.

About one century later, Galenos (131–201) published a detailed list of polypharmaceutical drugs, including mainly the preparation of plants which are today still named the "galenica." He introduced the tinctura opii, which was later named "laudanum" by Paracelsus. He prepared also an alcoholic extract from the root of *Atropa mandragora*, to be used in diseases of the eye and as a soporific in surgery. Avicenna (980–1037) considered in his important medical *Canon* 760 drugs. From the 12th to the 17th century this work served as the main guide in medical practice in the West.

During the Middle Ages, polypharmacy was in a luxuriantly flourishing condition. One of the most typical preparations was the triaca or theriaca, containing about 110 constituents.

The materia medica had to wait until the Renaissance when Paracelsus (1493–1541) heavily attacked the galenical polypharmaceutical system and suggested the submission of drugs to a critical investigation. In 1546, the *Dispensatorium* by Valerius Cordus (1515–1544) was published in Nüremberg. It was the first step toward a pharmacopoeia. The *Dispensatorium* by Cordus was translated and its use made compulsory in Venice (1558), in Amsterdam (1592), and in many other cities. The main adaptation of the *Dispensatorium* was published in 1648 by a pharmacist of Antwerp, Pieter Coudenberg. More than forty editions of this book were published and used as an official pharmacopoeia in many cities for about a century.

In 1548, a book was published in Lyon by Jacques Dubois (or Sylvius) (1478–1555), which bore the name of *Pharmacopoeia, Libri Tres*. In 1560, the *Pharmacopoeia in Compendium Redacta* by the German physician Bretschneider Placothomas appeared in Antwerp, and in 1561, the *Pharmacopoeia Mediomatrica* (Pharmacopoeia of Metz), prepared by the Alsacian physician Anutius Foesius, was published in Basle. These three books were, however, private publications without any official character.

It was not until 1564 that the first official pharmacopoeia was published in Augsburg and became, in 1573, the legally enforced pharmaceutical guide for the pharmacists and physicians of this city. Many official pharmaceutical books were then published by numerous cities, either under the designation of "Antidotarium" or "Pharmacopoeia." The latter designation became predominant from the end of the 16th century on, and it gradually gained the distinctive quality of an official term for a legally enforced pharmaceutical book.

After the pharmacopoeias of cities or districts came the pharmacopoeias of countries, such as the *Pharmacopoeia Austriaco-Viennensis* (1729), the

Pharmacopoeia Dannica (1772), the *Pharmacopoeia Svecica* (1775), and many others. Tentative international pharmacopoeias were also published: the *Pharmacopée Universelle* by Lemery in 1697, the *Pharmacopoeia Generalis* by Spielman in 1783, and the *Pharmacopoeia Universalis* by Geiger-Mohr in 1835–45.

At the International Congress of Pharmacy in Chicago in 1893, the problem of unification of the different pharmacopoeias arose. In 1937, an international committee was appointed by the League of Nations in order to prepare a *Pharmacopoeia Internationalis*. The activities of this committee were interrupted by the war in 1939. A new committee was appointed in 1947 by the World Health Organization and the first volume of the *Pharmacopoeia Internationalis* appeared in 1951. Many countries continue, however, to use and republish their own national pharmacopoeia. In my opinion, the International Pharmacopoeia ought to become the legally enforced pharmaceutical guide in all countries of the world. The pharmacopoeia does indeed meet the obvious need of uniformity in directions for the same recipe when made by different apothecaries and, thus, enable physicians to expect some resulting uniformity in the effect produced in response to dosage.

Although pharmacology (pharmacos = drug—logos = knowledge, study) is a subject of ancient interest, it is a relatively new science. Pharmacology could, indeed, not develop until the rise of modern experimental physiology and modern chemistry at the end of the 18th and the beginning of the 19th century. During many years, the teaching of drugs was limited to the descriptive materia medica and to some information concerning the therapeutic use of drugs. The situation of the materia medica was still so bad in 1860 that Oliver W. Holmes of Harvard Medical School stated: "I firmly believe that if the whole materia medica as now used could be sunk to the bottom of the sea, it would be all the better for mankind and all the worse for the fishes."

At the end of the 18th and the beginning of the 19th century, methods became available for the isolation of active principles from crude drugs, and the development of chemistry made it possible to synthesize new compounds. Thus, these fundamental contributions started modern pharmacology. The first pure active principle from a crude drug was isolated by F. W. Sertürner (1783–1841) who in 1806, isolated morphine from opium. Many more chemically pure active compounds have been isolated from crude drugs, for instance, emetine, by J. Pelletier (1788–1844), from ipecacuanha root; quinine, by J. B. Caventou (1795–1877), from chinchona bark; strychnine, by Fr. Magendie (1783–1855), from nux vomica; and cocaine from coca leaves by Wöhler in 1856. Nativelle isolated cristalline digitaline in 1868 as well as many other chemically pure active compounds.

A very notable further development of pharmacology took place when attempts were made to improve the naturally occurring drugs. These attempts started with the rise of structural organic chemistry and made possible the preparation of new not naturally occurring compounds.

Many new drugs have, thus, been synthesized. I would like to mention the arsenical compound (Salvarsan) first investigated by Ehrlich (1854–1915), the sulfonamides discovered and synthesized by Domagk (1895–1965) in the laboratories of Bayer, and also studied by Tréfouel, Nitti, and Bovet at the Institut Pasteur in Paris; the synthesis of new compounds, such as the curarizing agents, the antihistaminics, and many others by the pioneer of drug design, E. Fourneau (1872–1949), who worked at the Institut Pasteur with D. Bovet. Many new synthetic antipyretics and analgesics were developed, such as aspirin by F. Hoffmann, phenacetin by C. Duisberg, aminopyrine by F. Stolz, and antipyrin by L. Knorr. As it became clear that quinine could not be readily synthesized, attempts were made to obtain simpler synthetic compounds with antimalarial activity. Thus, pamaquine (Plasmochin) and mepacrine (Atabrine) were both developed in the Bayer laboratories by Hörlein and Schuleman, and chloroguanide (Paludrine) in the laboratories of I. C. I. by Curd, Rose, and co-workers.

In the field of antibacterial chemotherapy, beside the sulfonamides, the antibiotics produced by microorganisms, such as penicillin and streptomycin, were discovered and developed by Fleming, Florey, and Chain, and by Waksman. The result of this was the discovery of a whole range of new and most important chemotherapeutic drugs. Antibacterial chemotherapy has had a dramatic effect on the mortality rate for many infectious diseases. Many other important developments in the field of pharmacology could be quoted, such as the general anesthetics, the psychotropic drugs, the sympathomimetic and parasympathomimetic drugs, the vitamins, the steroids and other hormones, the antitrypanosome drugs, the insecticides, etc. Most of these new and important drugs have been developed by means of synthetic chemistry. Although the main advances in the 18th and 19th centuries were due to the progress of chemistry, we must note that these centuries also saw serious attempts to establish the physiological basis of action of drugs. Experimental pharmacology, the study of the action of drugs on living material, started, indeed, with the development of experimental physiology.

The first physiologist to enter the field of experimental pharmacology was François Magendie (1783–1855) who investigated the action of several pure chemicals in animals and who published, in 1821, his observations in a very interesting small book called *Formulaire pour la Préparation et l'Emploi de Plusieurs Nouveaux Médicaments*. Magendie investigated in animals the pharmacological actions of strychnine, morphine, narcotine, emetine, veratrine, cyanide, delphine, and iodine. He was also a pioneer in clinical pharmacology. He investigated, indeed, the actions of these drugs in man as well as in animals.

Claude Bernard (1813–1878), the most distinguished pupil of Magendie, was not only the founder of modern experimental physiology, but kept also closely interested in experimental pharmacology, using mainly drugs as "scalpels" in physiology. Thus, he investigated the mechanism of action of

curare and made some fundamental observations in which he demonstrated the independent muscular excitability and the fact that curare acts by blocking the transmission of nervous impulses from motor nerves to muscles. Another famous pupil of Magendie was James Blake (1815–1893) who showed that drugs act in the mammalian body only after reaching the responsive tissue and not indirectly by reflex nervous mechanisms. He also developed a fundamental approach to the relationship between chemical constitution and pharmacological action, which was extended by Brown (1839–1923), Fraser (1841–1920), and many other investigators such as Ehrlich (1854–1915), Cushny (1866–1926), and Fourneau (1872–1949).

The first Institute of Pharmacology was founded in 1844 by Philip Phoebus in Giessen. For the organization and equipment of his laboratory, Phoebus received support mainly from Julius Wilbrand, Liebig, and Heinrich Emmanuel Merck, the founder of the Merck pharmaceutical industry. This Institute was, however, chiefly devoted to pharmacognosy and pharmaceutical chemistry. Phoebus' successor at Giessen in 1867 was Rudolf Buchheim (1820–1879) who had started the first exclusively pharmacological laboratory and chair at Dorpat, Estonia, in 1847. He also published the first textbook of pharmacology based on mammalian organ systems. He performed many investigations and proposed the action of drugs on the basis of physicochemical reactions between the cell constituents and the drug.

Oswald Schmiedeberg (1838–1921), a pupil of both Buchheim and Carl Ludwig (1816–1895), extended the work of his teachers and developed experimental pharmacology as an autonomous science in medicine. He organized his first Laboratory of Pharmacology in Strasbourg just after the French–Prussian war in 1870. He also founded the first journal of experimental pharmacology which is still one of the leading journals in this field. Schmiedeberg trained a large number of German and foreign pharmacologists who started or developed departments of experimental pharmacology in Germany and many other countries, including Abel (1857–1938) in the United States, Cushny (1866–1926) in Great Britain, Hans-Horst Meyer (1853-1939) in Vienna, and many others, such as Dale, Richards, Wallace, Dixon, Gottlieb, Magnus, Trendelenburg, Führer, and Heubner.

The contributions of pharmacology to medical sciences soon became tremendous, thanks also to the fast development of chemistry, physiology, and biochemistry. Pharmacology also became related to many other biological sciences such as biophysics, pathology, psychology, and sociology. Furthermore, pharmacology became widely applied in toxicology, public health, veterinary medicine, agriculture, agronomy, and forestry.

The contributions of pharmacology to physiology are very important. Many problems of physiology were, indeed, solved, thanks to the use of chemicals and drugs. Let us just remember the role of pharmacology in the discovery by Loewi and Dale of the chemical transmission of nervous excitation, the discovery of the role of the reflexogenic chemoreceptors, the drugs

blocking the α- and β-receptors of the adrenergic innervation, the anticholinesterase drugs, the catecholamine-releasing drugs, the biological functions of histamine, the antihistaminics, the parasympatholytic drugs, the psychotropic drugs, and many other compounds which contributed so largely to solving physiological and biochemical problems.

Many of these compounds so useful in medicine and biological sciences have been synthesized and investigated in the chemical and pharmacological laboratories of the pharmaceutical industry. In the last fifty years the pattern of the organization of pharmacological research has, indeed, undergone a marked change, and the pace of this change has become increasingly rapid. Industrial research laboratories, many of which are much larger and better equipped than university laboratories, have come into being in many countries and play an increasingly important role in scientific research. As E. B. Chain stated so correctly in his lecture on Academic and Industrial Contributions to Drug Research: "Both university and industrial laboratories have made equally important contributions, each in its own specific manner and that the best results often obtained in the past, are likely to be obtained in the future by the closest collaboration between academic and industrial research laboratories." The deciding factor for success in scientific research is not the place where it is carried out, but the qualities of the man who is carrying it out. As for the term "applied science," often used in a derogative manner to industrial research, I can do no better than to quote the words of Louis Pasteur, one of the purest scientists of all time, that "Il n'y a pas de sciences appliquées. L'union même de ces mots est choquante. Mais il y a des applications de la science, ce qui est bien différent."

In recent years, pharmacology, which was formerly mainly a physiologic science, became more closely correlated with biochemistry and biophysics, in order to investigate more closely the mechanism of action of drugs at the cellular level. New branches of pharmacology thus arose, such as biochemical pharmacology and molecular pharmacology.

No branch of medical science, however, has reached a final stage. Progress in pharmacology will continue with both development in knowledge and development in technique. But, as stated very correctly by Maurice Visscher: "Automatic analyzers, electronic recorders, on-line computers, and the rest of the essential gadgetry of much of modern science are still no substitute for painstaking personal intellectual labor in science, though they do eliminate much drudgery and make possible some kinds of study which would be completely unrealistic without them. The motivation of the scientist is still as important as is his or her brain." The dependence of pharmacology today upon the physical and biochemical sciences, mainly upon technical knowledge, is very pervasive, but the latter involves certain dangers. Techniques in pharmacological as in other medical research, requiring highly specialized training, may become so complicated that the goal, i. e., the development of our knowledge and understanding of biological problems may,

indeed, be more or less obscured by technical details. In a general way we may postulate that the progress of pharmacological research will largely depend on the pharmacologist's ability to assimilate the different technicalities of today and of the future in a harmonious and balanced way without losing sight of the orientation and survey of pharmacology and medicine as a whole. Analysis is of course necessary, but the value of the information chiefly depends on the light it may throw on general problems. After careful analysis of a limited problem, integration of the collected information into a larger problem is indeed necessary. In my mind, pharmacological research actually needs fewer ultraspecialized investigators, but more good "brains" able to integrate the information in a harmonious and well coordinated way. As the famous physiologist Cannon said so nicely to the head of a new and very well equipped research institute for medical research: "Your research building and equipment are superb. Have you given as much thought to securing the brains to use them?" Let us never forget that pharmacology is above all a biological and medical science. We hope that the recently founded autonomous International Union of Pharmacology may also contribute to this objective of integrating and coordinating the activities of the different branches and disciplines of pharmacology.

Research in pharmacology will also be influenced to some extent by the increasingly important problems involving it. One of the important problems facing clinical pharmacology today is the control and evaluation of new compounds. The discovery and clinical application of a series of new drugs has deeply changed the therapy of many diseases. But many drugs are not devoid of toxic effects. According to public and some administrative opinion it is believed that if pharmacologists and clinicians would perform their work properly, they could provide medicine with very effective drugs, free of any risk or side effects. However, as stated by René Dubos, it can be taken for granted that a biologically active substance will have some form of toxicity if it is capable of reacting with structures or functions of living beings. In contrast, the more selective the activity of a drug, the better the chance is that its toxicity will be minimal. The selectivity of a drug will, however, at best remain relative. Thus, every drug may have some side effect which will depend not only on the drug itself, but also on the reaction of the living structure to it. The drug without risk or side effect has, indeed, still to be discovered, and it is most unlikely that such a drug will ever be found. The risk of toxic side effects of a drug must, however, be limited as much as possible. Therefore, a very accurate investigation and evaluation of the toxicity and side effects of any new drug is absolutely necessary before its use and release for medical application. The problems and responsibilities in assuring the safe use of new drugs from the moment of discovery to the days of general clinical use are today overwhelming. Rules and regulations for the control and evaluation of new drugs are, of course, essential. But, as also stated by W. W. Goodrich, we must see that these regulations are executed to achieve

their high purpose without imposing any nonessential restraint on scientific research, the pharmaceutical industry, or the physician on the front line of medical practice.

May I close this short review concerning the role of pharmacology in medicine with the hopeful statement of Sir Henry Dale:

> I ask you to contrast the helplessness of medicine in the presence of most infections when this century began with its rapidly growing powers of specific healing today, and to remember that these still represent only early harvest from the sowings made by the experimental method in the field of medicine during the latter half of the nineteenth century. Who can appraise the gain of human health and the enrichment of human happiness which the continued growth of such knowledge may bring? The future is bright with promise, indeed, if mankind can be brought to forsake the folly of using the gifts of science for its own destruction.

As Dr. Cutting insisted so kindly that I ought to add some reminiscences and autobiographical information, I am going to do so. I hope, however, the readers may forgive this personal note. I was born on March 28, 1892, in Ghent, an old and very picturesque Flemish town. My father, J. F. Heymans, was just appointed professor and head of the new department of pharmacology at the Medical School of the University of Ghent. My father was the son of a farmer and because of good results at the primary school of his village, he received a fellowship to study at a secondary school and later at the University of Louvain. He first became a doctor in natural sciences and went to Paris for postgraduate work at Ranvier's department of histology at the Collège de France. After his training in histology and the publication of papers showing for the first time that nerve fibers are present in the heart, he returned to the University of Louvain and studied medicine. After his M.D. graduation, he became an assistant at the department of physiology. A fellowship was awarded for his thesis and he went to Berlin for postgraduate training at the department of physiology, headed by Dubois-Reymond, the famous physiologist. My father spent four years with Dubois-Reymond as an assistant. In 1890, he received a call from the Medical School of the University of Ghent, asking him to start and organize the first department of experimental pharmacology in Belgium. He accepted this invitation on the condition that a laboratory for research would be available. This laboratory started in three rooms at the Faculty of Philosophy, since no other space was available. But rapidly the philosophers were disturbed in their thinking by the barking of the dogs and the smell of the rabbits, cats, and rats. There was a lot of fuss until, thanks mainly to the action of the philosophers, a new and large Institute of Pharmacology was built in the area of the Medical School and inaugurated in 1900. This now-named "J. F. and C. Heymans Institute" is still in use. My father also founded, in 1895, together with E. Gley, the *Archives Internationales de Pharmacodynamie et de Thérapie*, the first international journal of pharmacology, publishing papers in

all scientific languages. More than 160 volumes of this journal have been published today at an average of six volumes of 500 pages a year.

My father was very active in research and teaching; he also trained many Belgian and foreign pupils, among them Morishima, who founded the first department of pharmacology in Japan.

I started my medical studies at the University of Ghent in 1911, but in 1914 I was called for military service when the German army invaded Belgium. Thus, I was involved in the fighting of August 1914 when the German army was stopped at a trench line running from the North Sea down to Ypres and, hence, could not reach Dunkirk and Calais. In 1915, I was switched from the infantry to the field artillery. I ended the war in 1918 as first lieutenant of field artillery after having been involved in several heavy battles. After having been released from the army, I resumed my medical studies until I passed the M.D. examination in 1921. After graduation, I married a classmate after six years of engagement. My matrimonial companion, also an M.D., served during the World War as a voluntary nurse in a military hospital close to the front line. We spent our honeymoon in Paris, but on the first day I went to Gley's laboratory at the Collège de France for postgraduate training in physiology, and my wife to the Hospital Hôtel-Dieu in order to start her postgraduate training in ophthalmology. We were very lucky on the family side and now, after forty-five years of marriage, I am glad to say that both my wife and I have been and still are very happy, because we shared everything in our career and family life. We had many sunny, but also a lot of very dark days during the second World War. At that time I was in charge of the Department of Medicine of the Belgian Relief Committee acting in very close connection with the Belgian and International Red Cross. Thanks to the activities of this Committee, the health situation in Belgium was quite good. I would like to note that the children's death rate was lower on an average during the four years of war than before or during the first year after the war. Food and drug supplies were afforded mainly by the International Red Cross and a Belgian Relief Committee located in Portugal.

The question may arise: Why did you enter pharmacology? The answer is an easy one: for genetic reasons. My father started to be a physiologist, but changed to pharmacology. I simply followed the same way. I started in experimental physiology and had the privilege of having, besides my father, my first and best teacher, such excellent teachers as Gley in Paris, Arthus in Lausanne, Starling in London, and Carl Wiggers in Cleveland. Gley's laboratory was located in a small building in the courtyard of the Collège de France. Four rooms, one assistant, and one laboratory helper constituted the laboratory, but the spirit was excellent and Gley very inspiring. At the suggestion of Gley, I investigated the action of methylene blue on the excitability of the cardiac vagus nerve. Starting with the frog, I observed that methylene blue blocked the heart slowing induced by vagal stimulation and

by acetylcholine. Switching over to the dog, I observed that the intravenous injection of methylene blue induced a marked increase of metabolic rate and hyperthermia. These experiments were extended after my return to the pharmacological department in Ghent and my promotion to assistant professor under my father. One day, on the occasion of a visit by Mathews, professor of biochemistry at Cincinnati and a good friend of my father, he drew our attention to one of his papers which stated that injections of dinitronaphthol into the guinea pig induced fever. Starting from this information, we observed that dinitronaphthol, dinitrophenol, and other related compounds injected into a dog, cat, or pigeon, provoked a very marked increase of metabolic rate and hyperthermia.

I then went to Lausanne, to the department of physiology, headed by Arthus, an excellent teacher and investigator who contributed greatly to the progress of knowledge in the field of anaphylaxis and immunity. His book entitled *De l'Anaphylaxie à l'Immunité* is a standard work. Arthus was a follower of Claude Bernard and, thus, believed first of all in brain training. He accepted each year a group of about twenty postgraduates in his laboratory and repeated with this group step by step the experiments he had performed himself in order to show that hypersensitivity or anaphylaxis may lead to immunity if the antigen has been administered repeatedly. Arthus also developed his own way of thinking during his investigations and pointed out the mistakes he made himself. In my opinion, this method of brain training was an excellent one which impressed me very much.

After my stay with Arthus, I went to Vienna and spent several months in the famous department of pharmacology, whose chief was Hans-Horst Meyer, a pupil of Schmiedeberg. While I was active in this department, my wife received further postgraduate training in Fuchs' clinic of ophthalmology. We both had an excellent and very stimulating time in Vienna. After our stay in Vienna I went to London to the department of physiology of University College, where I had the fortunate privilege to be accepted as pupil by the very famous cardiovascular physiologist Starling. At that moment, de Burgh Daly and Anrep were also active in this department and nearly every day made a heart-lung preparation with Starling. It was really a very thrilling time. I shall never forget Starling's outstanding way of thinking. One of the best and most interesting moments of the day was at tea-time, when Starling was developing for the group his opinion on the progress of his experiments and giving many ideas concerning various problems in the field of cardiovascular physiology. Starling was, indeed, a very great man and physiologist.

In 1927, I was awarded an advanced fellowship of the C.R.B. Foundation, now named the Belgian-American Educational Foundation. Established with funds from the World War I Commission for Relief in Belgium (C.R.B.), the Belgian-American Educational Foundation (B. A. E. F.) is a corporation chartered to foster educational and cultural exchanges between

Belgium and the United States. This Foundation has promoted in a very efficient way the scientific and cultural development in Belgium during the last forty years.

When, in 1927, I arrived in Carl Wiggers' department of physiology at Western Reserve University Medical School, he asked me which experiments I had performed recently? Answering his question, I explained carefully my observations concerning the baroreceptors regulating arterial pressure and the chemoreceptors involved in the regulation of respiration. Carl Wiggers listened and then said: "Heymans, do you really believe what you said? Because I suppose you know that it is in full contradiction with classic opinions. Now, let us not argue, but tomorrow we shall provide a dog and you are going to demonstrate what you stated."

The next morning then, I performed the demonstration while Carl Wiggers was watching it very carefully. At the end of the demonstration, pointing to the dog, he said: "Heymans, the dog is right, textbooks are wrong!" This striking behavior of Carl Wiggers showed how open-minded he was and explained why he made so many important and fundamental contributions to cardiovascular physiology. A free and open mind is, indeed, fundamental in research and, as Claude Bernard advised: "L'expérimentateur doit douter, fuir les idées fixes, et garder toujours sa liberté d'esprit" (The investigator must doubt, avoid settled opinions, and always maintain a free mind). Too many investigators are, indeed, bound by hypotheses and theories, which soon become dogmatic and irreversible opinions. Let us also never forget the so true statement by the famous biochemist Frederick Gowland Hopkins that "all dogmatic teaching about any aspect of the phenomena of life is apt to be checked by the ultimate discovery that the living cell is before all things a heretic." The brain and technical training I enjoyed in the department of Carl Wiggers had a deep influence on my career as an investigator.

The attitude of nonconformism, which should prevail in experimental pharmacology, is permanently illustrated in one of the main rooms of our laboratory, where the young investigators also have their tea. Here a large picture is hanging on the wall, representing a funny dog looking in a very sceptical way at a syringe ready to give him an injection. Under this drawing the so genuine statement of Mark Nickerson is written: "Under the most perfect laboratory conditions and the most carefully planned and controlled experimental procedures, animals will do what they damned please!"

Between and after the periods of training in foreign laboratories I had the privilege of performing investigations, mainly with my father, in the department of pharmacology at Ghent University. When, in 1930, my father had to retire, I was appointed his successor and head of the department of pharmacology. My father had, however, still his office and laboratory in the Institute. He passed away in 1933, after about forty-five very fruitful years devoted entirely to teaching and research.

I had the privilege of having many excellent pupils and co-workers from Belgium and many foreign countries. Several of them are now heads of departments.

Numerous problems in the field of physiology and pharmacology have been investigated. The research was mainly focused on problems related to the physiology and pharmacology of circulation and respiration.

The question has been asked several times: "How did you find the chemoreceptors located in the aortic and carotid sinus areas?" The primary observations on the chemoreceptors of the aortic arch area were made, with my father, in the course of experiments, performed for other purposes, in which the isolated perfused head of a dog, connected to his body by means of the cervical vagus nerves only, was used. This experimental method was first described by my father in 1912. We observed that asphyxia or oxygen need, induced in the body of the dog, provoked a reflex stimulation of the respiratory center of his isolated perfused head. This astonishing and unexpected observation started a series of planned experiments which continued until the location and functions of the chemoreceptors in the aortic arch area, in the aortic glomi, were identified. The discovery of the chemoreceptors of the carotid sinus area occurred in the following way: my father always advised his pupils never to kill an animal at the end of a planned experiment if the animal might still be used for any other experimental purpose, but to take advantage of this animal to perform any experimental trial, even if it looked foolish, and to keep their eyes well open in order to catch any unexpected event. One day, also having in mind the advice of Darwin "I like to perform foolish experiments," we finished a planned experiment on the functions of the carotid sinus baroreceptors. One carotid sinus area of the dog was denervated, the other being still innervated. Wondering for what experimental purpose this dog could still be used, we injected into the circulation of the common carotid artery with normal carotid sinus innervation some potassium cyanide solution. According to expectation, a very marked hyperpnea occurred. But, when similar amounts of cyanide were next injected into the circulation of the common carotid artery, the carotid sinus of which was denervated, no hyperpnea occurred. The alternate injections were repeated several times and the same very unexpected respiratory responses were observed. The next day a planned experiment was performed and it gave the same results. The primary unplanned experiment, at first sight a very foolish-looking trial, thus started a series of planned experiments, performed with several methods, which led to the identification of the chemoreceptors of the carotid body and their fundamental functions in the reflex physiological regulation of respiration and the reflex responses of the respiratory center to many drugs, such as lobeline, acetylcholine, nicotine, and many others.

The discovery of peripherally located chemoreceptors acting reflexly on respiration was, however, not accepted immediately without resistance coming from several sources. Anyway, I may repeat what the famous Belgian

physiologist Léon Fredericq also felt when he said: "I had many happy days when good luck gave me the opportunity to discover some new facts." Today, the role of the chemoreceptors in physiology and pharmacology is generally accepted. It is, of course, a very nice feeling when, after about forty years of teaching and research, one has to retire and then, looking back, one sees that the efforts have not been in vain.

As far as I am concerned, I may say that it was a wonderful experience, and to the young pharmacologically inclined investigators I would like to say with Renan: "Young men, be interested in research, it is still the most thrilling activity in life!"

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