1

Structural Organisation of the Nervous System

1.1 Nervous Systems

An important characteristic of higher animals is their possession of a more or less elaborate system for rapid transfer of information through the body in the form of electrical signals or nervous impulses. At the bottom of the evolutionary scale, nervous systems of some primitive invertebrates consist simply of interconnected networks of undifferentiated nerve cells. The next step in complexity is a differentiation into *sensory* nerve cells responsible for gathering incoming information, and *motor* nerve cells that execute an appropriate response. The nerve cell bodies are grouped together to form *ganglia*. Different specialised receptor organs detect every kind of change in the external and internal environment. Likewise, different types of effector organ formed by muscles and glands receive and execute the outgoing instructions. In invertebrates, the ganglia that link the inputs and outputs remain to some extent anatomically separate. In vertebrates most of the nerve cell bodies are collected together in the *central nervous system*. The *peripheral nervous system* comprises *afferent* sensory nerves conveying information to the central nervous system, and *efferent* motor nerves conveying instructions from it. Within the central nervous system, the different pathways are connected up by large numbers of *interneurons* which have an integrative function. Fuller accounts of nervous system structure are summarised elsewhere (Brodal, 2016; Waxman, 2017).

Certain ganglia involved in internal homeostasis remain outside the central nervous system. Together with the preganglionic nerve trunks leading to them, and the postganglionic fibres arising from them, which innervate smooth muscle and gland cells in the animal's viscera and elsewhere, these constitute the *autonomic nervous system*. The preganglionic autonomic fibres leave the central nervous system in two distinct outflows. Those in the cranial and sacral nerves form the *parasympathetic* division of the autonomic system, while those coming from the thoracic and lumbar segments of the spinal cord form the *sympathetic* division.

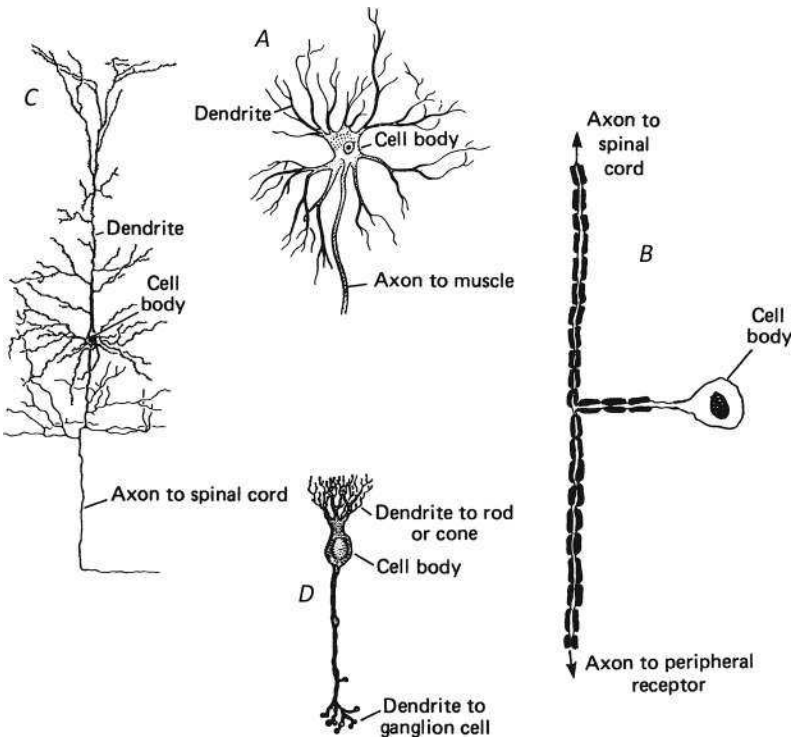

Figure 1.1 Schematic diagrams (not to scale) of the structure of: (*A*) a spinal motoneuron; (*B*) a spinal sensory neuron; (*C*) a pyramidal cell from the motor cortex of the brain; (*D*) a bipolar neuron in the vertebrate retina. (Adapted from Nicholls *et al.*, 2001.)

1.2 The Anatomy of a Neuron

Each neuron has a cell body containing its nucleus and a number of processes or *dendrites* (Figure 1.1). One process, often much longer than the rest, is the *axon* or nerve fibre which carries outgoing impulses. The incoming signals from other neurons are passed on at junctional regions known as *synapses* scattered over the cell body and dendrites; discussion of their structure and of the special mechanisms involved in synaptic transmission is deferred to Chapters 7 and 8. The cell body is essential for long term maintenance of the axon (Section 1.5). However, it does not play an immediate role in axonal conduction of impulses. A nerve continues to function for a significant time after being severed from its cell body: electrophysiologists would have a harder time if this were not the case. We first concern ourselves with properties of peripheral nerves.

1.3 Unmyelinated Nerve Fibres

Vertebrates have two main types of nerve fibre, larger fast-conducting *myelinated* axons, 1 to 25 μm in diameter, and small slowly conducting

unmyelinated axons (under 1 μm). Most autonomic system fibres and peripheral sensory fibres subserving sensations like pain and temperature, where a rapid response is not required, are unmyelinated. Almost all invertebrates are equipped exclusively with unmyelinated fibres, but those showing particularly rapid conduction may have diameters as large as 500–1000 μm. Subsequent chapters will discuss the use of giant invertebrate axons in experiments clarifying the mechanism of conduction of the nervous impulse. The major fundamental advances made in electrophysiology have often depended heavily on technical possibilities opened up by opportunities offered by comparative zoology (Chapter 4).

All nerve fibres consist essentially of a long cylinder of cytoplasm, the *axoplasm*, surrounded by an electrically excitable *nerve membrane*. The electrical resistance of axoplasm is relatively low, by virtue of its appreciable concentrations of K^+ and other ions. That of the membrane is relatively high. The electrolyte-containing extracellular fluids outside the membrane are also good electrical conductors. Nerve fibre structure therefore parallels that of a shielded electric cable, with a central conducting core surrounded in turn by insulation and a further conducting layer. Many features of the behaviour of nerve fibres depend intimately on their *cable structure* (Section 6.1).

The layer analogous with the insulation of the cable does not, however, consist solely of the high-resistance nerve membrane, owing to the presence of *Schwann cells*. These are wrapped around the *axis cylinder* in a manner which varies with the different nerve fibre types. In the olfactory nerve (Figure 1.2), a single Schwann cell serves as a multi-channel supporting structure enveloping a short stretch of 30 or more tiny axons. Elsewhere, groups of individual axons may be associated with a single Schwann cell, with some deeply embedded within the Schwann cell, and others almost uncovered. In general, each Schwann cell supports a small group of up to half a dozen axons (Figure 1.3). In large invertebrate axons (Figure 1.4) the ratio is reversed, the whole surface of the axon being covered with a mosaic of many Schwann cells interdigitated with one another to form a layer several cells thick.

In all unmyelinated nerves, whether large or small, the axon membrane is separated from the Schwann cell membrane by a ~10 nm wide space sometimes termed the *mesaxon* by anatomists. This space freely communicates with the remaining tissue extracellular space. It provides a relatively uniform pathway for electric current flow during passage of an impulse. However, it can be tortuous and so ions entering it from the active nerve may temporarily accumulate within it, leading to events contributing to the *after-potential* (Section 6.5). Nevertheless, for the immediate purpose of describing nerve impulse propagation, unmyelinated fibres may be regarded as having a uniformly low external electrical resistance between different points on the outside of the membrane.

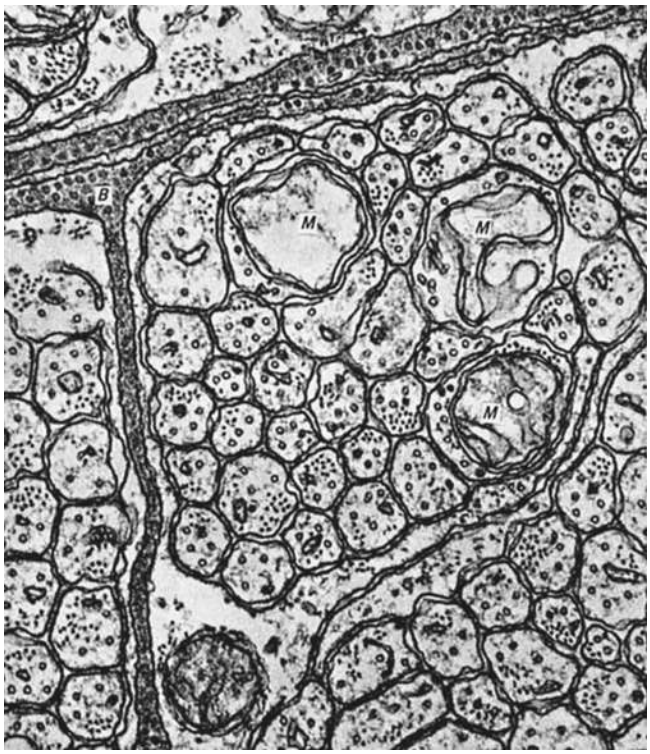

Figure 1.2 Electronmicrograph of a section through the olfactory nerve of a pike, showing a bundle of unmyelinated nerve fibres partially separated from other bundles by the basement membrane *B*. The mean diameter of the fibres is 0.2 μm, except where they are swollen by the presence of a mitochondrion (*M*). Magnification 54 800 ×. (Reproduced by courtesy of Prof. E. Weibel.)

1.4 Myelinated Nerve Fibres

In vertebrate myelinated nerve fibres, the axon is electrically insulated by the *myelin sheath* everywhere except at the *nodes of Ranvier* (Figures 1.5, 1.6, 1.7). In peripheral nerves, each stretch of myelin is laid down by a Schwann cell that repeatedly envelops the axis cylinder with many concentric layers of cell membrane (Figure 1.7). In the central nervous system, it is *oligodendroglial* cells that lay down the myelin. All cell membranes consist of a double layer of lipid molecules with which some proteins are associated (Section 3.1). This forms a structure that after appropriate staining appears under the electron-microscope as a pair of dark lines 2.5 nm across, separated by a 2.5 nm gap. In an adult myelinated fibre, the adjacent layers of Schwann cell membrane are partly fused together at their cytoplasmic surface, and the overall repeat distance of the double membrane, as determined by X-ray diffraction, is 17 nm. For a nerve fibre whose outside diameter is 10 μm, each stretch of myelin is about 1000 μm long and 1.3 μm thick, so that the myelin is built up of some 75 double layers of Schwann cell membrane. In larger fibres, the internodal distance, the thickness of the myelin and hence the number of layers, are all proportionately greater. Since myelin has a higher lipid content than cytoplasm, it also

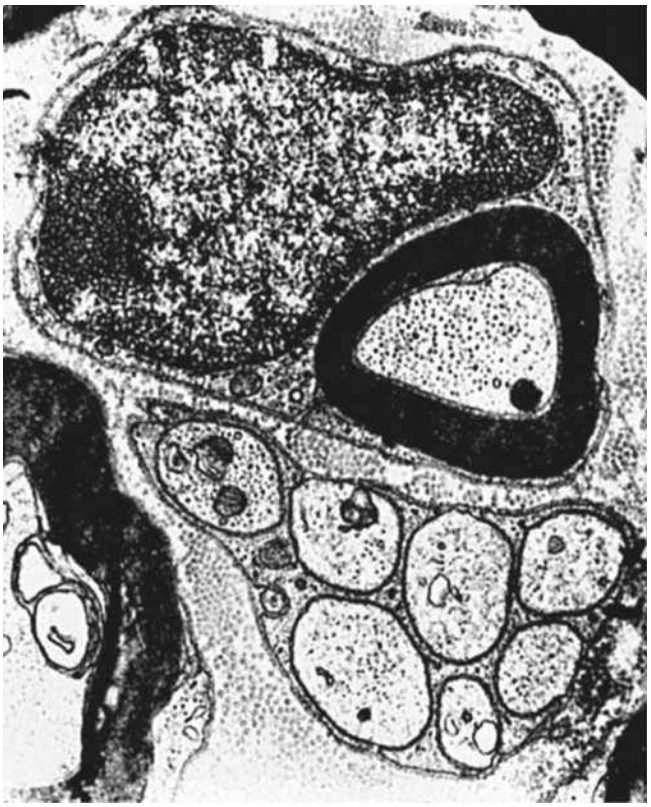

Figure 1.3 Electronmicrograph of a cross-section through a mammalian nerve showing unmyelinated fibres with their supporting Schwann cells and some small myelinated fibres. (Reproduced by courtesy of Professor J. D. Robertson.)

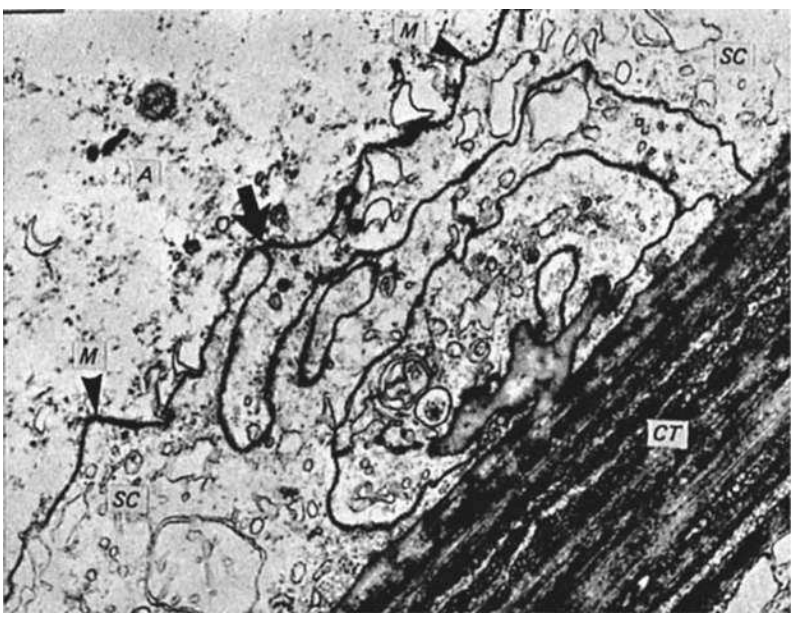

Figure 1.4 Electronmicrograph of the surface of a squid giant axon, showing the axoplasm (*A*), Schwann cell layer (*SC*) and connective tissue sheath (*CT*). Ions crossing the excitable membrane (*M*, arrowheads) must diffuse laterally to the junction between neighbouring Schwann cells marked with an arrow, and thence along the gap between the cells into the external medium. Magnification 22 600 ×. (Reproduced by courtesy of Dr F. B. P. Wooding.)

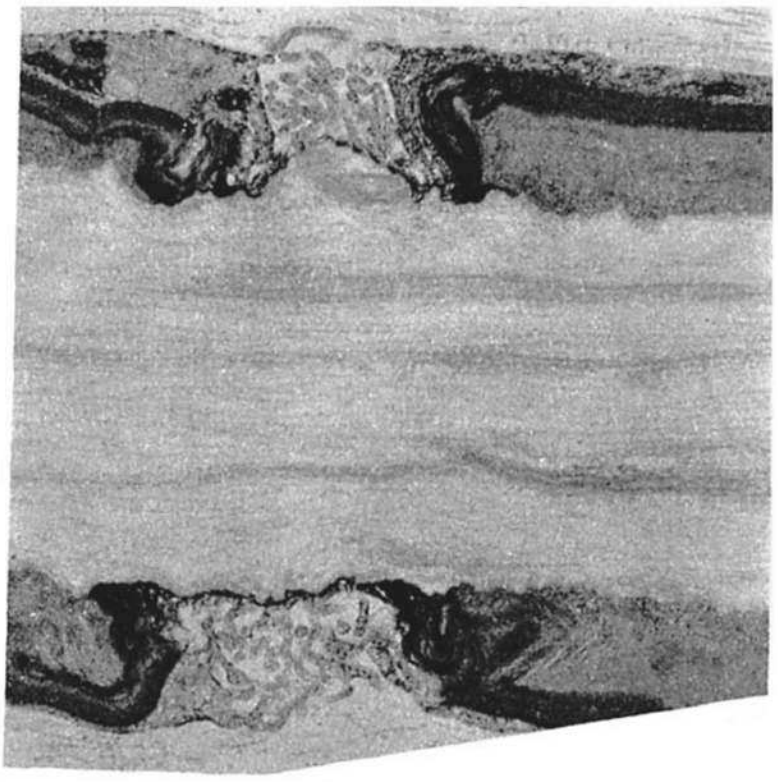

Figure 1.5 Electronmicrograph of a node of Ranvier in a single fibre dissected from a frog nerve. (Reproduced by courtesy of Professor R. Stämpfli.)

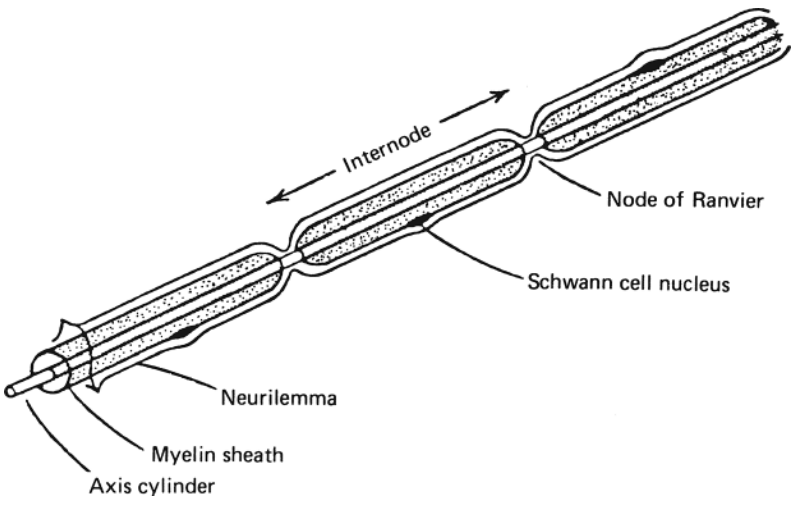

Figure 1.6 Schematic diagram of the structure of a vertebrate myelinated nerve fibre. The distance between neighbouring nodes is actually about 40 times greater relative to the fibre diameter than is shown here.

has a greater refractive index. In unstained preparations it has a characteristic glistening white appearance. This accounts for the name given to the peripheral *white matter* of the spinal cord, consisting of columns of myelinated nerve fibres. In contrast, the central core of

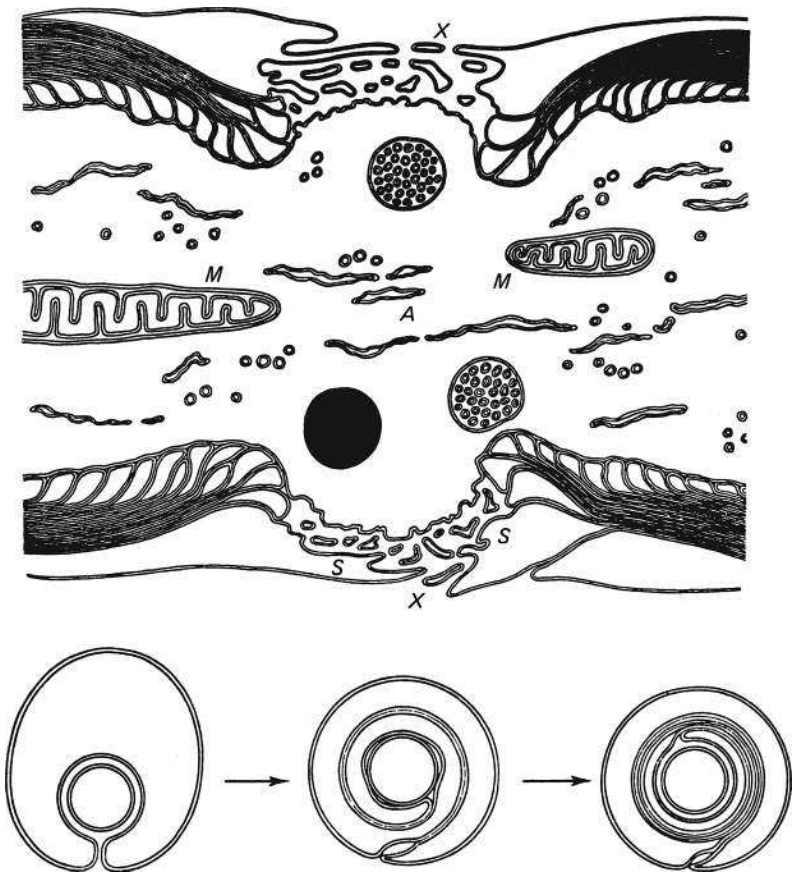

Figure 1.7 Drawing of a node of Ranvier made from an electronmicrograph. The axis cylinder (*A*) is continuous through the node; the axoplasm contains mitochondria (*M*) and other organelles. The myelin sheath, laid down as shown below by repeated envelopment of the axon by the Schwann cell on either side of the node, is discontinuous, leaving a narrow gap *X*, where the excitable membrane is accessible to the outside. Small tongues of Schwann cell cytoplasm (*S*) project into the gap, but do not close it entirely. (From Robertson, 1960.)

grey matter mainly comprises nerve cell bodies and supporting tissue. It also accounts for the difference between the white and grey rami of the autonomic system, containing respectively small myelinated nerve fibres and unmyelinated fibres.

At the node of Ranvier, the closely packed layers of Schwann cell terminate on either side as a series of small tongues of cytoplasm (Figure 1.7), leaving a gap ~1 μm in width where there is no obstacle between the axon membrane and the extracellular fluid. The external electrical resistance between neighbouring nodes of Ranvier is therefore relatively low, whereas the resistance between any two points on the internodal stretch of membrane is high because of the insulating effect of the myelin. The difference between the nodes and internodes in accessibility to the external medium is the basis for the *saltatory* mechanism of conduction in myelinated fibres (Section 6.3), which enables them to conduct impulses some 50 times faster than a non-myelinated fibre of the same overall diameter. Nerves may branch many times before terminating, and the branches always arise at nodes.

In peripheral myelinated nerves, the whole axon is covered by a thin, apparently structureless basement membrane, the *neurilemma*. The nuclei of the Schwann cells are found just beneath the neurilemma close to the midpoint of each internode. The fibrous connective tissue which separates individual fibres is known as the *endoneurium*. The fibres are bound together in bundles by the *perineurium*, and the several bundles which in turn form a whole nerve trunk are surrounded by the *epineurium*. The connective tissue sheaths in which the bundles of nerve fibres are wrapped also contain continuous sheets of cells which prevent extracellular ions in the spaces between the fibres from mixing freely with those outside the nerve trunk. The barrier to free diffusion offered by the sheath is probably responsible for some of the experimental discrepancies between the behaviour of fibres in an intact nerve and that of isolated single nerve fibres. The nerve fibres within the brain and spinal cord are packed together very closely, and are thought to lack a neurilemma. The individual fibres are difficult to tease apart, and the nodes of Ranvier are less easily demonstrated than in peripheral nerves by such histological techniques as staining with silver nitrate.

1.5 Nerve Fibre Responses to Injury

Of major clinical importance is the limited capacity for nerve regeneration following injury leading to nerve transection. The cell bodies of the neurons involved undergo a chromatolysis reflecting dissolution of their contained *Nissl bodies* made up of rough endoplasmic reticulum. The nerve region distal to the injury shows a *Wallerian degeneration.* The myelinated sheaths retract from the nodes and break down into separate ellipsoidal structures (Figure 1.8). There is a loss of excitability in the distal nerve fibres within days after interruption. The distal axons are phagocytosed, leaving persistent tube-like Schwann cell sheaths. A process of regeneration commences from the nerve proximal to the lesion. There the fibre ends develop buds or sprouts that elongate into regenerating fibres. In the event that these reach and penetrate the sheaths left by the distal degenerating part of the nerve, further growth occurs along the sheaths at a rate of 3–4 mm/day. This can eventually lead to reinnervation of their effector structure. The regenerated axons recover their diameters and regain their myelination over the succeeding 4–12 months (Mulroy *et al.*, 1990).

It has been suggested that guidance of regenerating fibres into their distal stumps may involve chemotropic effects, but it is unlikely that there are long-range neurotrophic effects related to specific neuroeffector structures. Regenerating fibres appear to be directed in their growth by the degenerated sheaths, likely along their contained

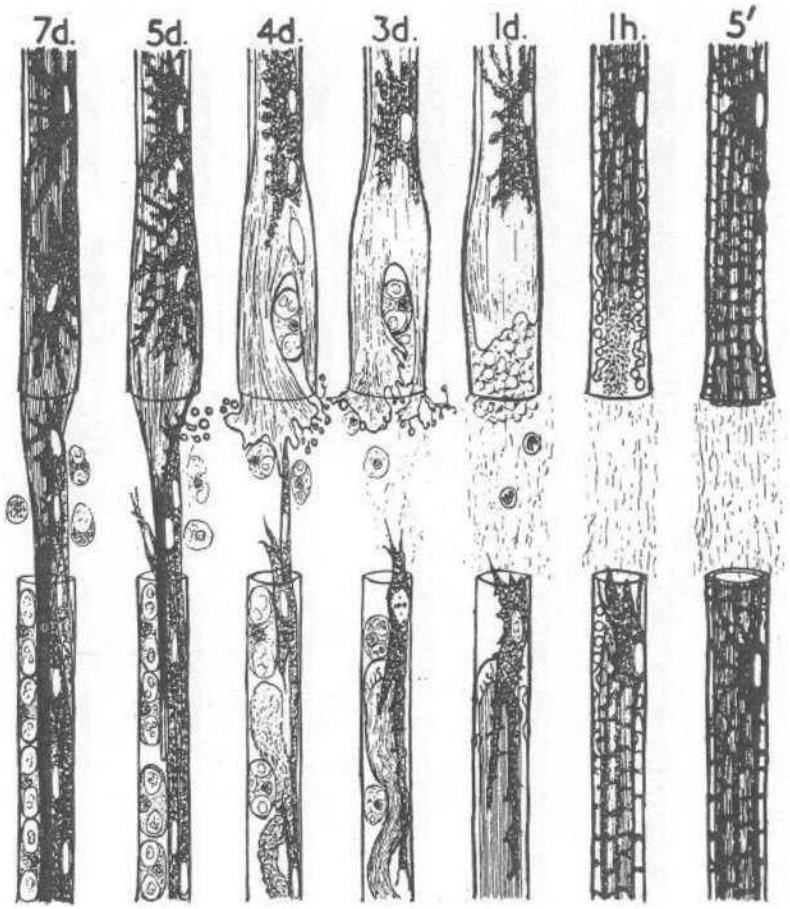

Figure 1.8 Wallerian degeneration and regeneration from 5 min to 7 days following nerve fibre transection. There is retraction of the central portion of the distal portion of the cut axon from 1 h, budding at the proximal portion from the 3rd and 4th day, and axon growth into the distal stump on the 5th and 7th days. (From Young, 1949.)

basement membrane material. The latter appears to support nerve growth even when derived from tissue other than nerve, such as basement membrane preparations from freeze-treated muscle tissue (Keynes *et al.*, 1984). In experimental surgical studies, use of appropriately oriented preparations promoted nerve regrowth and ultimate return of function (Glasby *et al.*, 1986a, 1986b). Such findings prompted explorations for future clinical applications in the surgical repair of nerve injury or transection (Gattuso *et al.*, 1988).