The nerve cell considered as the basis of neurology (Presidential Address delivered at the Annual Meeting of the Neurological Society, 19 January 1893), by Edward A. Sharpey-Schafer (FRS). Brain 1893: 16; 134-169.

While it is obvious that the nerve cell ‘must form the basis of the science of neurology’ only now are its structure, functions and relationships to other elements of the nervous system being understood. Therefore, Professor Edward A. Sharpey-Schafer sets out to gather up such threads of knowledge as are available for his 1893 Presidential Address to the Neurological Society. The subject has recently benefited from the applications to histology of methods described by Vittorio Marchi (1851–1908) using the Wallerian model of nerve degeneration (Augustus Waller, 1816–79); Paul Ehrlich’s (1854–1915) introduction of intra vitam staining using methyl blue; and the use of silver nitrate staining developed by Camillo Golgi (1843–1926). ‘Amongst recent physiological methods the investigation by the galvanometer and electrometer of the paths taken by action currents has in the hands of (Francis) Gotch (1853–1913) and (Victor) Horsley (1857–1916) given results of great interest.’ While it is regrettable that Heinrich Waldeyer’s (1836–1921) concept of the neuron as the unit made up by the nerve cell and its various processes has not been pursued, Professor Schäfer will apply his own meaning to the term ‘neuron’ in a different sense ‘because it has not yet readily come into general use in Waldeyer’s sense, and it is, I think, undesirable that it should do so’ (Figs 1 and 2). In a footnote to his chapter on the nerve cell in the Textbook of Physiology (see page 2173), Schäfer reminds readers that the ‘term was suggested by me [Brain, London, 1893, vol. xvi, p. 134 (this article)] to denote that the process in question is a nerve fibre, and I regret that only one or two prominent neurologists have employed it in this sense. The terms neuraxon and neurite are also used by authors to express the same idea’. But Gordon Shepherd considers that ‘one can feel grateful that this suggestion died quietly’ (see Foundations of the Neuron Doctrine, Gordon Shepherd, 1991, p. 215).

The nucleus of the nerve cell is absolutely (and relatively) large by comparison with other cells; it contains a prominent nucleolus and intranuclear network. The protoplasm of the cell body is often pigmented—a feature that Professor Schäfer considers to reflect activity rather than ‘decadence’. The size of the cell body often—as with the motor neurons of the spinal cord, pyramidal cells originating in the cerebral cortex and retinal ganglion cells—bears a direct relationship to the length of the processes. Two types of nerve fibre are described: the axis cylinder or nerve fibre process, which is invariably present and appears first during development; and the protoplasmic processes, which are not an essential part of the nerve cell. Leaning on his classical education (see page 2173), Professor Schäfer insists on the term ‘neuron’ to describe the axis cylinder and he will refer to the protoplasmic processes as ‘dendrons’. Combined processes, such as those occurring in the motor nerve cells of arthropods, might be designated ‘neurodendrons’. In the sense that every process eventually ends in a terminal arborization, each appendage of the nerve cell is strictly ‘dendritic’. The number of dendrons varies from none to many, and nerve cells may therefore, in theory, be designated as dendric or adendric. ‘Cajal has recently spoken of “apolar” nerve-cells, but this is completely a misnomer, for the cells in question (spongioblasts of the retina) have a well-marked process, which ramifies dendritically. What Cajal intends to imply is that they are devoid of an axis cylinder process, but it appears to me that the nervous nature of these cells is very doubtful.’ Almost all nerve cells possess at least one neuron (axis cylinder) and, although cells having two or more axis cylinders are described, most are ‘mono-neuric’. Nerve cells can therefore be classified as ‘dendric and mononeuric’ (anterior horn cells), ‘dendric and polynuclear’ (superficial cortical cells), ‘adendric and mononeuric’ (spinal ganglion cells) or ‘adendric and polynuclear’ (sympathetic ganglia cells: however, the recent observations of Cajal and others indicate that these are in reality dendric and mononeuric). The length of the axis cylinder varies, with Golgi concluding that those with a long process are efferent fibres and the short ones afferent. ‘But there can be little doubt that this distinction into motor and sensory cells can no longer be accepted…there may still be a functional difference between the two kinds…[but this] may perhaps better be expressed by using the term projection-cell for the cell…with long axis-cylinder process… and…intermediary cell for the…second type…[offering] an intermediary link between centripetal impressions which may be brought to a nerve-centre by the neuron of a sensory projection-cell, and the centrifugal impressions which pass away from the nerve centre by the neurons of motor projection-cells.’ Lateral processes are seen on dendrons as triangular enlargements whereas those on neurons (axis cylinders) are single perpendicular processes. Cajal considers that axis cylinders give off fine collateral ‘ramuscles’ very early in their course.

The Golgi method of staining may allow the neuron and dendrons to be distinguished within an interlaced matrix of nerve...
fibres. The processes of each are fibrillar making them difficult to distinguish. But the practiced eye can tell the difference. Whether this is through some special appearance or merely by detecting the invariable diameter of the neuron, smooth in outline by comparison with the rough configuration and steady reduction in calibre as the dendron is traced centripetally, is less clear (Fig. 3). The fibrillar appearance of the axis cylinder and dendron has prompted much discussion as to the organization and function of these processes (and their parent cell body). One view is that the fibrillar patterning depends on bundles of independent fine fibrils aligned within the fibre that subserve conduction. Other commentators interpret the appearance merely as a continuation of the reticulated fibril patterns that occur within the protoplasm of all cells, here drawn out along the elongated fibre to such an extent that the lateral meshes of the original reticulum now appear parallel and with the cross-links rendered indistinct. Professor Schäfer is not convinced by this argument and he has photographed nerve fibres in cross-section, observing fibrils in tubes with absolutely no collateral connections (Fig. 4). The varicosities that he and others have observed at the termination of the fibrils can only be understood if the fibril is a fluid-filled tube.
through which, by mechanisms that remain to be elucidated, the nerve impulse is conducted. Yet more controversial has been the possibility of connections between nerve cells or their dendrons in the form of a reticulated lacework. This is the position argued by Golgi and, eventually, refuted by Cajal. Professor Schäfer’s own views are unambiguous. ‘We can now state... that... there is never a direct union of nerve-cells by comparatively coarse fibres... not even a union... by means of a net-work of fine fibrils... and... every nerve-cell with all its processes is a distinct and isolated anatomical unit.’ Rather, the only inter-neuronal connection is physiological and it depends on contacts between the arborizations of one nerve cell with the cell body or processes of another.

But what can be said of the scaffold within which nerve cells are suspended, and their connections? There remains an issue with respect to the nature of the granular-looking material in which nerve cells are apparently embedded and which Professor Schäfer considers to be ‘an extremely fine interlacement of ramified processes made up not only of the nerve cells which actually lie in that particular grey matter, but also of nerve cells which lie in other parts of the nerve-centres... and which on arriving at the grey matter... break up into a fine arborescence of nerve-fibrils’. This analysis refers to the presence throughout the nervous system of Punksubstanz (‘dotted substance’, see page 2173) made up of finely ramified and somewhat varicose terminations of the processes derived from local nerve cells and those projecting from more remote sites (Fig. 5).

As for function in the nerve cell and its processes, the nucleus is critical to survival of the cell body and processes because it provides ‘nutrition’. Any part of the nerve cell disconnected from the nucleus perishes. Once it is also appreciated that the nerve fibre is a dependent process of the nerve cell, it comes as no surprise that an axis cylinder (neuron), separated from the intact cell body containing the nucleus, ultimately dies. ‘This is in fact the basis of what is known as Wallerian degeneration’. It happens equally to nerve fibres that conduct impulses towards and away from a nerve centre—as application of the Marchi method, which allows the myelin sheath and axon to be distinguished, clearly reveals. Summarizing this dependence of the extremities of the nerve cell on the cell body, Fridtjof Nansen ‘has even gone so far as to deny to the cell body any function other than that of presiding over the nutriment of the whole cell and especially over that of the axis cylinder process’. But, especially for bipolar cells and those with a single axis cylinder, it must also be the case that the cell body can conduct a nerve impulse communicated to that mono- or adendric and mononeuric nerve cell by a lacework of nerve fibres originating from other cells that wrap the (spinal motor) nerve cell. Conversely, ‘there are many instances in which nerve impulses...[are]...transmitted along nerve-fibres without...passing through a nerve-cell at all’. This is best illustrated by spinal (dorsal root) ganglia cells that bifurcate into processes, one passing towards the periphery and the other to the nerve centre: ‘sensory impulses which originate in the periphery and pass along the fibre can perfectly be conceived as being conducted directly to the nerve-centre, past the T-shaped junction...without passing through the nerve cell at all’. And, in support, a dose of nicotine sufficient to block passage through the sympathetic ganglion does not impede conduction along fibres of the posterior root. Although difficult to prove, other than in the context of pattern generators such as the respiratory centre (which may be driven by chemical stimulators delivered in the blood stream), it is reasonably clear that the origin of the nerve impulse is the nerve cell. However, in the invertebrate nervous system, ‘sensory impulses which are brought to...the central nervous system may perfectly well become converted into motor impulses within the Punksubstanz without necessarily traversing the motor-nerves at all...being connected with the Punksubstanz by dendritic collaterals which pass off from their large neuro-dendritic processes’. These impulses do not occur de novo without any obvious external cause—mechanical, chemical or electrical—resulting from activity of the cell-substance. Although
an unlikely proposition, it is worth asking whether impulse generation is different in the cell body from that seen in its dependent processes. The axonal impulse is carried as a wave that may pass in either direction. It seems likely that the cell body transmits its impulse to the axis cylinder. Activity generates heat and renders the nerve and adjacent tissue, normally surrounded by ‘alkaline lymph’, acid. In the cell body, it is also accompanied by chemical processes that may ‘fatigue’. But since nerve fibres are merely elongations of the nerve cell and activity generates heat and fatigue in each, it is reasonable to suppose that similar chemical processes occur in the axis cylinders of nerve fibres as in the cell body even though these have not directly been detected. Considering the nature of nerve fibrils as hollow tubes (see above), ‘we can readily understand how waves of surface tension change may be possible’ and generated by contraction of the cell body ‘so slight as to escape observation... or confined to the fibrillae... nerve impulses pass along nerve-fibres with a regular rhythm... rapid [mechanical] stimulation... applied to the brain, or to the pyramidal tract, respond[s] by an incomplete tetanus of the voluntary muscles... having a rhythm of about 10 per second’. With respect to frequency of the mechanical stimulus, the nerve is only able to transmit the pulse wave at around 10 per second, perhaps one-tenth of the rate at which it is stimulated—this transformation occurring where the descending pyramidal cell projects onto the motor nerve cell of the spinal cord, or in an intermediary cell. The epileptiform convulsions that follow electrical excitation of the cortex represent another example of rhythmic production of nerve impulses by nerve cells. Somatic, visual, auditory and gustatory sensations (or in the worm nerves in the integument that respond generically to any one of these stimuli) receive impressions and convert these into nerve impulses that activate bipolar or unipolar cell processes, or (perhaps) in the case of vision, the nerve cell itself. ‘Nerve impulses are conveyed along afferent fibres to the ultimate ramifications of those fibres within the Punksubstanz... [where] they are collected... as new impulses by the... collaterals of neurons or neurodendrons of the motor cells and by these neurons are conveyed directly to the muscles.’

There is no continuity between adjacent nerve cells, only a contiguity of connections between their processes; and (physiologically) there is always a partial block to passage of the nerve impulse at the conjunction of one nerve cell with another, measured as a delay of ~0.01 s during which excitation is latent. Because there is a physical gap, it follows that the mechanical or surface tension wave may not immediately traverse or synchronize with activity in the adjacent axis cylinder or dendron. And Professor Schäfer considers that: ‘it is open to us to suppose that the electrical change (action current) which accompanies the passage of the nerve-impulses to the arborescence may itself be the excitant of the nerve cell, and that the nerve cell may respond to this excitation by a rhythmic change of some kind... possibly contraction, possibly rhythmic chemical action, possibly molecular vibration’, or all of the above. But here anticipation of discoveries not made until 1952 deserts Professor Schäfer and he considers electrical activity as comparable to the heat and acidity that follow propagation of the nerve impulse. His explanation for the relative inexcitability of antidromal impulses in the axis cylinders of motor nerves is mechanical and due to the anatomical arrangement of terminations of the pyramidal tract fibres around motor cells.

Overall we sense a near-miss in Schäfer’s account of cellular structure and function in the brain and spinal cord. Many of his observations are correct but the explanation and putative sequence of events are wrong. And the concept of ‘mechanical vibration’ is reminiscent of David Hartley (1705–57) who summarized views on neurology, moral psychology and spirituality, explaining activity in the brain through the concept of ‘vibratunules’ and locating mind in brain (Observations on Man, his Frame, his Duty, and his Expectations, 1749). On the issue of structure, Schäfer had himself already come close to describing the neuron doctrine in his work from 1877 on the microscopic structure of the nerve plexus in the jelly fish (Medusa). Here he shows that ‘the nerve cells are separate with points of mutual contact’—an observation on which he is remarkably reticent in the 1893 Presidential Address (see Foundations of the Neuron Doctrine by Gordon Shepherd, 1991, p. 216). But the future Sir Edward A. Sharpey-Schäfer moved on, and in 1894 made physiological discoveries that led him to found a new discipline and coin the term ‘endocrinology’—observations that are of lasting value.

Alastair Compston
Cambridge