SOME CONCEPTS OF NERVE STRUCTURE AND FUNCTION IN BRITAIN, 1875–1885: BACKGROUND TO SIR CHARLES SHERRINGTON AND THE SYNAPSE CONCEPT

by

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INTRODUCTION

HISTORICAL accounts of the development of concepts of nerve structure and function[1] make it clear that, for most of the nineteenth century, the variety of approaches in neurophysiology and neurohistology combined with the technical infancy of these sciences to prevent any single and coherent account of nerve from forming.[2] In retrospect, it is clear that conceptual advance awaited the elucidation of the structure of nerve.

Over the course of the century, the contributions of a number of investigators, notably Remak (1838), Hannover (1840), Helmholtz (1842), Koelliker (1849), Waller (1850), and Dieters (1865) developed a portrait of nerve emphasizing that nerve fibres (our *axons*), nerve cells (our *cell bodies*),[3] and protoplasmic processes (our *dendrites*) were different parts of the same anatomical unit. Questions about the structural and functional interrelationships between these anatomical units came to the fore.

In 1872, Joseph von Gerlach used the results of his own carmine stains and gold chloride stains of nervous tissue to hypothesize, in the words of a recent historian, '. . . that the ultimate divisions of Deiters' protoplasmic processes, or dendrites, formed a fine-fibred, diffuse plexus that connected together all cells, and from it axons arose to form a second, much coarser network'.[4]

This idea of anatomical interconnection of nerve units, one with the other, became known as the continuity theory, or the nerve net theory, or the reticular theory.[5]

[1] e.g. M. A. B. Brazier, 'The historical development of neurophysiology', in J. Field (ed.), *Handbook of Physiology—Neurophysiology*, Washington, 1959, i, 1–58. E. Clarke and C. D. O'Malley, *The Human Brain and Spinal Cord*, London, 1968. F. Fearing, *Reflex Action: A Study in the History of Physiological Psychology*, Baltimore, 1930. E. G. T. Liddell, *The Discovery of Reflexes*, Oxford, 1960.

[2] See, e.g. H. McIlwain, 'Chemical contributions, especially from the nineteenth century, to knowledge of the brain and its functioning', in F. N. L. Poynter (ed.), *History and Philosophy of Knowledge of the Brain and its Functions*, Oxford, 1957, p. 183.

[3] *Nerve cell*, in its modern usage, did not attain real currency until around the turn of the century. 'I do not know why one should restrict the term "nerve-cell" to the body of the cell and thus exclude from that term the cell-processes. This is not done for any other kind of cell, and it appears to me that the custom which has hitherto prevailed with regard to nerve-cells in this matter is not only inadvisable but even misleading'. E. A. Schäfer, 'The nerve cell considered as the basis of neurology', *Brain*, 1893, **16**, 134.

[4] Clarke and O'Malley, 'The neuron versus nerve net controversy', op. cit., 87–138. Quote from p. 88.

[5] For other general accounts, see A. Andreoli, *Zur geschichtlichen Entwicklung der Neuronentheorie*, Basle, Stuttgart, 1961. C. McC. Brooks, 'Current developments in thought and the past evolution of ideas concerning integrative function' in F. N. L. Poynter (ed.), op. cit., 235–52. F. Fearing, *Reflex Action*, 182–85. E. G. T. Liddell, *The Discovery of Reflexes*, 25–30. See also the studies of Sherrington cited below.

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It attained wide, indeed universal currency, becoming the paradigm (in one or another of its forms) for the neurohistology of the seventies and eighties. Its leading proponent, the Italian Camillo Golgi, introduced his excellent but difficult method of silver staining of nervous tissue in 1873. Although he rejected von Gerlach's dendritic plexus, he described lateral branches in the axon and adduced further evidence for an axonic net. It is important to note that reticular theory coincided nicely with the contemporary requirements of neurophysiology. On any of the then current theories of the nature of nerve force, anatomical interconnection of nerve units was an absolute necessity for the transmission of impulses from unit to unit through the nervous system. In fact August Forel referred to reticular theory as a 'physiological postulate'.[6]

In 1888 and 1889, the reticular theory was challenged by Santiago Ramón y Cajal, an obscure Spanish histologist, whose silver stains of the central nervous systems of various organisms seemed to him to show only contact and not anatomical continuity or anastomosis between adjacent axons and dendrites. Cajal's insistence on the point led large numbers of investigators to enter the field. The subsequent controversy between the reticularists or continuity theorists, and the neurone or contact theorists, as they were called, was not resolved until well into the twentieth century.[7]

Very soon after the neurone theory became a matter of scientific dispute, however, its implications were adopted as the basis for an approach to neurophysiology by Charles Scott Sherrington (1857–1952). Sherrington's contribution to neurophysiology has been well assessed in two recent studies.[8] His book, *The Integrative Action of the Nervous System* (1906)[9] has been compared with Newton's *Principia* and Harvey's *De Motu Cordis*. The recent studies, and earlier ones,[10] have named a number of individuals who may have turned Sherrington toward neurophysiology and influenced his approach to it. His teachers, the great Cambridge physiologists Michael Foster, John N. Langley, and especially Walter H. Gaskell, must be mentioned. David Ferrier and Friedrich Goltz, whose debates over issues of cerebral localization Sherrington followed in the early eighties, were both mentors.[11] Cajal's contribution was certainly vital. Nevertheless, Sherrington's rapid development of the physiological consequences of neurone theory, which was, when he adopted it, at best a highly controversial histological hypothesis, has not been satisfactorily explained. Granit, in whose study the crucial importance of the unitary nerve or neurone to Sherrington's work is emphasized,[12] can only say, 'When Sherrington started experimenting, the nerve-cell or neurone theory did not exist. But by the instinct (for want of a better

[6] Translated in Clarke and O'Malley, op. cit., 106. Cf. the later viewpoint of Ramón y Cajal in his *Recollections of My Life*, trans. E. H. Craigie. (Two volumes edited as *Memoirs of the American Philosophical Society*) Philadelphia, 1937, 336–37.

[7] See notes 4 and 5 above.

[8] R. Granit, *Charles Scott Sherrington: An Appraisal*, London, 1966. J. P. Swazey, 'Sherrington's concept of integrative action', *J. Hist. Biol.*, 1968, **1**, 57–89. J. P. Swazey, *Reflexes and Motor Integration: Sherrington's Concept of Integrative Action*, Cambridge, Mass., 1969.

[9] C. S. Sherrington, *The Integrative Action of the Nervous System*, London, Constable, 1915. Originally published 1906.

[10] Lord Cohen of Birkenhead, *Sherrington: Physiologist, Philosopher and Poet*, Liverpool, 1958. D. Denny-Brown, 'The Sherrington School of Physiology', *J. Neurophysiol.*, 1957, **20**, 543–48. E. G. T. Liddell, 'Charles Scott Sherrington 1857–1952', *Obit. Not. Fell. R. Soc. Lond.*, 1952, **8**, 241–70.

[11] Sherrington studied under Goltz in the winter of 1884–85 in Strasbourg. *The Integrative Action* is dedicated to Ferrier.

[12] Granit, *Appraisal*, 24–44. See also Swazey, *J. Hist. Biol.*, 1968, **1**, 63–69, 76; *Reflexes and Motor Integration*, 74–78, 175–77.

word for man's inaccessible mental activity) that guides the true scientist, Sherrington laid out his course from the very beginning in such a fashion that he was able to avail himself of every parallel advance in the histology of the spinal cord, being a good enough histologist to be able to sift the wheat from the chaff.'[13]

It is the intention of this paper to show that Sherrington's alacrity in accepting neurone theory and interpreting it physiologically may be referable to something more than 'instinct'.[14]

Before Cajal and his fellow neuronists raised their theory to wide notice in the late eighties and nineties, completely independent research by Wilhelm His, using embryological methods, and August Forel, using degeneration methods, obtained results showing that internerve anastomosis did not take place, that nerves were not anatomically continuous, but merely in contact with one another.[15] Their papers, published in 1887, argued forcefully and explicitly against the reticular theories of Gerlach and Golgi,[16] but were largely ignored.[17] There is no evidence that Sherrington read these papers before he read Cajal.

The same cannot be said, however, of a series of physiological researches by George J. Romanes[18] and allied histological work by Edward A. Schäfer,[19] conducted between 1873 and 1879 and published between 1876 and 1885. This research was closely connected with the cardiological research carried out at Cambridge by Walter Gaskell in the first half of the eighties. During this period Sherrington was in intimate contact with Gaskell, as pupil and research student. Sherrington's major work, *The Integrative Action of the Nervous System*, and earlier writings show him to have been as familiar with Romanes' and Schäfer's work as was his teacher.

An examination of Romanes' and Schäfer's papers, cited above, and of the reception of Schäfer's paper by the Royal Society, reveals the beginning of explicit discussion of anatomically discrete nerve units (later the 'neurones' of neurone theory) and the physiological implications thereof. This discussion is interesting, not only for what it tells about physiology in Britain at a time when it was just emerging from the German shadow, and not only as a case study in institutional resistance to new ideas, but also as a most important signpost to the subsequent career of Charles Sherrington. In particular, Romanes' and Schäfer's work seems to have provided Sherrington with a part of the comparative context of his *Integrative Action*. Their concepts and speculations in many cases became crucial parts of Sherrington's neurophysiology,

[13] Granit, op. cit., 29–30. See also p. 32. Sherrington was a good pathologist and histologist; he used this training to advantage in his physiological research.

[14] We know, for example, that Sherrington favoured the concept of localization of function in the cerebrum, sympathizing with Ferrier against Goltz. It is thus interesting that the arch reticularist Golgi interpreted his results as weighing against localization. On Golgi, see Clarke and O'Malley, op. cit., 96.

[15] Forel's account of his work and its reception is interesting. A. Forel, *Out of My Life and Work*, 1935, trans. B. Miall, London, 1937, 162–64, 197.

[16] Clarke and O'Malley, op. cit., 99–109.

[17] '. . . our two papers suffered the fate of the majority of new ideas: they were simply ignored.' Forel, *Out of My Life and Work*, 163.

[18] G. J. Romanes, 'Preliminary observations on the locomotor system of medusae', *Phil. Trans. R. Soc.*, 1876, **166**, 269–313; 'Further observations on the locomotor system of medusae', *Phil. Trans. R. Soc.*, 1877, **167**, 659–752; 'Concluding observations on the locomotor system of medusae', *Phil. Trans. R. Soc.*, 1880, **171**, 161–202; *Jelly-Fish, Star-Fish, and Sea-Urchins*, London, 1885.

[19] E. A. Schäfer, 'Observations on the nervous system of *Aurelia aurita*', *Phil. Trans. R. Soc.*, 1879, **169**, 563–75.

where they were elaborated and placed on a firm scientific basis. Sherrington certainly did not draw directly from Romanes and Schäfer, except in a few instances. Rather his exposure to their work during his early development as a physiologist may be seen as a conditioning which allowed him to entertain certain ideas about nerve structure and function with a readiness which, if we can judge by published work, was not at all evident in his contemporaries.

THE BEGINNINGS

George J. Romanes (1848–1894) was a wealthy young physiologist who had trained under Michael Foster at Cambridge and John Burdon Sanderson at University College, London. In 1873, while at his summer home on the coast of Scotland, Romanes decided to study the jellyfish in order to determine whether or not it possessed a nervous system. This question was at the time still open, though nervous systems had been shown to exist in the known forms higher than the jellyfish on the zoological scale.[20]

Romanes used the method of section to demonstrate the presence of a nervous system in the conical swimming-bell of the jellyfish. He excised the marginal tissue around the rim of the swimming-bell and found that the bell 'thus mutilated' became paralysed, while the marginal tissue continued the rhythmic contractions which had originally been characteristic of the bell as a whole. This 'fundamental observation' showed that the marginal bodies or lithocysts possessed the property of spontaneity. On the other hand, the paralysed bell retained the ability to contract in response to a nip of the forceps or an electric shock. Was this ability to respond the result of direct stimulation of the muscle or did the bell itself also possess nerves which responded to the artificial stimuli? To answer this question, the tissue of the bell was severely sectioned. Waves of contraction passing down the resulting strips of tissue were still observed to follow upon artificial stimulation. This result seemed to rule out the idea that nerves were involved, since differentiated nerves could scarcely be thought to coincide so precisely with the variety of severe forms of section which Romanes used. He found, however, that progressively narrowing a strip of tissue always resulted in a point of narrowness over which waves of contraction could not pass. Since this 'blockage' took place 'completely and exclusively' at a single point, Romanes hypothesized that it resulted from the section of some more or less differentiated 'line' of nervous 'discharge': 'All we have to assume is that there exists *a more or less intimate plexus** of such lines of discharge, the constituent elements of which are endowed with the capacity of vicarious action, and that in some cases the section happens to leave a series of their anastomoses in a continuous state.'[21]

At this point, in his first Royal Society paper (1876), Romanes had been unable to detect histologically the hypothesized nervous elements. His hypothesis is couched in the terms of the prevailing reticular theory. The 'constituent elements' of the 'plexus', in order to be capable of 'vicarious action' (i.e. functional interaction with one

* Unless otherwise noted, italics in the quotations in the text are the original writer's.

[20] *Jelly-Fish* . . ., 13.
[21] *Phil. Trans. R. Soc.*, 1876, **166**, 272–75. The quote is from p. 292. Romanes' use of the term 'vicarious action' is not quite our modern one—see below.

another), had to have their anatomical interconnections or 'anastomoses' in a 'continuous state', that is, intact. The point was that the uncanny ability of the tissue to sustain section (such as a series of interdigitating cuts along a strip) required that the plexus be a rather dense criss-crossing grid of *highly interactive* nerve elements.

In a footnote to a lecture delivered in May 1877, Romanes outlined his views on the interfunctioning of nerve elements, comparing the primitive nervous system of the jellyfish with the peripheral and central nervous systems of the more highly evolved animals. It would not do to draw too close a parallel between the nerve fibres of the jellyfish and those of the peripheral system of the higher animals, since the latter possessed an 'insulating coat' evolved to prevent just that phenomenon of vicarious action which was so prominent a feature of the former. The more fruitful analogy would be between the jellyfish fibres and those of the central nervous system of higher animals, where physiological experiments indicated that a certain degree of vicarious action took place.[22] In his Royal Society papers, Romanes pointedly noted the similarities between observations of nerve function in the jellyfish and the known properties of nerve in higher animals, especially with regard to their response to poisons.[23]

Just as Romanes delivered this lecture, he was arranging that his friend Edward A. Schäfer (1850–1935) spend the late summer with him in Scotland. As he wrote to Darwin early in August, 'Possibly the microscope may show something and so I have asked Schäfer to come down, who, as I know from experience, is what spiritualists call 'a sensitive'— I mean he can see ghosts of things where other people can't. But still, if he can make out anything in the jelly of Aurelia, I shall confess it to be the best case of clairvoyance I ever knew.'[24] Schäfer, at that time assistant to Burdon Sanderson at University College, London, spent his holidays at Romanes' summer home.

[22] '. . . we must remember that in a peripheral nervous plexus as we meet with it in the higher animals—i.e. in the fully evolved form of such a structure—each of the constituent nerve-fibres is provided with an insulating coat for the very purpose of preventing vicarious action among these fibres, and the consequent confusion among the reflex mechanisms which such vicarious action would manifestly occasion. But because insulation of peripheral nerve-fibres is thus an obvious necessity in the case of a fully evolved nervous plexus, it by no means follows that any high degree of insulation should be required in the case of an incipient nervous plexus. On the contrary, any hypothesis as to the manner in which nerve-fibres first begin to be differentiated from protoplasm, must suppose that the conductile function of the incipient nervous tracts precedes any structure, such as that of nerve coats, whereby this function is strictly confined to particular tracts. The antecedent probability being thus in favour of the view that insulating structures are a product of later evolution than are the essentially nervous structures which they insulate, it would clearly be very hazardous to draw any analogy between an incipient nervous plexus such as I suppose to be present in the Medusae, and a fully evolved peripheral plexus of any of the higher animals. A less hazardous analogy would be furnished by the fibres which occur in the *central* nervous system of the higher animals; for here it may be said, both *a priori* from Mr. Spencer's theory, and *a posteriori* from histological indications, that nerve fibres occur in various degrees of differentiation. And that vicarious action is possible to some considerable extent through a bridge of the grey matter of the cord, has been shown by the double hemi-section experiments of Brown-Sequard. Moreover, the admirable experiments of Goltz would seem to indicate that vicarious action is also possible to some extent among the ultimate elements of the brain'. 'Evolution of Nerves and Nervo-Systems', *Proc. R. Instn Gt Br.*, 1879, **8**, 435n.—436n. Lecture delivered 25 May, 1877. The implications of evolution for Romanes' work (e.g. impact of Spencer) may be clearly traced. See my forthcoming paper in the *Journal of the History of Biology*.

[23] *Phil. Trans. R. Soc.*, 1876, **166**, 286, 295–301, 305; *Phil. Trans. R. Soc.*, 1877, **167**, 736–45; *Jelly-Fish . . .*, 213–33, esp. 232, 233.

[24] E. Romanes, *The Life and Letters of George John Romanes*, 2nd ed., London, 1896, p. 64.

Using gold chloride stain, Schäfer showed that Romanes' hypothesis of a plexus of lines of nervous discharge in the swimming-bell (or 'umbrella') of the jellyfish was correct. He described ' . . . an interlacement of nerve-fibres, which covers the whole of the under surface of the muscular sheet, lying between the muscular fibres and the ectoderm-cells, and partly amongst the latter, and which may be termed the *subumbrellar plexus*'. Schäfer emphasized the similarity of the tissues he observed to those of higher animals.[25]

Despite this affinity, the nerve-fibres he observed presented a unique property. Though they formed 'wonderfully intricate interlacements', ' . . . each fibre is entirely distinct from, and nowhere structurally continuous with, any other fibre'.[26] Schäfer did not find it easy to reconcile this surprising observation with Romanes' findings:

> It seemed at first sight almost incredible that with such a prodigious number of nerve-fibres, exhibiting so close an interlacement, there should be no actual junctions of the intercrossing nerves. And it was especially difficult of credence because some of the experiments of Mr. Romanes, performed with the view of testing the amount of section which the tissue could endure without loss of nervous (or excitational) continuity, seemed to point to the existence of a structurally continuous network of nerve-fibres. *Nevertheless, there can be no doubt that the fibres do not come into an anatomical continuity. On the other hand, it can readily be seen that each nerve-fibre comes at one or more points of its course into very close relations with other nerve-fibres . . . . although there is no actual anatomical continuity, abundant opportunity is afforded for inductive action, whether electrical or of some other kind. That physiological continuity is thus maintained it seems as yet premature to conjecture.*[27]

According to Schäfer, it was clear that the subumbrellar nerve plexus was responsible for the rapid spread of impulses over the swimming-bell, producing contractions of the elements of the muscular sheet such that the response of the entire bell was functionally a single beat. It was not necessary that the nerve fibres anastomose with one another:

> . . . as a result of the interlacements which occur, and the closely parallel course which the fibres take in them, *it is reasonable to conclude that nervous impulses are transmitted by some means or another from fibre to fibre*. If so, the result would be the same as if an actual network of nerves existed, viz., the production of a general co-ordination in the contractions—not absolute, it is true, but often nearly so.[28]

The remainder of his observations dealt with the neuro-histology of the marginal bodies or lithocysts around the rim of the bell. Certain tissues therein Schäfer likened to the neuroglia of the vertebrate brain and certain others to the embryonic central nervous system of vertebrates. 'Altogether there can be very little doubt', said Schäfer, 'that we here meet with the first beginnings (in a phylogenetic sense) of a central nervous apparatus.'[29]

IDEAS AND THE INSTITUTION

A reprint of this paper as it was ultimately printed in the *Philosophical Transactions*, 1878, together with the original drawings for the paper, is in the Sharpey-Schäfer

[25] *Phil. Trans. R. Soc.*, 1879, **169**, 564.
[26] Ibid., 565.
[27] Ibid., 566. Italics my own.
[28] Ibid., 567. Italics my own.
[29] Ibid., 570.

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Collection at the Wellcome Institute of the History of Medicine, London. It is the only early scientific paper remaining in the large amount of material which the then Professor, Sir Edward Sharpey-Schafer[30] of Edinburgh placed in a large trunk just before his death in 1935. On the cover of the envelope containing the paper, Schäfer wrote, 'So far as I know this paper contains the first account of a nervous system being formed of separate nerve units without anatomical continuity. Previously it was universally held that the nervous system was composed of networks of nerve fibres.'

Nevertheless the paper has remained more or less unnoticed by historians, with certain exceptions.[31] Schäfer submitted it to the Royal Society, 31 October 1877. It was read 10 January 1878, an abstract appearing in the *Proceedings of the Royal Society*.[32] At the 17 January meeting of the Committee of Papers, it was referred to E. Ray Lankester, newly arrived from Exeter College, Oxford, at University College, London (where he was a colleague of Schäfer's),[33] and to Allen Thomson, an older biologist. On 21 January, Lankester delivered a negative report to the Committee, the weight of his argument being that the nerve fibres described by Schäfer were probably connective fibres. For Lankester, the structural individuality of Schäfer's nerve fibres was a telling point:

> Against the view that the fibres are nerves is the fact that they do not branch and that they end abruptly at each end without being connected with one another or with any other histological element. Hence if they are nerves they differ *toto coelo* from all other known nerves—and Mr. Schäfer has been obliged to propound a hazardous physiological theory to explain the manner in which they might possibly be conceived to function as nerves.[34]

Since Lankester himself could not conceive any manner in which the fibres described might possibly function as nerves (i.e. interact without structural connection), he considered Romanes' results as evidence against Schäfer's.

This report was considered by the 21 February meeting of the Committee of Papers. Thomson, a member of the Committee, submitted his favourable report verbally. The decision was ultimately postponed while Thomson prepared a written opinion. This report, dated 8 March, reiterated his view that the paper should be printed in the *Philosophical Transactions*. He too, however, was suspicious of the free nerve endings described by Schäfer:

> I may however remark 1st that the free termination of the fibres in question described by the author as occurring after a course of three or four millimetres, seems to have led him into speculations respecting the transmission of nervous influence between one fibre and another

[30] Schäfer changed his name to Sharpey-Schafer in 1918.

[31] J. R. Baker, 'The cell-theory: a restatement, history and critique. Part III: The cell as a morphological unit', *Q. Jl Microsc. Sci.*, 1952, **93**, 2, 173–74. T. H. Bullock and G. A. Horridge, *Structure and Function in the Nervous Systems of Invertebrates*, London, 1965, i, 466–72. W. C. Gibson, *Creative Minds in Medicine*, Springfield, Ill., 1963, 58–59, or E. G. T. Liddell, *The Discovery of Reflexes*, 30.

[32] *Proc. R. Soc.*, 1878, **27**, 16–17.

[33] Lankester had had differences with Burdon Sanderson and Schäfer. Burdon Sanderson wrote to Schäfer on 28 July 1877: 'I have just received an extraordinary letter fr. Lankester in which he talks about the "meddling of irresponsible messengers in matters that do not concern them" and say that he has written to the Secretary (!!) to complain of such meddling.

'I write this in order that you may know that Lankester is a greater fool than we took him for & act accordingly'. Wellcome Institute of the History of Medicine, Sharpey-Schafer Collection, 'British Colleagues'. Lankester was an irascible, combative character.

[34] The Royal Society of London Library, *Referee's Reports* 8, no. 137.

which may be deemed premature in the present state of the inquiry; and 2nd that in the examination of some of Mr. Schäfer's specimens, while some fibres are seen to end suddenly or by free terminations as described by him, there appeared to me to be others in which by fine subdivision the fibres were gradually lost in the substance of the surrounding tissues—a possibility obviously contemplated by the author himself.[35]

Despite the report by Thomson, the next meeting of the Committee, 21 March,[36] instructed him to request that Schäfer withdraw the paper pending further research to confirm his conclusions. Accordingly Thomson wrote to Schäfer on 8 April 1878, informing him of the decision and mentioning Huxley's agreement with it.[37]

It may be assumed that William Carpenter and T. H. Huxley, as the leading biological members of the Committee, were the prime movers against publication. Lankester was Huxley's protégé and close friend. Lankester may indeed have expressed himself more forcefully in private than in his referee's report. Schäfer's student, F. H. A. Marshall, reported that Lankester had called the paper 'nonsense'. It seems likely that Marshall got this information from Schäfer himself, who was no man for exaggeration or gossip.[38] It is clear that Huxley's major reservation was likewise the structural individuality of Schäfer's nerve fibres. In a letter on 20 April 1878, after congratulating Schäfer on his election to the Royal Society, Huxley wrote,

> I was not one of the referees and must not 'reveal the secrets of the prison house'. But my own private opinion rather inclined to the conclusion that the paper would be all the better for a renewed exploration of the 'nerve fibres' so as to make sure about their terminations.
> There is not the slightest desire on anybody's part to do other than what is best for you & the paper—nor any doubt about the importance of the observations.[39]

The events of the next few months saw an about-face, summarized in a note inserted by Schäfer in the letter to him from Thomson, mentioned above: 'This letter concerns the reference of my paper on the nervous system of Aurelia to the Archives of the R.S. (A.T. & E.R.L. were the referees). Soon after a paper appeared on the same subject by the Hertwigs & my paper was then hastily exhumed and published in the Transactions.'

The paper, 'Observations on the nervous system of *Aurelia aurita*', was finally published in Part II of the *Philosophical Transactions* of 1878. It includes a postscript, prepared in October of that year, referring briefly to the Hertwigs' monograph. The latter did not supersede Schäfer's work directly in any sense,[40] but probably made Huxley sufficiently convinced of the probable nervous nature of the fibres Schäfer described, that he recommended publication. In his referee's report, Lankester had said, 'If it be considered that Mr. Schäfer has fairly demonstrated that his fibres are *nerve*-fibres, the observation would be of sufficient importance to render the paper

[35] The Royal Society of London Library, *Referee's Reports*, 8, no. 138.
[36] The Royal Society of London Library, *Minutes of the Committee of Papers*, 4. Meetings of 17 January, 21 February, 21 March, 27 June 1878.
[37] The Wellcome Institute of the History of Medicine, Sharpey-Schafer Collection, 'British Colleagues.'
[38] On the other hand, this account of Lankester may be as erroneous as Marshall's report that the paper in question was Schäfer's first. F. H. A. Marshall, 'Sir E. A. Sharpey-Schafer', *Dict. Nat. Biog. 1931–1940*, Oxford, 1949, 789.
[39] The Wellcome Institute of the History of Medicine, Sharpey-Schafer Collection, 'British Colleagues.'
[40] The Hertwigs' paper did not, for example, describe anatomically discontinuous nerve fibres. See Romanes, *Jelly-Fish* . . ., 21 or *Phil. Trans. R. Soc.*, 1881, 171, 201, and Schäfer's postscript.

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eligible for the *Philosophical Transactions*'.[41] Apparently, the independent, coincidental publication by the Hertwigs was the major reason for the ultimate publication of Schäfer's contribution.

NEURONE THEORY BEFORE 1887

Initially, Romanes too was sceptical of Schäfer's nerve fibres, for he wrote to Schäfer on 19 September 1877: 'I am much interested in what you say about the nerves of *Aurelia*. The subject is really most important but it will take a great deal of demonstration to convince me that, at any rate a large percentage of the fibres, do not communicate.'[42]

In his next Royal Society paper on the jellyfish, he referred to Schäfer's work, but remained unconvinced of its necessary significance for his own. He retained the term 'lines of discharge', rather than use 'nerve fibre', when discussing the structural correlatives of the functions he was investigating.[43] In this paper, Romanes again emphasized the probable 'vicarious action' of the nervous tissues which his experiments seemed to indicate.[44] It seems likely that when his third and final paper was published, Romanes was convinced of the truth and importance of Schäfer's observations. Certainly this was the case by the time he brought together all his work in invertebrate physiology in the book, *Jelly-Fish, Star-Fish, and Sea-Urchins* published in 1885. In this book, after describing Schäfer's observations of anatomically discrete nerve fibres underlying the muscle of the jellyfish bell, Romanes wrote the following passage:

> Now, if it is a remarkable fact that in a fully differentiated nervous network the constituent fibres are not improbably capable of vicarious action to almost any extent, much more remarkable does this fact become when we find that no two of these constituent nerve-fibres are histologically continuous with one another. Indeed it seems to me we have here a fact as startling as it is novel. There can scarcely be any doubt that *some* influence is communicated from stimulated fibre *a* to the adjacent fibre *b* at the point where these fibres come into close apposition. But what the nature of the process may be whereby a disturbance in the excitable protoplasm of *a* sets up a sympathetic disturbance in the anatomically separate protoplasm of *b*, supposing it to be really such—this is a question concerning which it would as yet be premature to speculate. But I think it may be well for physiologists to keep awake to the fact that a process of this kind probably takes place in the case of these nerve-fibres. *For it thus becomes a possibility which ought not to be overlooked, that in the fibres of the spinal cord, and in ganglia generally, where histologists have hitherto been unable to trace any anatomical or structural continuity between cells and fibres, which must nevertheless be supposed to possess physiological or functional continuity—it thus becomes a possibility that in these cases no such anatomical continuity exists, but that the physiological continuity is maintained by some such process of physiological induction as probably takes place among the nerve fibres of Aurelia.*[45]

[41] Indeed, Lankester himself was rather rapidly converted. See his article 'Hydrozoa', written probably in 1880, for the ninth edition of the *Encyclopedia Britannica*, reprinted in Lankester *et al*, *Zoological Articles contributed to the 'Encyclopedia Britannica'*, London, 1891, p.62.

[42] The Wellcome Institute of the History of Medicine, Sharpey-Schafer Collection, 'British Colleagues.'

[43] *Phil. Trans. R. Soc.*, 1877, **167**, 664n. Some of Romanes' experiments to elucidate the role of nervous as opposed to muscular elements in the jellyfish bell are extremely interesting. See 716–19, 719n.

[44] e.g. ibid., 706, 719n.–720n.

[45] *Jelly-Fish* . . ., 78–80. Last italics my own. The only commentator who seems to have noticed what he calls the 'prescience' of this passage is Bullock. Bullock and Horridge . . . *Nervous Systems of Invertebrates*, i, 495–497.

Any impact which all this discussion may have had on the substantive growth of neurone theory *per se* (i.e. on the histological researches of His, Forel, and their successors) is extremely difficult to trace. Even Cajal seems never to have learned of it. Apparently, Romanes' and Schäfer's work was simply too circumscribed by the restricted orbit of invertebrate physiology to have had any influence beyond that subject, with one significant exception.

IMPACT UPON SHERRINGTON

Sherrington unquestionably had a detailed grasp of all the Royal Society papers. He cited Romanes' and Schäfer's work in his chapter 'The Spinal Cord', in the second volume of Schäfer's *Textbook of Physiology*, 1900.[46] The circumstantial evidence, as noted above, indicates that he gained this acquaintance in the early eighties while studying with Walter Gaskell and Michael Foster at Cambridge.[47] He nowhere cites *Jelly-Fish, Star-Fish, and Sea-Urchins*, but a popular book, published in London in a well-known science series, and subtitled 'Being a Research on Primitive Nervous Systems', seems unlikely to have escaped his attention. In 1935, Sherrington contributed an interesting summary of Romanes' and Schäfer's joint efforts in the First Sharpey-Schafer Memorial Lecture in Physiology at Edinburgh, entitled 'Sir Edward Sharpey-Schafer and his Contributions to Neurology'.[48]

Romanes' jellyfish researches exemplified the use of concepts of nerve function to embrace behavioral, physiological, and histological data into an integrated whole, a method Sherrington used with such brilliance in *The Integrative Action of the Nervous System*. This work makes clear that for Sherrington, the investigations of Romanes and Bethe on the jellyfish provided a prototype of the primitive, diffuse, nervous system to be contrasted with the central nervous system of higher animals, with its more sophisticated integrative mechanisms.[49] *The Integrative Action* has continual references to the Medusa and a consideration of some of the interactions between Romanes' and Sherrington's researches is instructive.

It is essential to note first, that in 1904, when he wrote *The Integrative Action*, Sherrington was convinced that Apathy and Bethe's contentions that the nervous systems of certain invertebrates, including the jellyfish, were anatomically continuous syncitia, had superseded Schäfer's work.[50] He correlated this with Romanes' observations of the reversibility of waves of contraction in a strip of tissue of jellyfish bell, to adduce evidence in support of a valve-like function of the synapses of higher animals indicated by Ramón y Cajal's 'law of dynamic polarization'.[51]

In a lengthy discussion of refractory phase in relation to reflex discharge of nerve cells and to the simple reflex, Sherrington drew an analogy between the scalptor-reflex-arc (scratch reflex of the dog), the Medusa swimming-bell, and the heart wall,[52] which is extremely interesting in the light of the association of the last two

[46] E. A. Schäfer (ed.), *Textbook of Physiology*, London, 1900, ii, 785.
[47] Both Foster and Gaskell were familiar with Romanes' work. See my forthcoming paper in the *Journal of the History of Biology*.
[48] *Edinb. med. J.*, N. S. IV 1935, **42**, 8, 397–398.
[49] C. S. Sherrington, *Integrative Action*, 311–14. See also J. P. Swazey, *Reflexes and Motor Integration*, 136, 157.
[50] His 1935 lecture fully acknowledges the accuracy of Schäfer's work.
[51] *Integrative Action*, 18, 42.
[52] Ibid., 50, 62–65.

in the researches of Walter Gaskell.[53] He noted, 'Refractory phase was first called attention to by Kronecker and Stirling . . . in 1874, in the heart, and recognized by them as a fact of central importance for cardiac rhythm. In 1876 Marey . . . met the same phenomenon and gave it the name by which it is now known. A year later Romanes' fundamental work on Medusa demonstrated the existence of the same phenomenon there.'[54]

Sherrington pointed out that the crucial role of the refractory phase in each case is to prevent the kind of tetanic contraction which would defeat the purpose of the 'beat' of the cardiac muscle, the muscle of the swimming-bell, and the flexor muscles in the scalptor-reflex. Romanes did not use the term 'refractory phase', but he developed the concept considerably. His third paper on the jellyfish was mainly intended to suggest that the prevailing belief in discontinuous discharge of the ganglia in the marginal bodies, or lithocysts, as responsible for the rhythmic beat of the jellyfish bell may be incorrect.[55] Rather, ' . . . the natural rhythm of these tissues—and so, from analogy, of gangliomuscular tissues in general—is probably due to a double process, of which one part consists in the periodic discharge of the ganglia, and the other in the alternate exhaustion and restoration of excitability of the muscles.'[56]

Romanes utilized the unique properties of the jellyfish as experimental material for a more interesting and more significant use of the concept of inexcitability due to 'exhaustion'. His experiments and discussion of the significance of refractory phase in controlling the direction of waves of contraction in the excised marginal tissue of the jellyfish bell showed that successive firings of each lithocyst along the strip of tissue resulted in contraction only on that side of the lithocyst which had not just contracted in bringing the stimulation to it, owing to the exhaustion of the tissue on the latter side. Hence the absence of 'reflex waves' back toward the original point of stimulation.[57]

Sherrington dealt with this work at length, developing the successive, reinforcing firings of the lithocysts into a useful comparison of basic nervous function in jellyfish and higher animals, to make the point that irradiation of reflexes in vertebrates occurs discontinuously, '*per saltum*', rather than '*gradatim*'.[58]

Further examples of Romanes' impact upon Sherrington's thought could be discussed,[59] but Romanes' own summary of his observations on 'Period of Latency and Summation of Stimuli' may suffice to show how advanced his conceptions were:

> Thus, then, to summarize and conclude these observations, we have seen that if a single stimulation, whether of a natural or artificial kind, is supplied to the excitable tissues of a jellyfish, a short period, called the period of latency, will elapse, and then the jellyfish will give a single weak contraction. If, as soon as the tissue has relaxed, the stimulation is again repeated, the

[53] See Sherrington's lecture, cited above.
[54] *Integrative Action*, 45.
[55] *Phil. Trans. R. Soc.*, 1881, **171**, 161–202 or *Jelly-Fish . . .*, 175–212. But see Bullock and Horridge . . . *Nervous Systems of Invertebrates*, 502–3; and G. A. Horridge, 'The nerves and muscles of medusae. Part VI: The rhythm', *J. exp. Biol.*, 1959, **36**, 87.
[56] *Phil. Trans. R. Soc.*, 1881, **171**, 87.
[57] *Phil. Trans. R. Soc.*, 1877, **167**, 729. See also *Jelly-Fish . . .*, 130–36.
[58] *Integrative Action*, 168–169.
[59] e.g. Sherrington's use of Romanes' researches on *T. indicans* (*Phil. Trans. R. Soc.*, 1877, **167**, 699–709) in his discussion of local sign in reflexes (*Integrative Action*, 249–50).

> period of latency will be somewhat shorter, and will be followed by a somewhat stronger contraction. Similarly if the stimulation is repeated a third time, the period of latency will be still shorter, and the ensuing contraction still stronger. And so on up to nine or ten times, when the period of latency will be reduced to its *minimum*, while the force of the contraction will be raised to its *maximum*; so that in the jellyfish, the effect of a series of excitations supplied at short intervals from one another is that of both arousing the tissue into a state of increased *activity*, and also producing in it a state of greater *expectancy*. We have, moreoever, seen that this effect depends upon the repetition of the process of stimulation, and not upon that of the process of contraction.[60]

It was the accomplishment of Charles Sherrington that he placed concepts of nerve function similar to the above clearly and consistently in terms of the synaptic events of neurone theory. Not only did the researches of George Romanes and Edward Schäfer supply Sherrington with a significant part of the comparative context of his work, they also predisposed him toward thinking in physiological modes appropriate to an anatomically discontinuous nervous system. Sherrington was far from unprepared when he first encountered the arguments of Cajal and the neuronists in the late eighties and the nineties.

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[60] Romanes' use of the term 'summation of stimuli' corresponded more to the modern term 'facilitation' than to our 'summation'. Quote from *Jelly-Fish* . . ., 59–60. See pp. 50–60 and *Phil. Trans. R. Soc.*, 1877, **167**, 681–90. See also L. S. Hearnshaw, *A Short History of British Psychology*, London, 1964, 93.