Letter to the Editor

We welcome comments from our readers. Short communications stand the best chance of publication. The Editor reserves the right to take extracts from the longer ones.

Animal models of Huntington's chorea

SIR: Dr Pisa's[1] recent critique of Mason suggests a need to clarify the animal models of Huntington's disease. The kainate lesioned rat as described by Mason, Coyle and Divac most closely resembles the Westphal variant of Huntington's, as opposed to the adult onset form. Consequently, overt choreiform activity might be less expected, and a rigid akinetic presentation would be more likely. The explanation for this may best be understood by looking to a second degenerative disorder, Joseph's disease in which, as in the Westphal variant of Huntington's, striato-nigral degeneration is prominent. Striatal interneurons are spared in the latter case: again rigidity and akinesia predominate. These findings, taken together, suggest that under conditions of disruption of descending fibers, a concomitant disruption of motor output may occur. Some time ago, Arbuthnott suggested that the striato-nigral fibers may not be involved in feedback – these clinical findings support this.

What does this suggest? Possibly, if we wish to model adult onset Huntington's rather than the juvenile onset form, it might be better to pretreat a rat with GABA or substance P antagonists to protect the receptors for the feedback fibers while interneurons are being lesioned with kainate. To my knowledge, no one has attempted this, although I would predict that choreiform movements would be prominent in the rat if a pretreatment strategy was employed.

References

1 Pisa, M. (1982) *Trends NeuroSci.* 5, 36–37
2 Wright, A. K., Arbuthnott, G., Tulloch, I., Garcia-Munoz, M. and Nicalaou, N. M. (1977) *Psychobiology of the Striatum*, pp. 1–50, Elsevier

RICHARD J. KATZ

Department of Psychology,
The Johns Hopkins University,
Baltimore,
MD 21218,
U.S.A.

Perspectives

Interactions between Pavlov and Sherrington

Ragnar Granit

Sherrington and Pavlov were intellectual giants of this century who created the two major scientific approaches to the study of the CNS. The Sherringtonian approach through spinal reflexes was based on the insight that studies of the relatively simple and highly reproducible input–output relationships of the spinal cord would lead to an understanding of some of the fundamental mechanisms involved in brain function. Sherringtonian ideas have indeed provided a solid foundation for the success of modern physiology. For example, the discovery of the inhibitory post-synaptic potentials by Eccles and his colleagues in 1951. On the other hand, the Pavlovian approach through conditioned reflexes attempted to elucidate more sophisticated properties of the CNS. Because of the complexity involved, modern physiology has as yet been unsuccessful in embodying Pavlovian ideas expecially in fields of memory and learning. We have inherited so much from these giants at two strategic levels of essential importance. How they interacted with each other, living in the same age and viewing the CNS from these different positions, is much more than a drama, as witnessed in this article by Granit.

I have been asked to comment on the 'interaction between Sherrington and Pavlov', a difficult task because there is little evidence of significant interaction between them at the scientific level. I shall mention what I know, add my own interpretations and some reflections on their personalities and achievements.

Pavlov, born in 1849, was 8 years Sherrington's senior and so his best work, that I read in German in the 1920s *(Die Arbeit der Verdauungsdrüsen*[10]), must in 1897 have impressed the young Sherrington as a first-rate contribution as it did other contemporary physiologists. It rendered Pavlov his Nobel Prize in 1904, the year in which Sherrington delivered the Silliman Lectures at Yale University on the integrative action of the CNS, published in 1906[12].

The late Professor W. H. Gantt, on my visiting Baltimore in 1972, showed me a letter (I cannot recollect whether it was a photocopy or the original) in which Sherrington asked Pavlov to support his application for the chair in physiology at Oxford. Regrettably I did not ask for a copy. Most likely it concerned the competition with Gotch who then was preferred but whom Sherrington succeeded in 1913.

At any rate, the letter is good evidence of confidence on the part of the younger colleague. In 1916 Sherrington visited St. Petersburg. In his *Marginalia*[15] there is a vivid description of the occasion which included an apparently highly enjoyable dinner with the Pavlov family (there is a reprint of the article in the Sherrington biograph by Eccles and Gibson[5]). In the spring of 1928, while I worked in Sherrington's laboratory, Pavlov arrived on a visit with his son as an interpreter. Eccles, in the book with Gibson, mentions a visit in 1929 and speaks of a 'cordial atmosphere'.

Was there a change of atmosphere in the 1930s? When working on my book on Sherrington[6] I had access to John Fulton's diaries and papers. He reports from the International meeting of Neurologists in Bern in 1931 on Sherrington's opinion that Pavlov, in speaking on neuroses in animals (well-known experiments at the time), had amassed an enormous body of experimental facts but did not know how to interpret them. According to Fulton, Sherrington had called the interpretations 'infantile', but this word may well have been Fulton's own choice to illustrate what Sherrington had meant.

In the book with Gibson[5], Eccles describes an attack by Pavlov on Sherrington in a seminar as taken down stenographically in 1934 and reported – he says – in an interesting paper by Volicer in 1973. To this I have not had access. Pavlov's criticism is quoted at some length by Eccles and it implies violent denunciation of Sherrington's ideas on the role of central inhibition. It is a temperamental outburst ending in the statement: 'I simply suppose that he (Sherrington) is ill, although he is only seventy years old, that these are distinct symptoms

Elsevier Biomedical Press 1982 – 0378 – 5912/82/0000 – 0000/$02.75

of old age, of senility.' (Actually Sherrington at the time was 77 years old.) Pavlov died 2 years later but Sherrington lived until 1952 creating among other things his great synthesis *Man on His Nature*[14] that was published in 1941! It is not known whether the apparent estrangement between the two great experimenters in the years 1931–1934 was open or concealed, but somehow it must have originated in their wholly divergent attitudes to ways and means of approaching the CNS, perhaps in particular the problem of inhibition. Sherrington's line had in 1932 been 'sanctioned', so to speak, by the Nobel Prize together with Adrian but in 1931, at Bern, he had also been the subject of an impressive ovation. Their divergent attitudes had excluded scientific interaction of any consequence and, as far as I know, they did not quote one another. However, I have not searched their reference lists systematically.

What we are faced with then is the need for a brief description of the two 'divergent' lines and their impact on the neurosciences of the present day. Pavlov, the fine analyst of the neural mechanisms of secretion in the gastric glands, gave up that work and became a behaviourist. His competitor now was Thorndike, not Sherrington. From physiology he borrowed the term 'reflex' for highly complicated, time-consuming central processes. In spite of the extreme care Pavlov took in developing the technique of producing 'conditioned reflexes'[11] – perhaps his most lasting influence in this field[2,9,16] – my generation found the results too anecdotal to be worth pursuing. Sherrington, on the other hand, went for the neural sites at which reflex events took place. He came to the field from histology, familiar with neurons. The well-known opening words of the *Integrative Action*[12] illustrate his *credo*: 'Nowhere in physiology does the cell-theory reveal its presence more frequently in the very framework of the argument than at the present time in the study of nervous reactions.' These words are equally true today as when they were first printed. And the same can be said about the conceptual battery that he developed for dealing with the experimental findings[5,6,13].

I need not enlarge here on the terms excitation and inhibition of neurons. Ever since the work of Adrian[1] and Sherrington[12,13] these terms have had a precise meaning, confirmed and further qualified by the intracellular studies of Eccles[4] and his co-workers. In following the trend of classical physiology the generations succeeding Adrian and Sherrington could take advantage of the rising wave of electronics in their attempts to be at the sites where neural events could be analysed. This was indeed

C. S. Sherrington

the course that Pavlov had also taken in the first half of his life[2,16] when studying gastric secretion along lines established by his teachers, Heidenhain in Breslau and Ludwig in Leipzig. His great friend Robert Tigerstedt had asked him to give up conditioned reflexes and return to 'real' physiology! New perspectives had been opened in 1902 by the important discovery by Bayliss and Starling of secretin that introduced hormones into the neural control of digestion. To this very day, with the final elucidation of the functions and components of gastrin by R. A. Gregory, the field has been rewarding. Why did Pavlov desert it?

His biographer, B. P. Babkin[2], suggests that the discovery of Bayliss and Starling provided the impetus. This work, Babkin pointed out, 'shook the very foundation of the teaching of the exclusive nervous regulation of the secretory activity of the digestive glands', as formulated by Pavlov. Pavlov then asked V. V. Savich to repeat the secretin experiment. 'The effect of secretin was self-evident. . . . Then, without a word Pavlov disappeared into his study. He returned half an hour later and said, "Of course, they are right. It is clear that we did not take out an exclusive patent for the discovery of truth"' (Babkin)[2].

Personal impressions: Pavlov

While I had many opportunities of seeing Sherrington from different aspects, in experimentation, in supervising the mammalian class, at the Royal Society, as host in his home, at Magdalen College and at the Athenaeum, I met Pavlov only once – in Sherrington's laboratory. An impression may be of some interest since the number of physiologists who actually have spoken to Pavlov must rapidly be diminishing.

Finding a young man in the Oxford laboratory who came from Tigerstedt's institute, Pavlov would have recalled his many visits to that institute in the days of the older Tigerstedt (Robert), his friend who had actively promoted his candidacy for the Nobel Prize. Otherwise there is no explanation of why he spent so much time in conversation with the young physiologist. Pavlov was fluent in German and so we had a language in common. The precise subjects of our talk have eluded my memory but I can still visualize his face with its deep-set rather small grey eyes below a broad forehead; their penetrating look. An aura of sadness mixed with severity surrounded him but there was neither distance nor indifference in his bearing (he was approaching 80 at the time). He inquired about my work and plans speaking slowly and deliberately, evincing genuine interest in what the young man had to say. Pavlov's personality, more than his reputation, made the occasion memorable. A remarkable man, no doubt about that.

Pavlov's devotion to science pervades his testament written for the youth of his country (see the two biographies of the reading list[2,16]). Re-reading it now I still find it conveying a most true and noble message to those preparing themselves for a life of scientific endeavour. I only take exception to his statement at the end, that science requires the whole life of its adepts, even two lives if such were possible. This I think is an exaggeration. As a rule most scientists would do better by finding new channels for their activity in retirement rather than following old routines. Preserved creativity in that period is rare. The great bag of ideas need be shaken and emptied at the end of a career to leave room for the new generation to pick up treasures from the debris. Unexpected things may then turn up.

Personal impressions: Sherrington

The late Denny-Brown in his obituary[3] outlined a portrait of Sherrington that agrees perfectly with my picture of him. Said Denny-Brown: Sherrington 'was short in stature, about 5 feet 6 inches, very precise and neat in all his movements, and he tended to peer through rimless spectacles though not severely shortsighted. He had lively, humorous grey eyes and a light, easy, friendly manner. He was one of the mildest men I have ever known, rarely being vexed and at most saying, "Dear me" or "That is most annoying".' His mildness of manner did not exclude strong emotional engagement, but, as his coworker and friend, the late E. G. T. Liddell remarked in his excellent obituary[8], 'in the wisdom of maturity he sealed his lips against criticism of those others.' I can remember him saying

to me about a person we were discussing 'the sort of man you wouldn't like to camp with'!

To my mind's eye Sherrington is still alive. I can recall his genial chuckle and infectious laughter and hear him reaching with his exceptional visual memory to experiments from the last century and the men behind them. In that mood he was a *raconteur* of the first order. He had the observant mind of the true biologist. As he so often looked like the very image of absentmindedness, this came as a surprise, because when he came down to see what one was doing he presented the very opposite feature of keen concentration and interest, missing nothing essential. Also, when demonstrating in the classroom, there was nothing he missed in the movements and general appearance of the preparation. To the end he retained a secret love for his first apparatus, the microscope, with the aid of which he had done the beautiful work proving muscle spindles and tendon organs to be sensory endings. His final experimental paper with Sybil Cooper (Mrs Creed) was histological and dealt with the 'border cells' of the spinal cord.

Sherrington differed from most physiologists I have known in being deeply influenced by an early education in the humanities that still pervaded the old man's whole being. In his youth this found expression in poetry, in his old age in the works he wrote, *Man on His Nature*[14], *Jean Fernel*, *Goethe*, and, of course, in his perceptive attitude to people.

The Heritage

Pavlov's studies of the digestive glands[10] was a masterpiece that paved the way for much good work by physiologists of later generations. Of his conditioned reflexes[11] the carefully elaborated methodology of conditioning was an important contribution that had repercussions in the psychology of learning and in American behaviourism which had started independently in the 1890s. W. H. Gantt who had spent 6 years in Pavlov's laboratory (1923–29), introduced Pavlov's technique at Johns Hopkins in Baltimore and translated his master's leading works into English. It is neither within my present task nor within my competence to evaluate Pavlov's heritage to these fields.

The question I was supposed to answer concerned interactions between the two great savants in the field to which they both contributed, the physiology of the CNS. In view of the course this subject has taken, the Pavlovian conceptual world does not seem to have had any perceptible influence. Physiology, developing into neurophysiology, followed the line chosen by Sherrington. The really relevant conceptual and experimental advances that we have seen during this century (including cybernetics) are all based on studies of neurons and their various types of interaction, whether chemical, electrical, or topographical. What little we understand about 'learning' is likewise understood in cellular terms.

Reading list

1 Adrian, E. D. (1928) *Basis of Sensation*, Christophers, London
2 Babkin, B. P. (1951) *Pavlov, A Biography*, Victor Gollancz Ltd, London
3 Denny-Brown, D. (1952) *Am. J. Physiol.* 65, 774
4 Eccles, J. C. (1957) *The Physiology of Nerve Cells*, The Johns Hopkins Press, Baltimore
5 Eccles, J. C. and Gibson, W. C. (1979) *Sherrington*, Springer International, Berlin, Heidelberg
6 Granit, R. (1966) *Charles Scott Sherrington. An Appraisal*, Nelson Ltd, London
7 Gregory, R. A. (1980) Gastrin. The Natural History of a Hormone. *Accad. d. Lincei*, II, fasc. 5, p. 101
8 Liddell, E. G. T. (1952) *Obituary Notices of Fellows of the Royal Society* 8, 241
9 Mecacci, L. (1979) *Brain and History. The Relationship between Neurophysiology and Psychology in Social Research*, Brunner/Mazel, New York
10 Pavlov, I. P. (1898) *Die Arbeit der Verdauungsdrüsen* (Transl. Walther, A. and Bergmann, J. F., Wiesbaden). First English version (1902): *The Work of the Digestive Glands* (Transl. Thompson, W. H.), Charles Griffin & Co., London
11 Pavlov, I. P. (1927) *Conditioned Reflexes* (Transl. G. V. Anrep), Oxford Univ. Press
12 Sherrington, C. S. (1906) *The Integrative Action of the Nervous System*, Yale Univ. Press, New Haven
13 Sherrington, C. S. (1939) *Selected Writings*, compiled and edited by D. Denny-Brown, Hamish Hamilton, London
14 Sherrington, C. S. (1941) *Man on His Nature*, Cambridge Univ. Press
15 Sherrington, C. S. (1953) in *Essays etc. in honour of Charles Singer*, Vol. II, Oxford Univ. Press
16 Sherwood, E. and M. (1970) *Ivan Pavlov*, Heron Books, Edito-Service S. A. Geneva

Ragnar Granit, former Director of the Nobel Institute for Neurophysiology, Stockholm, is Emeritus Professor in the Karolinska Institutet, S-104 01 Stockholm, Sweden.

Reviews

Neuroendocrinology and brain peptides

Paul E. Cooper and Joseph B. Martin

Neuroendocrinology is a relatively young discipline. The impact of hypothalamic peptides on neurobiology and on hypothalamic-pututary functions has already been felt in clinical medicine. The future holds further promise for new discovery in this area of interface between clinical and basic research.

Neuroendocrinology is that branch of neuroscience concerned with complex interactions between the nervous and endocrine systems, Holding a key conceptual position in this discipline is the peptidergic neurone – a cell of neuronal origin which manufactures and secretes peptides in a fashion identical to that of peripheral hormone-producing tissue. This principle is best exemplified by neurones of the supraoptic and paraventricular nuclei, the source of the posterior pituitary hormones vasopressin and oxytocin, and the hypophysiotropic neurones of the hypothalamus which secrete the pituitary releasing factors. At first the gland-like characteristics of these hypothalamic neurones may seem incongruous and yet, all neurotransmission, even at the neuromuscular junction is a form of neurosecretion. Indeed, it would appear that there is a continuum from neurones such as the anterior horn cell at one extreme to glandular cells such as the pancreatic β-cell at the other, hypothalamic neurones and certain peptide-secreting cells in the gastrointestinal (GI) tract occupying an intermediate position.

Today, neuropeptides are the object of such intense research interest that it is hard to remember a time when they were not being actively studied. Yet it was only in the 1950s that the pioneering work of du Vigneaud and colleagues led to the characterization of oxytocin and vasopressin from posterior pituitary demonstrating the feasibility of isolating hormones from brain.

The postulation by Geoffrey Harris in the 1940s of the existence of hypophysiotropic factors which control the secretion of the anterior pituitary hormones led in the late 1960s and early 1970s to the discovery of the hypophysiotropic hormones – thyrotro-

0 Elsevier Biomedical Press 1982 0378 - 5912/82/0000 0000/$02.75