FREDERICK HUGHES SCOTT AND HIS CONTRIBUTION TO THE EARLY HISTORY OF THE TRANSMITTER CONCEPT

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THE first experimental evidence in favour of the theory of humoral transmission of nerve impulses was Otto Loewi’s classical observation on the vagus and accelerans substances in the frog’s heart (1). It is well known that ideas of this kind had been discussed earlier, and the literature that is often quoted includes work by T. R. Elliott (2), on the possibility of a release of adrenaline from sympathetic nerve endings, and that by Dixon (F.R.S. 1911), on the release of muscarine in the mammalian heart (3). There are, however, even earlier publications: in 1937 Sir Henry Dale read a paper (4) to the Physiological Society entitled: ‘E. Du Bois-Reymond and chemical transmission’. Dale refers to a paper by Du Bois-Reymond (For. Mem. R.S. 1877), in which ideas of chemical transmission were formulated (5).

The aim of this essay is to draw attention to two remarkable papers by F. H. Scott (6,7) that have in recent years been rescued from total oblivion. The present writer became aware of these at the occasion of the Royal Society Discussion on ‘Subcellular and Macromolecular Aspects of Synaptic Transmission’, held in 1970. Two of the contributors quoted Scott: A. D. Smith (8) the paper from 1905, and A. Dahlström (9) that from 1906 (7).

Reading these two papers one is at once struck by their quality and also by the modernity of outlook. The first of these two papers, entitled: ‘On the Metabolism and Action of Nerve Cells’ was published in Brain. The author, F. H. Scott, Ph.D., M.D., describes himself as ‘Formerly Demonstrator of Physiology, University of Toronto’. He refers to earlier work carried out at Toronto (10,11), on the histochemical properties of the so-called Nissl substance in nerve cells. He considers this substance to be a nucleoprotein, a view taken earlier by Held, a German anatomist. The most important new contribution of the paper from 1905 is the demonstration, that a substance with the same properties as the Nissl substance in nerve cells occurs also in secretory cells, and he describes this material particularly in the exocrine cells of the pancreas and in the chief cells of the fundus of the stomach.

He asks: What do these cells have in common with nerve cells? The exocrine cells make material for export, mainly protein and enzymes. So he proposes that it is this feature that is shared by nerve cells. He quotes the defini-
tion of an enzyme that was current at the time, as that of a catalyst, a substance that promotes a chemical reaction without entering into the balance sheet, and he refers particularly to specificity as a prominent property of enzymes. He writes:

Seeing that nerve-cells have great resemblance both in their constitution and in their action to these cells and believing that the nervous system is something more than a mere system of conducting paths, I formed the hypothesis that nerve-cells are true secreting cells, and act upon one another, and upon the cells of other organs by the passage of a chemical substance of the nature of a ferment or proferment from the first cell into the second; and that stimulation of the latter is made through a partial destruction of the proteid constituents of the second cell where the impulse acts. The nature of the alteration or destruction produced by this substance is, I believe, very similar to that which occurs in the ordinary digestion of proteids. This hypothesis has to do with the stimulation of cells, and not with conduction which proceeds in the substance between the neurosomes; nor has it anything to do with the ultimate action of the stimulated cell which acts according to its own nature and may, as in muscle, use chiefly carbohydrate. When the impulse reaches the nerve ending it causes, I believe, the discharge of some of the neurosomes, which are very numerous in that situation, and which have, I consider, the same relation to the proferment that the zymogen granules in gland cells bear to the proferment of those cells.

He goes on to say: 'In this place I shall not discuss this subject further than to point out that just as irritability and conductivity are not identical, so there is in all probability, a difference between conductivity and the process of excitation of the next cell.' He continues his discussion by referring to the controversy on 'contiguity v. continuity' that was taking place at that time, then comes out firmly in favour of the idea of contiguity. He says: 'Many physiological facts show that although nerve-cells may touch and appear continuous with certain technique, yet they are as distinct centres of metabolism as any other two cells of the body.'

The end of the paper says:

Just as in ferment-forming cells we have nucleus, prozymogen and zymogen, so in nerve-cells we have nucleus, pro- or Nissl substance and neurosomes. The process of excitation, like that of secretion, involves, I believe, the discharge of neurosomes in the region of the synapse. Since discharge into other cells means the using up of formed material, it must be
an exhaustible process, and the process of complete recovery at the synapse must depend on the integrity of the connection of the synapse with the nucleus and cell body which are the original seats of formation of the material involved in the activity. Of this relation I have experimental evidence, as well as direct evidence, showing the independence between the conducting property of nerves and their power of exciting other cells. These I hope to embody in another paper.

This paper carries no indication of its place of origin. The conclusions just quoted, which strike us as so remarkably modern in outlook, lead directly to the second paper, which was published in The Journal of Physiology, (7). In contrast to the paper from 1905, it gives the places where the work had been done; it has, below the title, these words: 'From the Physiological Laboratories of the Thierärztliche Hochschule, Berlin, and University College London.' Its title is 'On the Relation of Nerve Cells to Fatigue of their Nerve Fibres'. The author refers to his earlier work, and in the experimental part he describes observations according to which, during stimulation of dorsal roots of the frog’s spinal cord, irreversible fatigue sets in much earlier when the stimulation was carried out on roots in which a cut had been made between the dorsal root ganglion and the point of stimulation. In the summary, Scott (7) says:

The facts given above seem to me difficult to explain on the common view that the ineffectiveness of a nerve on protracted stimulation (so far as it is not due to fatigue in the cells of the activated organ) is due to abolition of the conductivity of the nerve ending. And it seems to me simpler to suppose that the nerve cells secrete a substance the passage of which from the nerve endings is necessary to stimulation. The recovery of effect after transient fatigue I attribute to the passage of a portion of this substance down the nerve fibre to the nerve ending. The absence of recovery after prolonged stimulation I attribute to the whole of the substance in the nerve fibres being used up, and to their being incapable of making more when severed from their nerve cells.

The paper ends with these acknowledgments: 'Before concluding I take this opportunity of thanking Professor Munk and especially Professor Starling for their kindly advice as well as the use of their laboratories and instruments, and also Professor Langley for suggestions and help in the publication of this paper.'

It is easy to see why these two papers have found resonance and understanding in recent years. The underlying idea, that of an analogy between the
activity of neurones and the secretion from glandular cells, is in line with the concepts that are widely accepted today. At the time at which Scott wrote these papers there was little support for the existence of a close relationship between neuronal and secretory tissues. It is perhaps not surprising, therefore, that these ideas were not followed up by others. One is left, however, with the puzzling fact that there was no further work from Scott in which these ideas were pursued. How is it that Scott’s name ceased to be familiar to students of neurobiology?

In order to understand this one has to learn more about Scott and his history. Frederick Hughes Scott was born in Toronto in 1876. According to an article in a University of Toronto alumni magazine now defunct, ‘Torontensis’, he entered the University of Toronto from the Collegiate Institute at Ottawa. He graduated with honours in Natural Science in 1897, and entered the Department of Physiology at Toronto University. The head of the Department was A. B. Macallum (F.R.S. 1906). Macallum, who became Scott’s principal teacher at Toronto, was an important figure in the development of physiological science in Canada (see the obituary notice by Leathes, (12)). It was he who established the Department of Physiology at Toronto.

When Scott arrived in the department, Macallum had completed some work that included a method for determining the phosphorus content of animal tissues (13). This was the method that Scott used in his studies. He carried out a critical examination of the so-called Nissl granules in nerve cells. These intracellular bodies had been discovered a few years earlier; Nissl had shown that these cell organelles, found in the cytoplasm of nerve cells, had characteristic staining properties and they could be shown up by the use of methods designed originally to stain the nucleolus. Scott followed up a suggestion made earlier by Held, that the Nissl substance was a nucleoprotein, and using Macallum’s method he demonstrated the presence of phosphorus in the Nissl substance. He published his findings extensively in the Transactions of the Canadian Institute, in a paper of over thirty pages that was copiously illustrated. Macallum seems to have been pleased with his student’s work, since in the following year it was re-published in the University of Toronto Studies, as Number 1 of the Physiological Series, which was edited by Macallum (10,11).

These two publications represent Scott’s work from Toronto. The monograph was accepted for his Ph.D. degree, which was awarded in 1900. He then studied medicine, combining his studies with a Demonstratorship in the Physiology Department. He obtained his degree of M.B. at Toronto in 1904. Scott’s movements after this period are uncertain. He may have gone from Toronto directly to Berlin to work with Hermann Munk at the
Physiological Laboratory of the Veterinary Academy there. H. Munk (1839–1912) was a well-known physiologist, who had been a student of J. Müller (For. Mem. R.S. 1840). Munk moved from the Physiology Department to the Veterinary Academy in 1876, as Professor of Physiology there, a post he still held at the time of Scott’s visit. Much of this information is taken from a memorial oration given by R. Du Bois-Reymond (14). In other words, at the time of Scott’s visit, Munk was approaching the end of his active life.

I have been unable to find out anything about Scott’s stay in Berlin. Upon enquiry, I learnt from Professor F. Jung, of the Humboldt University, Berlin, that the papers relating to the Veterinary Academy were lost in the war; the academy is now incorporated into the Humboldt University.

It is impossible, therefore, to assess how much of the work embodied in Scott’s (6,7) papers was carried out in Berlin and how much comes from University College London. It is clear, however, that under the leadership of E. H. Starling (F.R.S. 1899) the College was one of the great centres of physiological research.

Scott must have come to London with good credentials. He was the holder of the Royal Society’s MacKinnon Studentship for 1906–07; thus he must have arrived in London not later than 1906.

In the archives of the Royal Society, two letters in Scott’s hand are preserved. The first of these, dated 1 July 1907, is a report on the work done during his tenure of the Mackinnon Studentship. The second letter, dated 23 July 1907, is a request for the payment of £50 on account, from the Gunning Fund, for the purchase of several instruments.

The first of these letters is given here verbatim:

The Secretary, Royal Society.

Sir: In regard to yours of the 24th asking for a report of the work done while I held the MacKinnon Studentship, I may say that during the year I have held this studentship I have tried to follow the metabolic processes in nerve cells by trying the effect of the injection of nervous extracts on the sera of animals and the effect of this serum on the nervous system of other animals. Owing to the number of factors involved no definite conclusion has yet been reached on this point but some interesting observations on the effect of the injection of serum have been obtained. These results have not yet been published.

Also in conjunction with Drs Henry Head and W. M. Bayliss some interesting results have been obtained on the conduction in a nerve graft uniting the central ends of two sensory nerves. A demonstration of some of
the results was given at a meeting of the Physiological Society on September 29th.

In my previous microchemical work I had shown the importance of nuclein compounds in the metabolism of nerve cells. It is desirable to examine these further and to compare them with those of other tissues. This has been done in conjunction with Dr R. H. Aders Plimmer. One paper ‘On the methods supposed to localize phosphorus in cells’ has already been published (Journal of Physiology XXXV p. 119) while another on a method of separating nucleoproteids from phosphoglobulins is nearly ready for publication. Other work on nucleic acid, phosphopeptones, lecithin and kephalin is well advanced.

Faithfully yours
F. H. Scott, Ph.D., M.B.

The paper referred to in this report will be discussed in detail below (15). As to the joint work with Sir Henry Head and Sir William Bayliss, there is no subsequent publication. However, the meeting of the Physiological Society was a special meeting that was held at the occasion of a visit of I. P. Pavloff (For. Mem. R. S. 1907) to London. Its programme is preserved in the archives of the Physiological Society, where we read: ‘a Special Meeting took place in the Physiological Laboratory of University College, London, on Saturday, 29 September 1906, at 4 p.m., on the occasion of the visit of Professor Pavloff to London’. Five demonstrations were given at the meeting; under No. 2 we read: W. M. Bayliss, H. Head and F. H. Scott—‘Conduction in a nerve-graft uniting the central ends of two sensory nerves’. The programme contains just the title; the experiments were not published. The meeting of the Physiological Society and Pavloff’s visit are also recorded in the official History of the Physiological Society (16).

The value of Scott’s work must have been appreciated by his senior colleagues. At the termination of the Mackinnon Studentship, he was awarded a Sharpey Scholarship at University College London for the year 1907–08 and he received the Schaefer Prize for 1907. Also, in 1906, he was elected a member of the Physiological Society. Mr D. H. Steven, M.A., Vet. M.B., Hon. Archivist of the Physiological Society, has kindly sent me a transcript from the Society’s Candidates’ Book. Scott was proposed by W. M. Bayliss (F.R.S. 1903) and supported by R. H. A. Plimmer, E. F. Armstrong (F.R.S. 1920), N. H. Alcock, G. H. Burch, J. B. Leathes (F.R.S. 1920), C. J. Martin (F.R.S. 1901), Victor Horsley (F.R.S. 1886), L. Hill (F.R.S. 1907), A. R. Cushny (F.R.S. 1907), E. P. Cathcart (F.R.S. 1920), M. Hamill, O. Grunbaum, T. R.
Elliott (F.R.S. 1913), Hugh K. Anderson (F.R.S. 1907), T. Lewis (F.R.S. 1913) and E. E. Henderson.

The name of R. H. Aders Plimmer deserves special mention. R. H. Aders took the surname of his stepfather, H. G. Plimmer (F.R.S. 1910). He is today best remembered as one of the founders of the Biochemical Society, of which he became an Honorary Member and its first Historian (17). He had a long and close link with University College London (18). He had been an undergraduate at the College where he took his B.Sc. in 1899. He then spent some time in Berlin, in the laboratory of Emil Fischer (For. Mem. R.S. 1899), one of the pioneers in the study of proteins. He returned to England before Scott could have arrived in Berlin. From 1904, he was back at University College London, where he worked in the Physiology Department in close association with Bayliss and Starling. His connexion with Scott must have been a close one during the latter's stay, as they published two joint papers, to be discussed later.

Scott's contribution to the history of chemical transmission ends with the two papers of 1905 and 1906 (6,7). What remains to be discovered is why this work, obviously highly regarded by his contemporaries, met with almost complete oblivion, a fate it did not deserve.

The clue for this, it seems, can be found in the work that followed upon the two papers just quoted. Still in 1906, Scott (15) published another paper in the Journal of Physiology entitled 'On Methods supposed to localise Phosphorus in Cells'. This is the paper referred to in Scott's report to the Royal Society. It contains a critique of the histochemical method that he had used in his early work from Toronto, to determine phosphorus in tissues. This method had been described by his Canadian teacher, Macallum (19). He now shows that by the use of Macallum's method one does not obtain inorganic phosphate from a number of organophosphates, including nucleic acids. He ends his paper with these conclusions: 'The above figures show the failure of the nitro- or the hydrochloric molybdate reagent when applied to tissues. They show that acids readily remove most of the phosphorus from nucleic compounds in some soluble form but not as inorganic phosphate. The whole Lilienfeld-Monti-Macallum reaction is therefore wrong and all deductions as to the distribution of phosphorus compounds (other than inorganic phosphates) which have been deduced from the use of their reagents are valueless.' (15).

In the experimental part Scott mentions that the hydrolysis experiments had been done 'in conjunction with Dr R. H. Aders Plimmer who has kindly allowed me to make use of these results. The method followed was that used by Bayliss and Plimmer in their work on the liberation of phosphorus from
caseinogen'. The paper here referred to had appeared in the *Journal of Physiology* (20); it is entitled ‘The separation of phosphorus from caseinogen by the action of enzymes and alkali’. In it the authors show that upon hydrolysis by proteolytic enzymes phosphorus appears in soluble form, but most of it not as inorganic phosphate, but as organophosphate. We can assume, therefore, that Plimmer’s experience in this field was decisive for the work carried out by Scott (15).

That the method devised by his old teacher, Macallum, was at fault was probably a severe disappointment to Scott; moreover, it may well have been the reason why he did not continue with the work that he had begun with so much promise. In retrospect, this fact, that his method of phosphorus determination had been at fault does not much detract from the value of Scott’s work. What we remember today, is that he first demonstrated a relationship between secretory and neuronal tissue and that he postulated the existence of what he called ‘neurosomes’, particles that were filled with material destined for export at the nerve endings and that travelled down the axon, from the cell soma to the endings, before being liberated. To us this conclusion appears based mainly on the tinctorial similarities between neuronal and secreting tissues. However, it is unlikely that matters appeared to Scott in the same light.

In the remainder of his time at University College London, much of his work was carried out in collaboration with Plimmer. There are two joint publications (21,22). In these papers we can see some relationship to the earlier work: they are of mainly methodical character in which conditions for the determination of organophosphate compounds (phosphoproteins, nucleoproteins and phospholipids) are examined.

There is one additional publication by Scott from University College that is not related to his earlier research interests (23). In it he deals with changes that occur in the regulation of respiration after the section of the vagus nerve. This paper, in which helpful discussion with E. H. Starling is acknowledged, is Scott’s last work from University College London.

From London Scott did not return to his native Canada. One wonders if his harsh criticism of Macallum’s method had anything to do with this. Instead in 1908 he went to the Physiology Department of the University of Minnesota Medical School at Minneapolis, at first as Assistant Professor. At Minneapolis he stayed for the remainder of his life. He became an Associate Professor in 1912 and a Full Professor in 1918, a position from which he retired in 1944, and he died in Minneapolis on 21 June 1951, aged 75 years.

It so happens that there exists a good description of the University of Minnesota Medical School from the time of Scott’s arrival there. This can be found
in Abraham Flexner's classical study of 'Medical Education in the United States and Canada' (24), which was carried out under the auspices of the Carnegie Foundation. Flexner describes the laboratory facilities at Minneapolis in these terms: 'Excellent, exceedingly attractive and well organized laboratories are provided for all the branches. The instruction is in charge of full-time teachers, generously supplied with books, apparatus and material'. He also says: 'Minnesota is perhaps the first state in the Union that may fairly be considered to have solved the most perplexing problems connected with medical education...'. Finally, he gives the date of his visit: 'May 1909'. That must have been a few months after Scott's arrival at Minneapolis.

A fuller picture of the Medical School at Minneapolis is given in a recent collection of essays on Elias Potter Lyon (1867–1937), Dean of University of Minnesota Medical School from 1913 to 1936 (25). Lyon was a former student of Jacques Loeb, and for some time he also acted as Head of the Physiology Department at Minneapolis. There is no doubt that Scott's scientific training in physiology and his quality as a scientist were fully appreciated. During his period at the Medical School there was a constant stream of scientific papers, published mainly in the American Journal of Physiology. All these were joint papers, written with graduate students and with Scott's name usually in the last position. One of these students was M. B. Visscher, with whom he published a joint paper in 1924 (26). Visscher, who eventually became head of the Physiology Department at Minneapolis, published an appreciation of Scott after the latter's death (27). He refers to Scott's merit as a stimulating teacher of graduate students. However, a speech defect was a great handicap for him, as a lecturer to medical students. This is also referred to in Wangensteen's (25) book. It might be noted that the present writer on his first visit to University College London, in the spring of 1926, met M. B. Visscher in E. H. Starling's laboratory. A well-known paper is the outcome of Visscher's stay at University College (28). One wonders if Scott had been responsible for Visscher's coming to Starling's laboratory.

In his tribute, Visscher (27) emphasizes Scott's influence on his graduate students, and on his importance for shaping the development of the Medical School that he served for thirty-six years. Visscher writes: 'He was among a group of perhaps a score of the faculty in 1908 upon whom President Vincent relied in bringing about the transformation of the University from a school with almost no scholarly work being conducted in it, and one whose medical school was only a little better than a proprietary diploma mill, into an institution which has been placed by independent experts among the top dozen American Universities'.

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From the foregoing account, it seems possible to arrive at a tentative explanation of why Scott’s early pioneering was so long overlooked. In all his later work he himself never returned to the problems that had occupied his mind until 1906.

One would like to find out how it happened that in recent years Scott’s work has been ‘re-discovered’. In an attempt to answer this question, I have consulted the two authors who quoted Scott at the Royal Society Discussion of 1970. I learnt from Dr A. D. Smith that he is uncertain how he first became aware of Scott’s work. He thinks it probable that he saw Scott’s paper in the *Journal of Physiology* (7) by accident, when he was reading in that volume. This is quite possible, particularly since the paper immediately precedes Sir Henry Dale’s classical paper on the physiological actions of ergot (29), the first in the collection of Dale’s papers that were reprinted under the title *Adventures in Physiology*. What must be pointed out is that Smith not only read Scott’s paper, but that he proceeded to look up the earlier paper from *Brain* (6), because that is the one that he quoted.

Scott’s paper from 1906 (7) is that quoted by Dr A. Dahlström (9). I asked her also, and she kindly told me that she had seen a quotation from Scott’s paper in a review article on axoplasmic streaming by Dr L. Lubiniska (30). This article begins with a lengthy verbatim quotation from Scott (7). From this article it is clear that Dr Lubiniska was fully aware of the historic importance of Scott’s early contribution to neurobiology.

How did Dr Lubiniska become aware of the existence of Scott’s work that had apparently lain unnoticed for sixty years? Upon enquiry, she kindly told me that she had looked up the paper by Scott (7) when she saw a reference to it in an article by R. W. Gerard (31). This review, entitled ‘Nerve Metabolism’, is one of 123 pages, with 792 references. I have seen two mentions of Scott’s (7) paper in it; that of 1905 is not quoted. The more explicit reference to Scott takes the form of a footnote, where Gerard says: ‘See also Scott’s interesting results on frog dorsal roots’. This means that Dr Lubiniska did not get her quotation from Gerard; she must have gone back to the original paper in the *Journal of Physiology* and extracted the passage that she reproduced.

There is a second reference in Gerard’s review to Scott’s paper; this occurs in a group of papers quoted in a brief section on neurohumoral mechanisms. In this section Otto Loewi’s work and the transmitter theory are mentioned; Gerard does not come out in support of the theory, but adopts a somewhat ambiguous, waiting attitude that is typical of the period in which the review was written.

It might be mentioned in passing that R. W. Gerard was at University
College London at the same time as Scott’s colleague, M. B. Visscher. Gerard was working with A. V. Hill, on heat production in stimulated nerve, while Visscher was with Starling. The present writer remembers being introduced to Visscher by R. W. Gerard in 1926. Starling was Foulerton Research Professor of the Royal Society at that time.

To sum up, we can say that the survival of any knowledge of Scott’s work seems to have depended on two authors, R. W. Gerard (31) and L. Lubinska (30). However, since the Royal Society Discussion meeting in 1970, there have been several further papers in which Scott is quoted. These can almost certainly be traced to the references in the Royal Society Discussion (32, 33). It seems, therefore, that Scott’s papers have now been safely rescued from total oblivion.

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Notes


