THE PHARMACOLOGISTS OF EDINBURGH

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The Edinburgh Medical School was started about the year 1670 by a group of doctors who decided to lay out a herb garden and to start a college of physicians (9). Most drugs were made from plants and the only way to get reliable drugs was to grow the plants. A professor of botany was appointed in 1676 to teach the subject to medical students, and this arrangement continued for 64 years. In 1738, Dr. Charles Alston (1683 to 1761) was appointed professor of both botany and materia medica and started giving two courses of lectures on these two subjects. Materia medica was a large and important subject in those days, since the doctor was responsible for the preparation of his own medicines. Students were expected to know the properties of over 250 plants, 60 minerals, various gums and resins, and also snails, worms and vipers, and other less attractive substances used in medicine.

Dr. John Hope (1725 to 1786) was appointed professor of materia medica and botany when Alston died at the age of 77. He introduced the Linnaean system of classifying plants, which had been too newfangled for his predecessor.

In 1768 the two subjects were separated and an independent department of materia medica was started. The first professor, Francis Home (1719 to 1813), was a very original person (22). By the time he was 30 years of age he had served for six years as an army surgeon in Flanders. He issued an order that "The dragoons shall drink no water without it be first boiled and a little brandy or gin be mixed with it." Some of this advice was certainly good. He was awarded 100 pounds for showing that sulphuric acid could be used to bleach linen. He wrote a book on the principles of agriculture, in which he showed for the first time that there is nutrient matter for plants in air. In 1759 Home showed that measles could be transmitted by placing blood-soaked cotton wool in an incision in the skin, and leaving it there for three days. He hoped, in this way, to confer immunity "as the Turks have taught us to mitigate the small pox." He was the first to show that the sugar in diabetic urine is fermented by yeast.

Home gave the lectures on materia medica in Edinburgh for 30 years, and his classes included several names which are still remembered. Daniel Rutherford, for example, was one of the people credited with the discovery of nitrogen in 1772. Abraham Colles described a form of fracture of the wrist, which is still known as Colles' fracture. Charles Bell showed that the motor nerves in the spinal cord are in the anterior roots. James Gregory became professor of medicine in Edinburgh (1790 to 1821) and was famous for his advocacy of heroic treatment of all kinds—blood letting, blistering, and the use of tartar emetic and purges, including the rhubarb mixture known as Gregory's powder.

Francis Home was succeeded by his son, James Home (1760 to 1844), who did little original work but was a great teacher. Several of his pupils made names for themselves in later life. For example, one form of nephritis used to be called Bright's disease, in honour of Richard Bright, and adrenal deficiency was called Addison's disease, in honour of Thomas Addison, both of whom presumably attended James Home's lectures, although they did the work that made them famous at Guy's Hospital in London. At the age of 61, James Home applied for the chair of medicine vacated by James Gregory. At that time professors were elected by the town council, and James Home was chosen because he was a gentle Tory and his main opponent was a Whig, "and at one time something more than a Whig" (1), but this new appointment was not a success.

Andrew Duncan (junior) (1773 to 1832) was the next professor of materia medica. His application for the chair (14), which can still be seen in Edinburgh, was supported by 52 testimonials, and followed by 33 more, 10 days later. These came from such distinguished people as Archduke John of Austria, Prince Augustus and Prince George of Holstein Oldenburg, and from well-known doctors in Paris, London, Germany, Russia, Poland, Denmark, Portugal, Italy, and America. His most important contributions to knowledge were contained in a large textbook known as the *Edinburgh New Dispensatory*. The twelfth edition of this book, published in 1830, has over 1000 pages, and covers all branches of materia medica, including pharmacy, pharmacognosy, and therapeutics. It contains detailed discussions of the chemical work done at that time—when many of the more important alkaloids were isolated. He was not content to record the results of others, but did chemical experiments himself to settle doubtful points.

Robert Christison (1797 to 1882) succeeded Andrew Duncan as professor of materia medica in 1832. He was then only 35, but had already been professor of medical jurisprudence for 10 years. During this time he did fundamental work on the detection of crime. He gave evidence at the trial of Burke and Hare, who made money by selling corpses to the professor of anatomy, and obtained the corpses by murder! The evidence depended partly on bruises, and Christison carried our experiments to show that these could not have been caused after death.

Inspired by the work of Orfila in Paris, Christison decided to specialize in toxicology. His usual method was to inject large doses of poisons into animals and then to observe the symptoms and the appearance of the organs after death. He worked on the toxic effects of arsenic, and its detection in the corpse, oxalic acid, laburnum, cyanides, alcohol, and many other poisons. He was professor of materia medica for 46 years and much of this work on poisons was done during this time, but he analyzed the actions of drugs by more elaborate pharmacological methods and undertook investigations of the actions on the healthy body of the substances used in therapeutics.

His work in experimental pharmacology was done so long ago that most of it has been forgotten. In 1836 he published a paper on the poisonous effects

of hemlock and its active principle, coniine, which had then just been isolated. This must be one of the first pharmacological papers on the actions of an alkaloid. He showed that it caused paralysis in a dog and led to death from asphyxia but, if artificial respiration was applied, the dog survived with a normal heart beat as long as the respiration was continued. Christison discussed Plato's description of the death of Socrates and found it, on the whole, satisfactory, but he believed that it was "an embellished narrative written for effect"; he pointed out that Plato was not himself present at the death of Socrates.

Christison also worked on the "ordeal" beans from Calabar (which contain physostigmine) and published papers on this subject in 1855. He observed the effects on rabbits and on himself by swallowing a quarter of a bean on an empty stomach. This caused "a peculiar indescribable torpidity of the whole frame," auricular fibrillation, and twitching of voluntary muscles. Being now quite satisfied that he had got hold of a very energetic poison, he used the water in which he had just been shaving as an emetic, and got his son to call in James Young Simpson, the professor of midwifery and discoverer of the anaesthetic effects of chloroform. One of Christison's pupils, Thomas Fraser (1841 to 1920), followed up this work on the ordeal beans. He purified the alkaloid and demonstrated its effects on the heart, glands, voluntary muscle, and intestine. He showed that it constricted the pupil when applied to the surface of the eye and introduced it into medicine for this purpose (15).

In later life Christison became interested in cocaine and carried out experiments on himself at the age of 78. He must have been an energetic old man, since these experiments involved walking 15 miles at four miles an hour and climbing 2900 feet up a mountain. He found that cocaine removed extreme fatigue and made him temporarily less hungry and less thirsty, but eventually his appetite returned (1).

In 1872 Thomas Fraser, who was then 31, gave two lectures on pharmacology to the Royal College of Physicians of Edinburgh. He says he found himself in the difficult position of having too many things to choose from. Within his reach were the fruits, seldom altogether ripe, but without exception temptingly attractive, of numerous investigations in the field of pharmacological research. These two lectures were published in the *British Medical Journal* and are still well worth reading (16). It would be interesting to know what other fruits he rejected in favour of these two, which ripened early under his care.

The first lecture deals with the relation between the chemical properties and the physiological action of active substances (known today as SAR). This was a new idea at that time. With Professor Crum Brown, Fraser had shown that when a methyl group was combined with the nitrogen in strychnine to make a quaternary base, the convulsant action on the spinal cord disappeared, and the new drug caused paralysis at neuromuscular junctions. This was shown by experiments on frogs similar to those which Claude

Bernard had done with curare. The same chemical change produced a similar change in other drugs acting on the spinal cord, such as brucine and thebaine, which now caused paralysis instead of convulsions, but it did not have the same effect on drugs acting on other tissues; atropine, for example, when methylated, retained it actions on the cardiac vagus and the pupil. In the light of later work, we believe that the failure to cause convulsions is due to failure to pass the blood-brain barrier.

The observation that a small chemical change may greatly alter the actions of a drug was news in 1872; it seems less surprising now, when a great industry has been built upon it. On the other hand, Fraser was not the first person to believe that the actions of drugs depend on their chemical properties and, in this lecture, he mentions some of the theories that had been put forward. It is surprising to find how modern some of these sound today. Dr. Blake, for example, had discovered that, in some cases, the actions of drugs were correlated with the shapes of the crystals which they formed. Dr. Rabuteau had observed that the toxic effects of metals increased with the atomic weight.

At the end of this lecture Fraser discussed the reasons for the curious fact that some drugs act at one place and some at other, and said something which should encourage those who are trying to isolate receptors:

> There must undoubtedly be some difference between the chemical properties of each of the structures influenced. The discovery of the spectroscopic characters of haemoglobin has greatly extended our knowledge of the actions of such substances as carbonic oxide, by placing at our disposal a means of defining the chemical reactions that take place between it and the blood. In giving expression to the anticipation that similarly delicate tests of chemical reaction will yet be discovered for each of the special histological elements of the body, I do not think we err by being too sanguine.

These words suggest that, if receptors can be obtained in solution, it should be possible to detect the effect of drugs upon them by physical and chemical methods.

Fraser's second lecture dealt with drug antagonism. He points out that some antidotes destroy the poison in the stomach, but that others act after absorption. He emphasizes the fallacies which complicate the interpretation of clinical observations on the effects of antidotes, where it is not possible to know whether the patient would have died without any antidote at all. He then describes his own work on the antagonism between physostigmine and atropine, when both are injected subcutaneously in rabbits. This antagonism itself was a new idea at that time, but Fraser was interested in the quantitative aspects of it. After a given dose of physostigmine there is a range of doses of atropine that will save life. If too little is given the rabbit dies of physostigmine, and if too much is given it dies of atropine. As the dose of physostigmine increases this range gets less, and, if the dose of physostigmine is more than $3\frac{1}{2}$ lethal doses, life cannot be saved by any dose of atropine. He plotted the results on a graph, with atropine on a horizontal

scale and physostigmine on a vertical scale, and drew a line which separated combinations of doses which led to death from those which led to recovery. No one else made graphs like this for about half a century, and then Dr. S. Loewe, now of Salt Lake City, reintroduced them and called them isobols; they still provoke discussion.

Fraser's experiments showed that small doses of atropine saved life by opposing the lethal action of physostigmine, but he also obtained evidence that small doses of physostigmine caused death by increasing the lethal action of atropine. Unthinking persons may perhaps find this result surprising, but it was just the kind of thing that Fraser expected and his experiments were designed to detect it. He points out that, as both atropine and physostigmine possess a number of separate actions, it was not unreasonable to anticipate that several of them are not mutually antagonistic; in some cases the two drugs might be expected to work together.

At the end of this lecture Fraser compared the use of antidotes with the treatment of disease; rabbits can be killed by excess of antidote, and patients may be killed by excessive treatment, but, in both cases, careful work can determine the best dose.

Soon after Fraser had given these lectures he left the department and became medical officer of health in Cheshire, England. Christison retired in 1877, and Fraser was a candidate for the chair. He was supported by a large number of famous people, including Sydney Ringer, Paul Bert, E. Vulpian, Carl Ludwig, Oswald Schmiedeberg, and many others (17). Liebreich, who was professor of materia medica in Berlin and who had himself introduced the first hypnotic (chloral), said that Fraser's influence on the development of modern pharmacology was to be recognized as epoch making. The result was that Fraser was elected to the chair, which he occupied for 41 years (1877 to 1918), so that Christison and he, between them, lasted 87 years in the chair.

Fraser was not only professor of materia medica but also professor of clinical medicine in that stupendous institution, the new Royal Infirmary, which was built soon after his appointment. He was a great clinician and a great teacher. The different stages of the examination of the patient

> were done successively by pairs of students called down from the steep benches of the theatre to the area where the patient lay in bed, the chief lying back in a wooden armchair at the head of the bed, with a fierce expression on his face like a watching hawk ready to strike [McNeil (24)].

These students really learned their clinical medicine and they learned another thing—the precise use of words.

For many years Fraser was also active in the laboratory. He studied the actions of an arrow poison which, like calabar beans, came from Africa. He isolated the active principle, strophanthin, and introduced it into medicine as a substitute for digitalis, which was quicker to act and less likely to cause cumulative effects (18). He carried out a long series of experiments on snake venoms and produced immunity, not only by repeated injections, but also by oral administration.

His first assistant was Matthew Hay [Hay (21)] who says that the chief was courteous and considerate, but aloof and did not discuss research work with him; each worked independently on his own problem. In his later years Fraser was seldom seen in the labs, and all the work was done by assistants. W. G. Sillar did much of the teaching; Joseph Tillie did fundamental experiments on the action of curare on the central nervous system [McIntyre (23)]. This was in the tradition of the department where Christison had studied the paralytic action of coniine, and Fraser had studied that of the quaternary bases. In all these cases the action of the drug might have been either central or peripheral. James Gunn, who became the first professor of pharmacology in Oxford, was one of Fraser's last pupils. In the end, Sir Thomas Fraser, the pharmacologist, became a legend associated with a frail old man with bronchitis, carried forward by an indomitable spirit (19).

In those days it was not unusual for one man to be a clinician and a laboratory scientist as well. The professors of pathology, medical jurisprudence, and gynaecology were also professors of clinical medicine, but when Fraser retired his department was divided; even Fraser had been unable to remain active in both fields. Arthur Cushny became professor of pharmacology, and J. C. Meakins became professor of therapeutics. This division of duties has been very successful in Edinburgh, and it is surprising that more medical schools have not followed Edinburgh's lead. The two professors co-ordinate their teaching and combine in the conduct of examinations, and some of the students appear to learn more of the relation between theory and practice than they would be likely to learn from a single department.

At the same time a new department of chemistry in relation to medicine was started. George Barger was the professor, and fundamental work was done by Charles Harington on the structure and synthesis of thyroxine and by A. R. Todd on the structure of thiamine.

E. Stedman carried on the tradition that all the best work on physostigmine was done in Edinburgh. He determined its chemical structure and showed that it acted as an ester which competed with acetylcholine for an enzyme in blood, for which he proposed the name cholinesterase; he also made the first synthetic anticholinesterases—in one of the first applications of the principle of antimetabolites. G. F. Marrian succeeded Barger in 1939.

Arthur Cushny (1866 to 1926) was appointed Fraser's successor in 1920 (13). This was the first time that the chair had been occupied by a man trained outside Edinburgh. Cushny qualified in Aberdeen and worked as a young man with Schmiedeberg of Strassburg. At the age of 27 he was appointed to succeed Abel as professor of pharmacology at Ann Arbor, Michigan, where he worked for 12 years (1893 to 1905). It was there that he wrote his great *Textbook of Pharmacology and Therapeutics*, the first really comprehensive book in any language to deal with the subject primarily from the experimental side. It was there that he produced in dogs the condition to which he gave the name of auricular fibrillation, and, in association with Edmunds, recognized the condition in a human patient. It was there that he

started his classical studies on digitalis and on the different activities of optical isomers.

In 1905 Cushny became the first professor of pharmacology in University College, London. The lectureship in this college had been rendered illustrious by the name of Sydney Ringer, who was primarily a physician in the hospital, but the subject of pharmacology had grown, and it was decided to start a separate department. Cushny remained in London for 13 years, during which time he established himself as the leading British pharmacologist. In 1918 he succeeded Fraser in Edinburgh. The fine room which had held the museum of ancient drugs and arrow heads and poisons from all over the world was dismantled to make a large laboratory—to the horror of the old professor who appeared like a ghost and accused his successor of sacrilege. Cushny was professor in Edinburgh for only eight years; he died with high blood pressure at the age of 60. He was an impressive figure and a great man, but his hesitant manner and high pitched voice made him ineffective in open debate.

Cushny played an important part in establishing pharmacology as a science. He was responsible for purging the *British Pharmacopoea* of many useless substances and he did much to convince the world of the value of laboratory work on the action of drugs. His main interests were digitalis (11), the secretion of urine (10), and the actions of optical isomers (12), on each of which he wrote a monograph. His work on digitalis led to a better understanding, not only of the clinical effects of the drug, but also of the physiology of the heart and the causes of arrhythmias. His work on the secretion of urine helped to clarify thought and to establish the view that certain substances are reabsorbed in the tubules. His observations on optical isomers showed that laevorotatory hyoscyamine, hyoscine, and epinephrine are more active than their dextro rotatory isomers. These were the first examples of a pharmacological fact of wide significance.

Cushny was succeeded in 1926 by A. J. Clark (1885 to 1941) who had been his pupil and successor at Univeristy College. Clark was descended from a family of Quakers and was born in Somerset; it was the first time that the professor of materia medica in Edinbrugh was not a Scotsman. After a brilliant career as a student in Cambridge, Clark held appointments in various pharmacological laboratories in London. He served for four years in the army in the World War I and was DADMS (Deputy Assistant Director of Medical Services) to a division. After the war General Smuts was starting a medical school in Cape Town and offered posts to several brilliant young soldiers, including Clark who went out as professor of pharmacology. Clark found a South African wife, who shared his enthusiasm for hill climbing, but returned to England after little more than a year to be professor of pharmacology at University College, London.

He rapidly acquired a reputation as a very well read and thoughtful pharmacologist, with an especial interest in fundamental mechanisms and quantitative calculations. As a very small boy, he had impressed his elders by making calculations of the cubic capacity of Noah's Ark and comparing

it with that of a pair of elephants. In later life Clark calculated the area covered by a monomolecular layer of a small dose of acetylcholine and compared it with that of a muscle fibre on which the drug acted. In 1933 he wrote a book (4) which was full of such calculations and graphs showing the relations between dose and effect and time and temperature and the quantitative aspects of antagonism and synergism. He compared these graphs with similar graphs derived from experiments on enzymes and bacteria and adsorption and radiations; for example, he compared the relation between the dose of a drug and its effect on living tissues with the dose of light and its effect on a photographic plate. Clark did much to standardize methods of calculation, but pointed out that the errors of pharmacological experiments were generally so large that the results could be fitted equally well by a wide variety of simple mathematical formulae. "It seems fair to assume," he said, "as a general principle that, if a pharmacological reaction appears simpler than an analogous reaction in non-living systems, the simplicity must be apparent rather than real."

He wrote a longer book on the same lines in 1937 as an article in *Heffter's Handbuch*, entitled "General Pharmacology" (5). This is a thrilling book, bubbling over with ideas and written with speed and enthusiasm; it has stimulated thought by provoking arguments. If Clark had lived longer, general pharmacology would now be a separate branch of knowledge with a journal of its own.

Clark also wrote a textbook of *Applied Pharmacology* (2), of which seven editions were published in 17 years, and books on *Comparative Physiology of the Heart* (6), the *Metabolism of the Frog's Heart* (7), and *Patent Medicines* (3); the last book involved him in a libel action.

In World War II Clark was again in the army, as an authority on chemical warfare. His second visit to France was a dramatic one. He left his lectures in Edinburgh and crossed the channel when the German Army was advancing rapidly in 1940. After various exciting adventures, he found himself at Hazebrouck, where he took over, and ran for a few days, a convent hospital. He commandeered ambulances and applied treatment to wounds and sore feet. He came out at Dunkirk by destroyer and returned to continue his lectures in Edinburgh after an absence of only a fortnight.

A year later he underwent an operation for intestinal obstruction. A volvulus was found and treated, but Clark died of shock that night. His sudden, tragic death at the age of 54 must have been caused by exhaustion—intensified by the difficult conditions of war and rations. It was a great blow to pharmacology (8).

When I went to Edinburgh [Gaddum (20)] I was following a well-established route. Like Cushny and Clark, I had been professor of pharmacology at University College. My chief technician, Nelson E. Condon, had also come the same way; he was appointed by the college in London as a small boy before Cushny arrived in 1905. At first he was the only technician, and then he was head technician, and now he is still head technician under my

successor, Walter Perry. He came to Edinburgh with Cushny in 1920, but he is still obviously a Londoner, and a most amusing man. When we congratulated him at a dinner of the British Pharmacological Society for having been a pharmacologist for 50 years he made a most amusing and eloquent speech. He has invented many ingenious pieces of apparatus which are widely used; he has made an important contribution to the work of a series of different professors.

I managed to collect in Edinburgh a number of people who shared my interest in the use of biological methods of assay to estimate pharmacologically active substances in extracts of animal tissues. Marthe Vogt, Henry Adam, and T. B. B. Crawford all worked in this field, and I am especially indebted to Dr. Vogt, who came to Edinburgh in 1946; without her the department would have been a much lesser place. R. P. Stephenson is interested in quantitative pharmacology and receptors; R. B. Barlow is primarily a synthetic chemist.

In 1958 I retired from Edinburgh to become Director of the Agricultural Research Council's Institute of Animal Physiology, near Cambridge, and Dr. Vogt has now joined me there. The safest course for me would have been to stay on, as long as possible, as the head of a very famous department, but it will no doubt be better for that department to be directed once more by a young Scottish professor.

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