British Journal of Pharmacology (2001) 133, 945–950

www.nature.com/bjp

[Originally published: Volume vol 133(7), pages 945–950]

SEVENTH W.D.M. PATON MEMORIAL LECTURE
'THE MAN WHO NEVER WAS – Walter Ernest Dixon FRS'

Alan W. Cuthbert

Emeritus Shield Professor of Pharmacology, University of Cambridge, 1979–1999, currently at the Department of Medicine, University of Cambridge, Cambridge, CB2 3QQ

The title for this Paton Memorial Lecture was chosen without the slightest disrespect for the person about whom I shall speak. As I explain the reasons for my choice I hope you will agree it is apposite. Many of you will have read the book by Nigel Balchin or have seen the film of the same name 'The man who never was.' The story concerns an episode of naval espionage in World War II, in which the German High Command was fed false information contained in documents carried on the body of a naval lieutenant washed ashore on the Spanish coast. Not only were the documents not what they seemed to be, but neither was the lieutenant. Rather he was an unfortunate soul who had died of pneumonia in a British hospital and whose next of kin had given permission for the subterfuge. Thus this man's contribution to the war effort was of incalculable value, yet his name is lost in the mists of time. So it is with the person about whom I shall speak, a person relatively unknown in the pharmacological world, except perhaps in Cambridge, yet one whose seminal contributions are the basis upon which others, who we associate with the foundations of our subject, built their studies.

I shall speak of Walter Ernest Dixon FRS. Walter Dixon was born on June 2, 1871, the younger son of Robert Bland Dixon of Darlington. He went to school in Darlington and at Dulwich, gaining a Science Entrance Scholarship to St. Thomas's Hospital in 1890. He rapidly amassed both scientific and medical qualifications that were to lead him on the path to a pharmacological career. By the age of 27 years he had Bachelor of Science Degree from London University, Membership of the Royal College of Physicians, Licentiateship of the Royal College of Surgeons, a London University MB BS and MD and a Diploma in Public Health from Cambridge.

After obtaining his first medical qualifications Dixon became a house physician at St. Thomas's and then a Demonstrator in the Department of Physiology at the same institution. His connection with Cambridge started with the Diploma in Public Health. He must have impressed the people there, as he was appointed as assistant to J.B. Bradbury, the Downing Professor of Medicine in Cambridge, while still holding the Demonstratorship at St. Thomas's. For many years, Dixon continued to hold two appointments, being elevated to a Lecturership in Pharmacology at Cambridge, where he resided, going up to London to King's College to deliver his lectures, where he held the post of Professor of Materia Medica and Pharmacology. In 1919, Cambridge made him Reader in Pharmacology and he immediately resigned his chair at King's and devoted himself to setting up a department of pharmacology in Cambridge. You will be aware that the period up to 1919 included the time of the Great War. During the War, under the guise of a lieutenant in the Royal Navy, Dixon was engaged on diplomatic duties in Spain, a curious exactitude to the basis of my title, except fortunately Dixon was still very much alive. He was awarded an OBE for services to his country for his war work, but there is no record of his contributions during this time.

While W.E. Dixon's list of publications demonstrate an extraordinary breadth of endeavour, I shall not attempt to deal with them all. Rather I will concentrate on what is, I consider, his most important work. For those who might wish to follow up other parts of his oeuvre a list of publications can be found elsewhere (Gunn, 1932).

Dixon was acutely aware of the need to raise the subject of pharmacology beyond a mere description of phenomena and to give the subject proper scientific credibility. It was important to discover the precise location of the effects of drugs and the physico-chemical reasons for their selective actions. He was particularly interested in the effects of drugs on nerves and nerve endings and their selectivity for sensory nerves, studying apocodeine and cocaine in particular. Dixon was impressed by the speed at which volatile substances caused their effects and inclined to the view that many drugs acted by physical means on sensitive structures. This was a totally different view to the one taken by Ehrlich with his 'Corpora non agunt nisi fixata' (a drug will not work unless it is bound). To demonstrate that some drugs may act physically rather than chemically reacting with the system, he devised the following experiment. Mixing strychnine with emulsified brain tissue he showed that this had no effect on the lethal dose, but simply delayed the symptoms, as did inert substances such as starch or gum. Thus strychnine was not bound or consumed by nervous tissue, while it clearly acted at that site. What a bold experiment this was, to attempt to reduce the strychnine concentration by receptor binding and estimate the remaining alkaloid by bioassay. As there was no detectable disappearance of strychnine in this experiment his prejudice for a physical effect was strengthened. In principle, Dixon's experiment is no different to the first successful demonstration of quantitative receptor binding by Paton & Rang in 1965 using ^{14}C-labelled atropine. It also echoes other work, by Shaw and colleagues in 1967, who assayed the residual tetrodotoxin, after a low concentration had been used to block squid axons, in an attempt to measure an upper limit for the density of voltage sensitive sodium channels in nerve membranes.

Figure 1 Portrait of W.E. Dixon.

Dixon readily accepted that some agents, such as adrenaline and secretin, combined with tissues and were probably destroyed in consequence. The idea, that sympathetic nerves liberated adrenaline, had been suggested by Elliott in 1904. Dixon extended this idea to drugs in general, but by experimental observation rather than speculative argument. In 1907 he wrote in the Medical Magazine:

> 'If physiological activity is brought about by the chemical combination of an animal alkaloid with some substance in the activated tissue, as it is, probably, in the two examples given (adrenaline and secretin), why should not such a procedure be responsible for all forms of activity? That is to say, when a muscle contracts, when a gland secretes, or a nerve ending is excited, the cause in each case may be due to the liberation of some chemical substance, not necessarily set free in the circulation as in the case of secretin, but more likely liberated at the spot upon which it is to act.
>
> 'In order to test the validity of this reasoning, I investigated the action of the vagus nerve upon the heart. Animals were killed by pithing; they were bled, and the vagus nerves were then placed upon the electrodes and excited for half an hour. The heart was next extirpated, placed in boiling water for 10 s and extracted with alcohol. The alcoholic extract was evaporated to dryness and taken up once again with 100% alcohol. This was again evaporated off on the water bath, and a few drops of normal saline added. The solution so obtained was

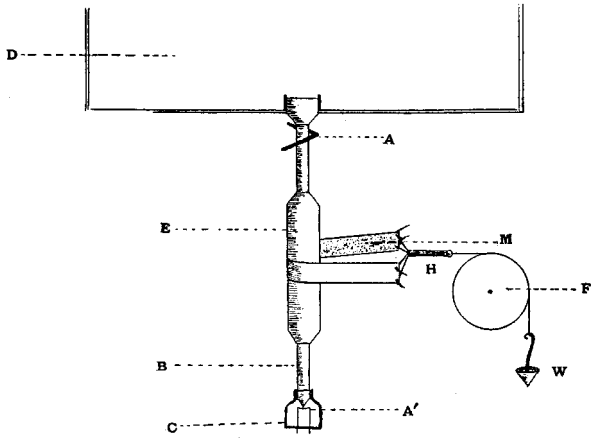
Curriculum vitae WALTER ERNEST DIXON

Born	**June 2 1871**	
BSc (London)	**1891**	
MRCP, LRCS	**1895**	**House physician St Thomas's**
MB, BS(London)	**1896**	**Salters Research Fellow**
		Demonstrator in Physiology
		at St. Thomas's
MD (London)	**1898**	
DPH (Cambridge)	**1899- 1919**	**Assistant to the Downing Professor**
		of Medicine, Cambridge
MA (Cambridge)	**1902**	
	1902?-1919	**Professor of Materia Medica and**
		Pharmacology, King's College, London
	1909-1919	**Lecturer in Pharmacology,Cambridge**
FRS	**1911**	
	1919-1931	**Reader in Pharmacology, Cambridge**
FRCP	**1930**	
Hon. LL D	**1931**	**University of Manitoba**
Died	**August 16 1931**	

Figure 2 Chronology of W.E. Dixon's career.

found to have the power of inhibiting the frog's heart, and, like muscarine, the effect was completely antagonised by atropine. Moreover, the substance disappeared from the solution if it were allowed to stand in the laboratory 24 h.

Hearts treated in an identical manner, but in which the vagus nerve had not been excited, also gave a supply of this inhibitory substance, but in a smaller degree than in the excited heart. I interpret these experiments to mean that some inhibitory substance is stored up in that portion of the heart to which we refer as a nerve 'ending,' that when the vagus nerve is excited this inhibitory substance is set free, and by combination with a body in the cardiac muscle brings about the inhibition. If cardiac inhibition is brought about in this way, drugs must act by liberating the inhibitory hormone. Atropine either prevents the liberation of the hormone, or saturates the substance in the end organ upon which it acts. The former seems the more probable explanation.'



A = lateral bearing supporting the spindle. *A'* = agate cup supporting the spindle *B*. *C* = detachable bell-cap. *D* = drum. *E* = ebonite cylinder on spindle *B*. *F* = pulley wheel. *H* = hooks holding the ciliated membrane *M*. *W* = weight.

Figure 3 Diagram of the cilioscribe.

This experiment was a remarkable *tour de force* and anticipated the well known studies of Loewi, published in 1921. Apart from the lack of immediacy of the result as with Loewi's frog heart perfusion experiments, I suggest the experiment is of equal standing. It is remarkable that Dixon was not tempted to coin a name for 'the body in the heart' or the 'substance in the end organ'. From what is written above he could have called the substance the muscarinic receptor. He did not do so, and the reason may be that one can detect a resistance to the idea that non-endogenous substances can have biological effects of their own, other than by releasing 'an animal alkaloid', i.e., muscarine can only act by releasing 'animal alkaloid' from the nerve ending. Similarly Dixon opted for atropine acting by preventing the release of the 'animal alkaloid' rather than saturating 'the body in the heart'. J.A. Gunn asked Dixon a few years later, when ideas about neurotransmission had clarified, why he had abandoned his studies on vagal transmission. He replied he was deterred by the universal scepticism with which his ideas had been received, illustrating once again that in science you not only have to be original, but also the climate of the time for the introduction of revolutionary ideas has to be right. One must wonder, nevertheless, how much these studies were to influence events over the next two decades.

Like Bill Paton, Dixon had an enduring interest in drugs of intoxication and addiction with a special interest in the development of tolerance. These drugs included alcohol, nicotine, morphine, cocaine, cannabis and mescaline. Here

Figure 4 The Dixon 'Hut'. Built around 1965 in the quadrangle of the Downing Site at the University of Cambridge. Now demolished and replaced with the McDonald Institute and occupied by archaeologists.

Figure 5 A view of the Dixon Laboratory, originally constructed for the Department of Chemistry in 1887 and currently occupied by the Department of Chemical Engineering. The glass boxes on the side of the building were the original fume cupboards. These operated by closing the internal sash window while the side windows were opened to the air (and anybody below).

are some of his own words describing observations made on himself after taking mescaline. 'When sitting with closed eyes, balls of red fire pass slowly across the field of vision. Later these changed to kaleidoscopic displays, with ever-varying colours, or revolving wheels of colour being arranged in a definite pattern, which constantly changes. Only seen with closed eyes. After images are prolonged'. This account was some 50 years before 'The Doors of Perception' by Aldous Huxley appeared, following self-experimentation with mescaline. Dixon argued vigorously against the retention of heroin in clinical practice, arguing that the slender advantage this substance had over morphine was outweighed by the greater danger of addiction, an argument that is still current. Because of his expertise Dixon was invited to join the Committee of the League of Nations on Drug Addiction.

Just after the turn of the century Dixon with Brodie carried out a great deal of work on the physiology of the pulmonary system. Probably the most important contributions were related to the introduction of new methods, such as placing one lobe of a lung in a plethysmograph for recording volume changes or measuring flow rates through organs perfused at constant pressure to determine effects on blood vessels. Dixon was also interested in ciliary action and developed the cilioscribe for its measurement. In this period biological scientists needed to be good gadgeteers, inventing machines to make the required measurements. In the cilioscribe a strip of tissue was held against the surface of a spindle, finely balanced on bearings, such that the cilia were in contact with the spindle. Ciliary motion slowly rotated this and activity was gauged from marks made at constant time intervals on the inevitable smoked drum. While this gadget is ingenious J.H. Burn's method, described years later, of simply timing the movement of lycopodium spores across a ciliated surface using a microscope with a graticuled eyepiece is much simpler.

Towards the end of his career, with Marshall, Dixon became interested in pituitrin, then used in clinical practice to induce labour. He showed that ovarian secretion caused uterine contraction *via* an indirect effect by release of pituitrin. It was discovered that this effect was inhibited by the presence of a corpus luteum. Thus at the end of pregnancy when the corpus luteum involutes, Dixon suggested that the restoration of normal ovarian metabolism, at term, was the mechanism by which labour was induced. It is reported that Dixon was amused that Nature's way turned out to be the same as used in practice.

Dixon's contributions to medicine and science were not exclusively through experimentation. He contributed to the work of the British Medical Association, Royal Medical Society and the Society of Apothecaries. He made contributions to standard texts such as Hale-White's Text Book of Pharmacology and Therapeutics and Heffter's Handbuch. Dixon served on the committees for The British Pharmaceutical Codices of 1911 and 1923, but above all his own book 'A Manual of Pharmacology' was used by generations of students. Published first in 1905 it reached the seventh edition in 1929, and there was a posthumous eighth edition, revised by W.A.M. Smart, in 1936. He also became the English editor for the Journal of Pharmacology and Experimental Therapeutics, succeeding Cushny in the post. It should be remembered that there was no British journal at this time, the British Journal of Pharmacology and Chemotherapy appearing only in 1946.

An account of Dixon's contributions would not be complete without remembering that together with Henry Dale and J.A. Gunn he was one of the three signatories to a circular letter, sent in June 1931, to 30 persons in charge of departments for teaching pharmacology or working in institutions of pharmacological research, suggesting the formation of a pharmacological Club, the first meeting to

be held at Oxford on July 3–4, 1931. Twenty one of those circulated came to the meeting and it was decided to call the organisation a Society rather than a Club. Only one meeting a year was planned, the second to be on July 1, 1932. Dale, Dixon and Gunn were appointed as the first committee, with the responsibility of drawing up the constitution. Dixon died prematurely, aged 60, on August 16, 1931, but can properly be considered as one of the founding fathers of the British Pharmacological Society. Dixon's home was for many years at Whittlesford, a village a few miles from Cambridge and is his final resting place.

Looking back at Dixon's contributions it is remarkable that he was not promoted to Professor while at Cambridge, especially because of his influence in promoting pharmacological research in Britain. His personal motto *'Dire n'est rien: faire est tout'*, was one of which he could be justly proud. Even so his words were influential, and by all accounts he was an inspiring teacher of generations of Cambridge medical students. As Dale commented 'Pharmacological teaching in England, when Dixon began, presented an unappetising mixture of half obsolete materia medica with empirical therapeutics. In Dixon's hands it became a lively adventure in experimental science'. When Dixon began researching around 1898 there were no chairs of Pharmacology in England although there were some in materia medica, all Scottish universities had chairs of materia medica, the one in Edinburgh being established as early as 1768. In Dixon's time the pharmacological world was dominated by Germany and the U.S.A. In the U.S., Abel and Cushny, both pupils of Schmeideberg, were, in 1898, appointed to Chairs in pharmacology at John Hopkins Medical School and Ann Arbor respectively. Cushny, however, returned to England in 1905 to the Chair of Pharmacology at University College, and Oxford established a readership in pharmacology in 1912 elevating it to a Chair in 1917. By 1932, Chairs in pharmacology were established at Sheffield, Liverpool and Belfast. Yet Cambridge still failed to recognize the importance of this new medical science and had not recognized Dixon's eminence. He was '*the man who never was*' a professor in Cambridge. Extraordinarily, Dixon has been more honoured by the University after his death than during his lifetime. Dixon was succeeded in Cambridge, in 1934, by E.B. Verney FRS, as Reader in Pharmacology, moving from the Chair of Pharmacology at University College. It was a further 12 years, in 1946, before Cambridge finally created a Chair in Pharmacology, Verney being appointed the first Marmaduke Sheild Professor, a post he held until 1961. Arnold Burgen, FRS was the second Sheild Professor appointed in 1962. The Department was poorly served by the University, it had only a few rooms in the Physiological Laboratory where it carried out its research, as well as held practical classes for medical and veterinary students. Arnold Burgen went off to see Sir Henry Dale, the upshot of which was that the Wellcome Trust provided support for a wooden building erected on the lawn in front of the Department of Botany, now Plant Sciences, and much to the annoyance of the botanists. This new structure was called the Dixon Building, or more colloquially the Dixon Hut. Its acquisition more than doubled the research space available to the Department, but a significant fraction of the new building was still occupied by teaching laboratories. It was not long before the growing department again found itself in need of space. In the late '70s I managed to persuade the then Vice Chancellor, Professor Jack Linnett FRS, to visit the Dixon Hut, while a medical class was in progress, and to see the level of crowding. I told the medical students that they could help the Department by ensuring full attendance for the Vice Chancellor's visit. The medical students did us proud, not only did the Thursday class turn up on mass, but so did the Tuesday one. Soon after that the University provided more teaching space, while research laboratories were situated elsewhere, at Hill's Road. The new teaching space consisted of the teaching laboratory formerly occupied by the Department of Metallurgy, and before them the Department of Chemistry, for whom it was built in 1887. This space was refurbished to suit the Department's needs and the new Dixon Laboratory opened for business. In 1989 the Department moved to its present premises in Tennis Court Road and was able to abandon its various out-posts, the Dixon Laboratory passing to the Department of Chemical Engineering. This space, now equipped for a fourth type of science, is now called the Lower Dixon Laboratory. Laboratory space on the next floor and also belonging to Chemical Engineering is now called the Upper Dixon Laboratory. I'm sure Walter Dixon would be amused to learn that the University that failed to make him a professor or provide more than modest facilities, is currently increasing the number of laboratories bearing his name.

In 1979, when I became the fourth Sheild Professor I received a long, handwritten letter from Bill Paton, then Professor Sir William Paton. It contained some of the soundest advice for which I have been continually grateful. Bill was a real enthusiast for both his subject and the history and development of its foundations. He was a stickler for attributing new ideas and discoveries to those who had actually made them and insisted that one could really learn from what had gone before. I am reminded again of that bit from Coleridge; 'If men could learn from history, what lessons it may teach us! But passion and party blind our eyes, and the light which experience gives is a lantern on the stern, which shines only on the waves behind us!' How many of us have missed making a new finding because of a failure to appreciate what had gone before. I submit that there were those who did appreciate what Walter Dixon had achieved and built upon it. Bill Paton was only 15 years of age when Dixon died so it is doubtful they ever met. I believe they would have got on well together.

In composing this lecture I have been heavily dependent on the obituary of W.E. Dixon, written by his friend and colleague J.A. Gunn and published in the Journal of Pharmacology and Experimental Therapeutics in 1932 and to the shorter obituary, not ascribed, published in the Proceedings of the Royal Society, Series B, also in 1932.

References

Biographical works about W.E. Dixon.

ANON. (1932). Walter Ernest Dixon 1871 – 1931. *Proc. Roy. Soc. Ser. B,* **110,** xxix – xxxi.

BYNUM, W.F. (1981). An early history of the British Pharmacological Society, pp. 9 – 10, a British Pharmacological Society publication.

GUNN, J.A. (1932). Walter Ernest Dixon. *J. Pharm. Exp. Ther.,* **44,** 3 – 21. (This obituary has a full list of Dixon's publications).

HOLMSTEDT, D. & LILJESTRAND, G. (1963). Readings in Pharmacology, pp. 181 – 184, Pergamon Press, Oxford.

Non-biographical references

COLERIDGE, S.T. (1831). T. Allsop's *Recollections*.

DIXON, W.E. (1907). On the mode of action of drugs. *Med. Megaz. (Lond)*. **16,** 454 – 457.

HUXLEY, A.L. (1954). *'The Doors of Perception'*.

INCHLEY, O. & DIXON, W.E. (1905). The cilioscribe, an instrument for recording the activity of cilia. *J. Physiol.,* **32,** 395 – 400.

LOEWI, O. (1921). Ueber humorale Uebertragbarkeit der Herznervenwirkung, (I. Mitteilung). *Pflug. Arch. ges. Physiol.,* **189,** 239 – 242.

MOORE, J.W., NARAHASHI, T. & SHAW, T.I. (1967). An upper limit to the number of sodium channels in nerve cell membranes? *J. Physiol.,* **188,** 99 – 105.

PATON, W.D.M. & RANG, H.P. (1965). The uptake of atropine and related drugs by intestinal smooth muscle of the guinea-pig in relation to acetylcholine receptors. *Proc. Roy. Soc. B,* **163,** 1 – 44.