# PHARMACOLOGY AND NERVE ENDINGS

## FIRST DIXON MEMORIAL LECTURE
## BY SIR HENRY DALE

The first lecture in therapeutics and pharmacology in memory of Professor Walter Ernest Dixon of Cambridge was delivered by Sir HENRY DALE, F.R.S., in the Barnes Hall of the Royal Society of Medicine on December 11th. The chair was taken by Professor J. H. BURN, president of the Section of Therapeutics and Pharmacology, and the proceedings were opened by Dr. ROBERT HUTCHISON, President of the Society, who expressed the pleasure with which the Society had accepted from the organizing committee the trusteeship of the sum collected to endow the lecture. Professor Dixon was highly esteemed in that Society, and they felt that his splendid scientific work deserved commemoration.

Sir WILLIAM WILLCOX, chairman of the organizing committee, said that Professor Dixon, who passed away on August 16th, 1931, was one of the most distinguished pharmacologists of the day. In addition to his great scientific qualities, he was extraordinarily human. The speaker had heard Cambridge undergraduates declare that they would rather go to a lecture by Dixon than to a musical comedy, but the lectures imparted scientific material of the highest kind. Dixon was altogether a most attractive personality, a true friend, loved and respected by all who knew him. After his death the examiners in pharmacology at Cambridge talked over the question of a memorial, and went to see Mrs. Dixon, who was in favour of the establishment of a memorial lecture. Eventually a fund was collected amounting to between £700 and £800, and this was handed over to the Royal Society of Medicine for the foundation of a biennial lecture on some subject in which Dixon had been interested. Therapeutics and pharmacology had been rather neglected from the point of view of lectureships, though Edinburgh had had the Cameron lectureship for some years. The subscribers to the fund included a large number of students. The Society of Apothecaries subscribed handsomely, as did the Pharmaceutical Society. The British Medical Association was not permitted under its constitution to make such donations, but it had perpetuated Dixon's memory in another way by the foundation of a scholarship. Sir William Willcox ended by introducing the first lecturer, Sir Henry Dale, whom he described as one of the greatest biochemists in this country.

### THE SCIENTIFIC CAREER OF W. E. DIXON

Sir HENRY DALE began by suggesting that Dixon's memory could best be honoured by considering some new and progressive phase of activity in the field of research and teaching which received so strong an impulse from his life and work. It would be a poor tribute to the memory of any man of science merely to recall at intervals the state of knowledge during his lifetime, or even newly to assess the value of each part of the harvest of discovery which fell to his own reaping. Far better to study some new and interesting growth from the ground where he dropped the seed, or, it might have been, only prepared the soil for later sowing. But with the loss of their friend still fresh in the memory, they could not be content on this first occasion to pay only an impersonal tribute. He was still remembered among them as a vivid and inspiring personality, who, more than any other, was responsible for the awakening in England of interest in pharmacology as a progressive science. Dixon went to Cambridge in 1899, and he was still there, as reader in pharmacology, at the time of his death, thirty-two years later. Sir Henry Dale said that he himself just missed the direct contact with him there, for Dixon went to Cambridge as he was about to leave, but from his immediate juniors he soon heard of the new life which had been breathed into pharmacology in the university, where the subject could now be studied, no longer in terms of traditional materia medica and empirical therapeutics, but as a living body of experimental science, closely linked with physiology.

The attraction which he had for young workers was a part of Dixon's charming and generous personality. His kindliness and robust humour endeared him to students and colleagues alike. He had real gifts as a raconteur, and his simple and vivid presentation of scientific matter made him an effective popular lecturer, and gave authority to his opinions far beyond the circle of those having expert knowledge of the subject. The subjects on which he worked and wrote had a wide variety. He had an almost exuberant interest in any new line of knowledge touching on pharmacology, and a desire to share in its exploration, and his conception of the scope of pharmacology tended to expand well beyond the study of drugs and their action, and to include any procedure finding application in therapeutics.

The lecturer dwelt upon Dixon's work with Brodie on the physiology and pharmacology of the bronchioles, which seemed to have provided a starting-point for the development of one of his predominant pharmacological interests. It was this work, he thought, which first brought vividly to his notice the remarkable resemblance between the actions of certain alkaloids and those of the autonomic nerves. With Brodie he reached the conclusion that adrenaline acted on sympathetic nerve endings.

### THE AUTONOMIC NERVOUS SYSTEM

The suggestion was first made by Elliott that autonomic nerves transmitted their effects by releasing at their endings specific substances which reproduced their action. This worker suggested that the resemblance between the effects of sympathetic nerves and those of adrenaline might mean that sympathetic impulses, on arriving at the nerve endings, released small quantities of adrenaline, or something like it, in immediate relation to the effector cells, which would then give the same responses as to adrenaline artificially applied. Dixon saw that if this were a true conception an analogous mechanism would almost certainly be used by parasympathetic nerves, and he pictured the substance transmitting their effects as something like muscarine. Dr. Dale showed a slide of Dixon's, illustrating what the latter held to be experimental evidence of its release when the vagus nerve was stimulated. It was now known that the vagus transmitter was not muscarine, but an extremely unstable ester of choline, and free choline was probably the substance responsible for the effects which Dixon observed. Dixon appeared to have been discouraged by the scepticism with which his evidence was received, but there was no doubt that he had grasped a true conception, with characteristic conviction and enthusiasm, though the evidence which really established it came many years later, from a much simpler type of experiment.

It was at the annual meeting of the British Medical Association in Toronto in 1906 that Dixon made the first mention of his heart–vagus experiments, and at the same meeting Hunt and Taveau described the intense activity of acetylcholine. (Both papers appeared in the same issue of the *British Medical Journal*, 1906, ii, 1807 and 1788.) Nobody at the time suspected any thread of connexion between the observations presented in two entirely independent communications. Sir Henry Dale himself made a thorough investigation of the actions of acetylcholine in 1914, but another fifteen years had to pass before the substance was found occurring in an animal organ in such quantity as to enable its isolation and

chemical identification to be made. This was done by Dale and Dudley in 1929 (*Journ. of Physiol.*, lxviii, 97).

### THE CHEMICAL TRANSMISSION OF NERVE IMPULSES

The lecturer next described the work of Otto Loewi, who established by a simple experiment the transmission of the effects of autonomic nerve impulses by the peripheral release of specific chemical stimulants, and said that it was now generally admitted that parasympathetic effects were so transmitted by release of acetylcholine and sympathetic effects by the release of a substance related to adrenaline. The detailed evidence for these two kinds of chemical transmission of autonomic effects had been frequently reviewed. More recent evidence indicated that a chemical mechanism of this kind also effected the transmission of nervous activity at the synapses in peripheral autonomic ganglia and at the motor nerve endings on voluntary muscle fibres.

Feeling the need of terms to describe nerve fibres, or their impulses, in terms of a chemical function, which could no longer be regarded as corresponding to their anatomical origin, he (Sir Henry Dale) had suggested the term " cholinergic " to describe those which transmitted their action by release of acetylcholine, and " adrenergic," those which employed a substance resembling adrenaline. He thought it no longer possible to doubt that the liberation of a small quantity of acetylcholine when a preganglionic impulse arrived at a synapse played an essential part in the transmission of the excitation to the autonomic ganglion cell, and that the post-ganglionic impulse was essentially a separate physiological event. The preganglionic fibres and their impulses might be classed as " cholinergic," though the process by which their effects were transmitted to the ganglion cells differed widely in detail from that by which post-ganglionic parasympathetic impulses used acetylcholine to produce their modifying actions on the spontaneous activities of plain muscle and gland cells.

Sir Henry Dale asked his audience to consider the bearing upon all this of data, long available, which displayed the functional similarities and differences between different fibres of the peripheral nervous system by the method of regeneration after artificial cross-suture of nerves. He referred in particular to a series of papers published by Langley and Anderson between 1897 and 1904. Their work could be summarized in the statement that any cholinergic fibre would functionally replace any other cholinergic fibre, and that any adrenergic fibre would replace any other adrenergic fibre, but that neither could assume the function of the other.

### REVISION OF PHARMACOLOGICAL CONCEPTIONS

The general conception of the mode of transmission of the effects of nerve impulses which was even now taking shape would obviously entail some revision of pharmacological conceptions and terminology. It had no longer any scientific meaning to say that acetylcholine and adrenaline reproduced the effects of parasympathetic and true sympathetic nerves, because they acted on the respective types of nerve endings. It was truer to say that parasympathetic nerve impulses reproduced the peripheral effects of acetylcholine, because, when they arrived at the nerve endings, they liberated that substance in relation to the effector cells ; and the same was true of sympathetic nerve impulses and adrenaline, with the still necessary reservation as to the chemical identity of the transmitter —namely, that it was still open to question whether it was adrenaline itself. In either case the action of the chemical substance must be on the effector cells and not on the nerve endings. When atropine or ergotoxine produced its specific paralysis it did so by rendering the effector cell specifically insensitive to acetylcholine or to adrenaline. Similar conceptions, *mutatis mutandis*, applied to the actions of acetylcholine on ganglion cells and striated muscle fibres, and to the annulment of those actions with blockage of the corresponding nervous excitations by nicotine and curare respectively. It was still necessary to account for the fact that when a substance like acetylcholine was artificially applied the effector cells responding to its action were predominantly those in relation to which it was normally liberated as the transmitter of nerve impulses. It was similarly difficult to trace more than a general chemical similarity between adrenaline and some of the substances which shared, in varying degrees, its selective action. He doubted whether the use of such terms as " myoneural junctions " or " receptive substances " to describe hypothetical components of the effector cells, to which their selective responses might be attributed, would serve any longer to clarify the issue.

### PROBLEMS YET AWAITING SOLUTION

As to the manner in which the nerve impulse on reaching the nerve ending caused the chemical transmitter of its action to appear, the evidence was meagre as yet, and not wholly consistent. The latest results supported the view that the transmitter was not newly formed by synthesis as each impulse arrived, but held in some inactivating and protective complex from which the nerve impulse released it, and from which it was easily separated by ordinary methods of chemical extraction. In the one case yet investigated, by Engelhart (1931), this " depot " was dependent for its maintenance on the integrity of the nerve endings, and disappeared or became depleted when the nerve fibres degenerated. By the interpretations given to the earlier evidence this disappearance might be taken to mean that the " depot " belonged to the nerve ending, but it might merely mean that its maintenance was dependent on the arrival of nerve impulses at a normal rate, and that its depletion with nerve degeneration was comparable to an atrophy of disuse. On either conception it seemed possible to give a clearer interpretation to the actions of the only two specifically stimulant bases for which an action on nerve endings appeared to be really supported by evidence. One of these cases was that of eserine, in connexion with which Anderson, nearly thirty years ago, recorded certain experiments showing that the normally potent constrictor effect of eserine disappeared entirely with degeneration of the post-ganglionic fibres. To-day Sir Henry Dale thought that the effect of eserine might be more reasonably attributed to the accumulation of acetylcholine, the liberation of which, by the play of impulses in post-ganglionic fibres, was normally balanced by the destructive action of the cholinesterase, which eserine inhibited. The other case was that of tyramine, certain sympathomimetic actions of which had been found to disappear with nerve degeneration and under the action of cocaine. Tyramine might act by liberating the transmitter from the depot, cease to act when this was depleted, and act again when it was replenished ; and the same might be true of ephedrine.

In conclusion, Sir Henry Dale said that no nearer approach had been made to the fundamental pharmacological problem why a particular type of chemical structure, or several unrelated types, should be associated with a specific action on particular types of reactive cell. The newer evidence merely exposed the nature of the problem and cleared the ground for eventual attack. He could picture the eager interest with which Dixon would have welcomed this clarification. As pharmacology approached one of its fundamental tasks it would sadly miss his fertility in ideas and the stimulus of his buoyant optimism.

### VOTE OF THANKS

Professor J. H. BURN, in proposing a vote of thanks to Sir Henry Dale, expressed astonishment at the progress which had been made in this pharmacological field. Even within the last twelve or eighteen months a very big step forward had been taken in respect of the fundamental facts of pharmacology, and the whole terminology was being revised. Since the time of Langley and Anderson (the beginning of the century) there had been no such important development as that which began with Loewi's work in 1921, and which had made astonishing progress during the last year or two.

## REGISTRATION OF OSTEOPATHS BILL

### LORD MOYNIHAN'S SPEECH

In the House of Lords, on December 11th, Viscount Elibank moved the second reading of the Registration and Regulation of Osteopaths Bill. This motion was carried by 35 votes to 20, and the Bill was referred to a Select Committee, with full power to call witnesses. A report of the debate, from our Parliamentary Correspondent, appeared in the *Journal* of December 15th (p. 1132). We print below the full text of Lord Moynihan's speech in moving the rejection of the Bill.

#### REASONS FOR REJECTION

It is to me a matter of no little regret that I feel myself compelled to oppose a Bill introduced by my noble friend Lord Elibank. I do not forget that when, a shrinking and timorous novice, I had the audacity to introduce a Bill to your Lordships' House, the fact that the Bill passed its third reading was due in part to the invaluable help and wise counsel of the noble Lord in special Committee. But, if I may be permitted to say so, I fear that the noble Viscount has not fully perceived the implications, still less foreseen the irreparable calamity that would result if your Lordships gave your assent to this measure. My objections come from two quarters.

#### LEGAL ASPECTS

In the first place the Bill involves a negation of all the principles already embodied in the Medical Act of 1858. Before this Bill, if passed by Parliament, could become effective this Act would surely have to be repealed. This Bill would defeat the intention and effect of the Medical Acts, which through the *Medical Register* provide a clear line of discrimination between those who have, and those who have not, passed through the recognized medical curriculum. The relevant purpose of this Act is the protection of the public from the ignorant and dangerous attentions of those who have undergone no adequate training or any training in the sciences upon which medicine is based, who know little or nothing of the normal structure of the human body by dissection, of the morbid changes appearing in disease, of the proper or disordered functions of organs, or of that multitude of scientifically discovered and scientifically tested truths upon which the clinical work of physicians and surgeons is founded. The Medical Act of 1858 is primarily an Act for the safeguarding of the public ; and this Bill seeks to set aside all the carefully constructed substantial defence which time, circumstance, and opportunity have so frequently shown to be necessary, and to substitute a very frail protection and simulacrum. If by some miracle of perversity the Legislature should accept such a Bill as this, the claim now put forward would assuredly not end with osteopaths. If one particular "theory" of medicine were granted recognition contrary to the Medical Act of 1858 (Sections 23 and 28) a precedent would be created for the official recognition of any other cults which cared to include a smattering of medical subjects in the curriculum. There is nothing in the Medical Act to prevent any man, qualified or unqualified, from practising osteopathy. Many of your Lordships are far more competent than I to express a considered opinion upon this first point I raise—namely, that acceptance of this Bill would require that the Medical Act at present in force, by which, so far as legislation can secure it, the safety of the public is protected, should be repealed.

#### PROFESSIONAL ASPECTS

The second objection I venture to offer concerns not the legal, but the professional aspect of this Bill. Its acceptance would involve a denial of, and would hold up to obloquy, the whole scientific basis of medicine. If there is one country in the world which should regard itself as the custodian, protector, and guardian of scientific medicine, it is our own ; for it was in this country that modern scientific medicine had birth, and it was in this country that the greatest discoveries, foundation stones, and landmarks in the history of medicine were made. The claim may justly be made that medicine is at once parent and nurse of all science. For the methods by which all science advances are those first introduced, or in their origins most successfully applied and established, by practitioners of medicine.

The inductive method of logic was created not by Aristotle, nor by Socrates, nor by any philosopher, but by Hippocrates, of whose ancient and serious diligence Bacon reminds us: the full value and right application and appreciation of the experimental method we owe to Galen. It is by these two methods, and by these alone, that all scientific advance takes place. After Galen the methods used by him and by Hippocrates were submerged in the reign of authority which lasted for over a thousand years, a dark, sterile period in which denial of the teaching of Hippocrates was not only disloyal, but heretical, and might, and not seldom did, cost a man his life, as unhappy Servetus, discoverer of the pulmonary circulation, learnt at the guilty hands of Calvin in 1553. The first gleam of light was seen in Italy, in Salerno, oldest of her universities, and so far as medicine was concerned in the wealthier University of Bologna and in Padua, famous for great teachers.

#### THE FOUNDATIONS OF SCIENTIFIC MEDICINE

It was the magic of Fabricius of Padua which attracted our own William Harvey to that university, where he undertook those researches which ended in his discovery of the circulation of the blood a little over three centuries ago. That discovery is the one indestructible foundation upon which all scientific medicine is based ; and Harvey was empowered to make it by bringing together once again the Hippocratic and Galenic methods of inductive inquiry, comparison, generalization, and experimental proof. But until John Hunter, the patron saint of the Royal College of Surgeons of England, created with the help of Morgagni the science of pathological anatomy, little was known of those structural changes in organs which enabled men to correlate them with the symptoms of disease to which they give rise. The lot of the patient was, however, little improved, in surgical matters at least, until immortal Lister, a member of your Lordships' House, basing himself upon Pasteur (already medallist of our Royal Society) and his work on fermentation, attributed infection in wounds to the propagation of living organisms within the wound, and so made possible the immense, almost incredible, advances that have taken place not in surgery alone, but in medicine also, since the recognition of the part played in general disease by focal infection. It is chiefly upon the work of Harvey, Hunter, and Lister that the science and art of medicine have been founded: three great Englishmen. That is my reason for asserting that we in this country are in special degree the custodians of scientific medicine.

#### OSTEOPATHY A DENIAL OF SCIENTIFIC MEDICINE

Osteopathy has not only no connexion with the main stem of scientific medicine: it is a complete denial of the truth of scientific medicine. If there be any truth in the fanciful and fallacious basis of osteopathy, there is none in the true science of medicine. The two systems do not run side by side, they are not complementary or mutually supporting. They are in direct and hostile opposition. If one is true the other must be false. If osteopathy is true the foundations of scientific medicine are not well and truly laid ; then scientific physiology created by Harvey, pathological anatomy as founded by John Hunter, our knowledge of its infection and its relation