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1

Structural organization of the nervous system

1.1 Nervous systems

One of the characteristics of higher animals is their possession of a more or less elaborate system for the rapid transfer of information through the body in the form of electrical signals, or nervous impulses. At the bottom of the evolutionary scale, the nervous system of some primitive invertebrates consists simply of an interconnected network of undifferentiated nerve cells. The next step in complexity is the division of the system into *sensory* nerves responsible for gathering incoming information, and *motor* nerves responsible for bringing about an appropriate response. The nerve cell bodies are grouped together to form *ganglia*. Specialized receptor organs are developed to detect every kind of change in the external and internal environment; and likewise there are various types of effector organ formed by muscles and glands, to which the outgoing instructions are channelled. In invertebrates, the ganglia which serve to link the inputs and outputs remain to some extent anatomically separate, but in vertebrates the bulk of the nerve cell bodies are collected together in the *central nervous system*. The *peripheral nervous system* thus consists of *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.

Certain ganglia involved in internal homeostasis remain outside the central nervous system. Together with the preganglionic nerve trunks leading to them, and the post-ganglionic fibres arising from them, which innervate smooth muscle and gland cells in the animal's viscera and elsewhere, they 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.

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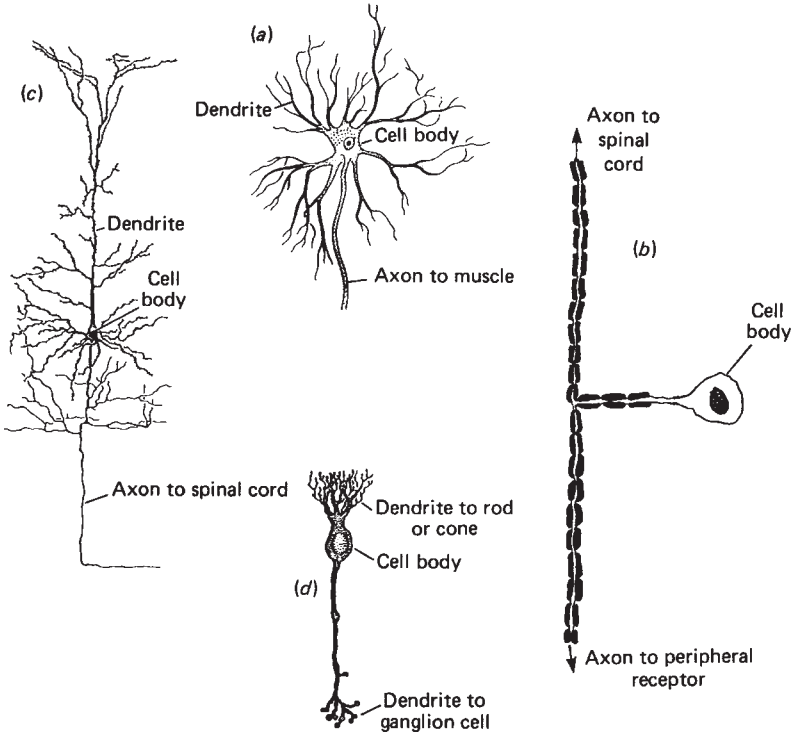

Figure 1.1 Schematic diagrams (not to scale) of the structure of: (*a*) a spinal motoneuron; (*b*) a spinal sensory neuron; (*c*) a pyramidal cell from the motor cortex of the brain; (*d*) a bipolar neuron in the vertebrate retina. (Adapted from Nichols *et al.*, 2001.)

1.2 The anatomy of a neuron

Each neuron has a cell body in which its nucleus is located, and a number of processes or *dendrites* (Figure 1.1). One process, usually much longer than the rest, is the *axon* or nerve fibre which carries the outgoing impulses. The incoming signals from other neurons are passed on at junctional regions known as *synapses* scattered over the cell body and dendrites, but discussion of their structure and of the special mechanisms involved in synaptic transmission will be deferred to Chapters 7 and 8. At this stage we are concerned only with the properties of peripheral nerves, and need not concern ourselves further with the cell body, for although its intactness is essential in the long term to maintain the axon in working order, it does not actually play a direct role in the conduction of impulses. A nerve can continue to function for quite a while after being severed from its cell body, and electrophysiologists would have a hard time if this were not the case.

1.3 Non-myelinated nerve fibres

Vertebrates have two main types of nerve fibre, the larger fast-conducting axons, 1 to 25 μm in diameter, being *myelinated*, and the small slowly conducting ones (under 1 μm) being *non-myelinated*.

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Most of the fibres of the autonomic system are non-myelinated, as are peripheral sensory fibres subserving sensations like pain and temperature, where a rapid response is not required. Almost all invertebrates are equipped exclusively with non-myelinated fibres, but where rapid conduction is called for, their diameter may be as much as 500 or even 1000 μm. As will be seen in subsequent chapters, the giant axons of invertebrates have been extensively exploited in experiments on the mechanism of conduction of the nervous impulse. The major advances made in electrophysiology during the last 50 years have very often depended heavily on the technical possibilities opened up by the size of the squid giant axon.

All nerve fibres consist essentially of a long cylinder of cytoplasm, the *axoplasm*, surrounded by an electrically excitable *nerve membrane*. Now the electrical resistance of the axoplasm is fairly low, by virtue of the K^+ and other ions that are present in appreciable concentrations, while that of the membrane is relatively high, and the salt-containing body fluids outside the membrane are again good conductors of electricity. Nerve fibres therefore have a structure analogous to that of a shielded electric cable, with a central conducting core surrounded by insulation, outside which is another conducting layer. Many features of the behaviour of nerve fibres depend intimately on their *cable structure*.

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*, which are wrapped around the *axis cylinder* in a manner which varies in the different types of nerve fibre. In the case of 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, each axon may be more or less closely associated with a Schwann cell of its own, some being deeply embedded within the Schwann cell, and others almost uncovered. In general, as in the example shown in Figure 1.3, each Schwann cell supports a small group of up to half a dozen axons. In the 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 non-myelinated nerves, both large and small, the axon membrane is separated from the Schwann cell membrane by a space about 10 nm wide, sometimes referred to by anatomists as the *mesaxon*. This space is in free communication with the main extracellular space of the tissue, and provides a relatively uniform pathway for the electric currents which flow during the passage of an impulse. However, it is a pathway that can be quite tortuous, so that ions which move out through the axon membrane in the course of an impulse are prevented from mixing quickly with extracellular ions, and may temporarily pile up outside, thus contributing to the *after-potential* (see Section 6.5). Nevertheless, for the immediate

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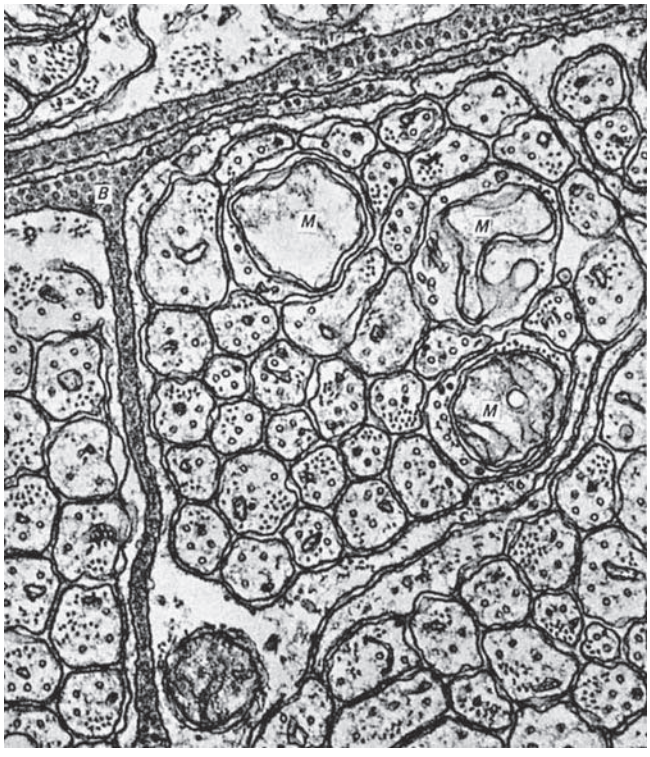

Figure 1.2 Electron micrograph of a section through the olfactory nerve of a pike, showing a bundle of non-myelinated nerve fibres partially separated from other bundles by the basement membrane *B*. The mean diameter of the fibres is 0.2 μm, except where they are swollen by the presence of a mitochondrion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

purpose of describing the way in which nerve impulses are propagated, non-myelinated fibres may be regarded as having a uniformly low external electrical resistance between different points on the outside of the membrane.

1.4 Myelinated nerve fibres

In the myelinated nerve fibres of vertebrates, the excitable membrane is insulated electrically by the presence of the *myelin sheath* everywhere except at the *node of Ranvier* (Figures 1.5, 1.6, 1.7). In the case of 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 the cells known as *oligodendroglia* that lay down the myelin. All cell membranes consist of a double layer of lipid molecules with which some proteins are associated (see Section 3.1), forming 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

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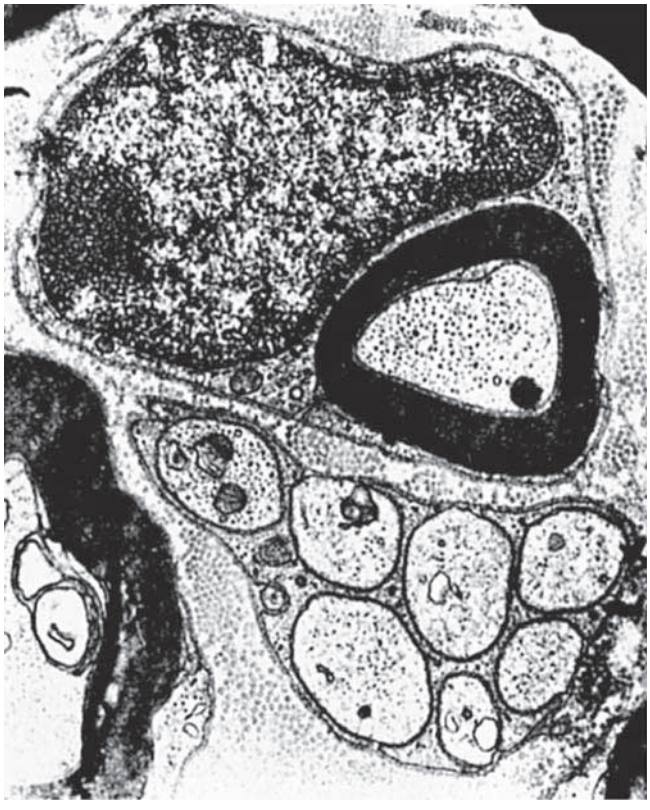

Figure 1.3 Electron micrograph of a cross-section through a mammalian nerve showing non-myelinated fibres with their supporting Schwann cells and some small myelinated fibres. (Reproduced by courtesy of Professor J. D. Robertson.)

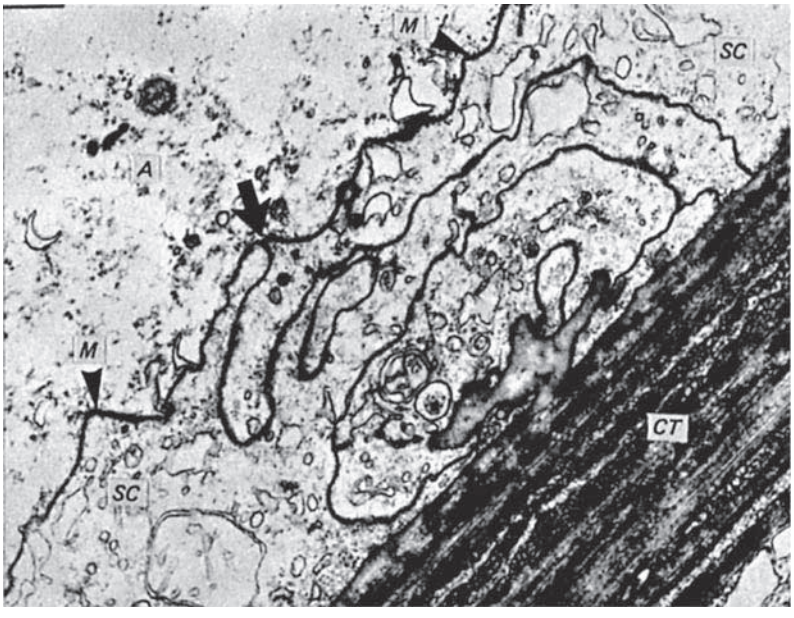

Figure 1.4 Electron micrograph of the surface of a squid giant axon, showing the axoplasm (*A*), Schwann cell layer (*SC*) and connective tissue sheath (*CT*). Ions crossing the excitable membrane (*M*, arrowheads) must diffuse laterally to the junction between neighbouring Schwann cells marked with 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.)

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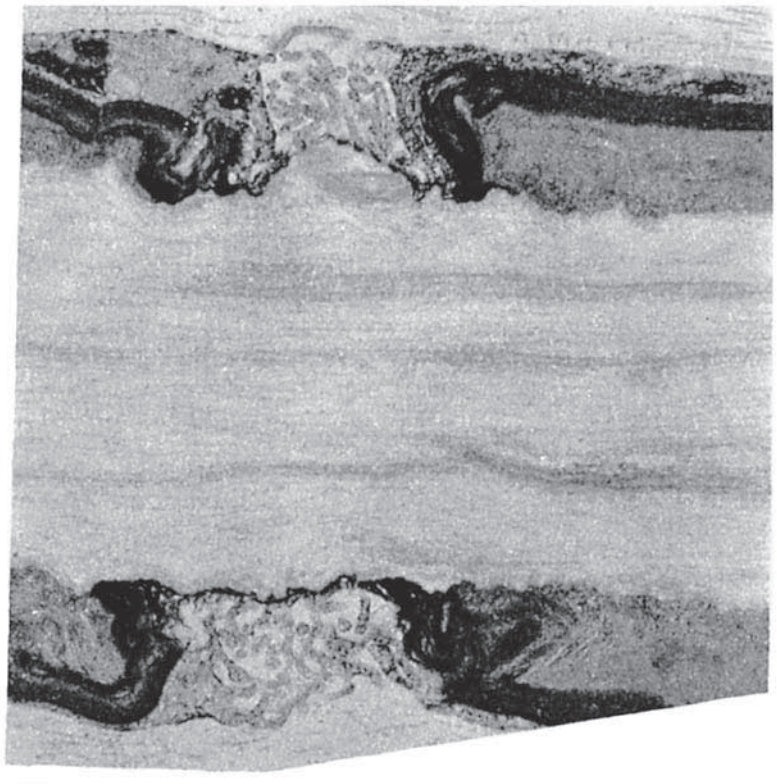

Figure 1.5 Electron micrograph of a node of Ranvier in a single fibre dissected from a frog nerve. (Reproduced by courtesy of Professor R. Stämpfli.)

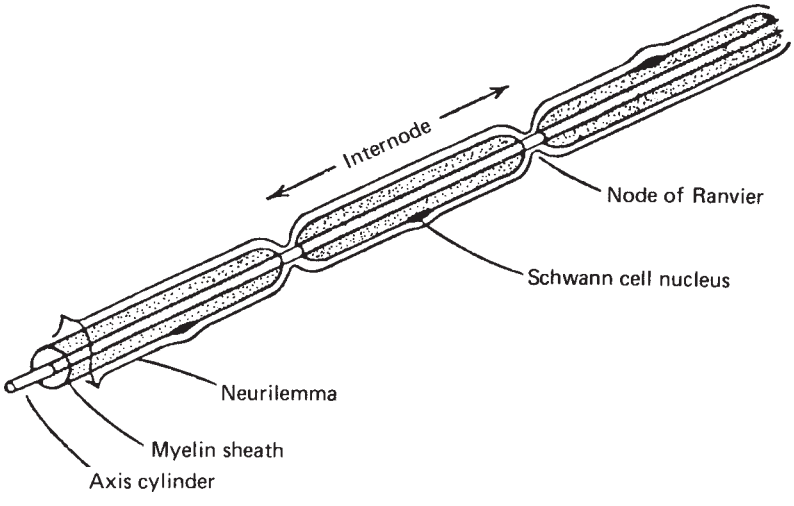

Figure 1.6 Schematic diagram of the structure of a vertebrate myelinated nerve fibre. The distance between neighbouring nodes is actually about 40 times greater relative to the fibre diameter than is shown here.

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 much higher lipid content than cytoplasm, it also has a greater

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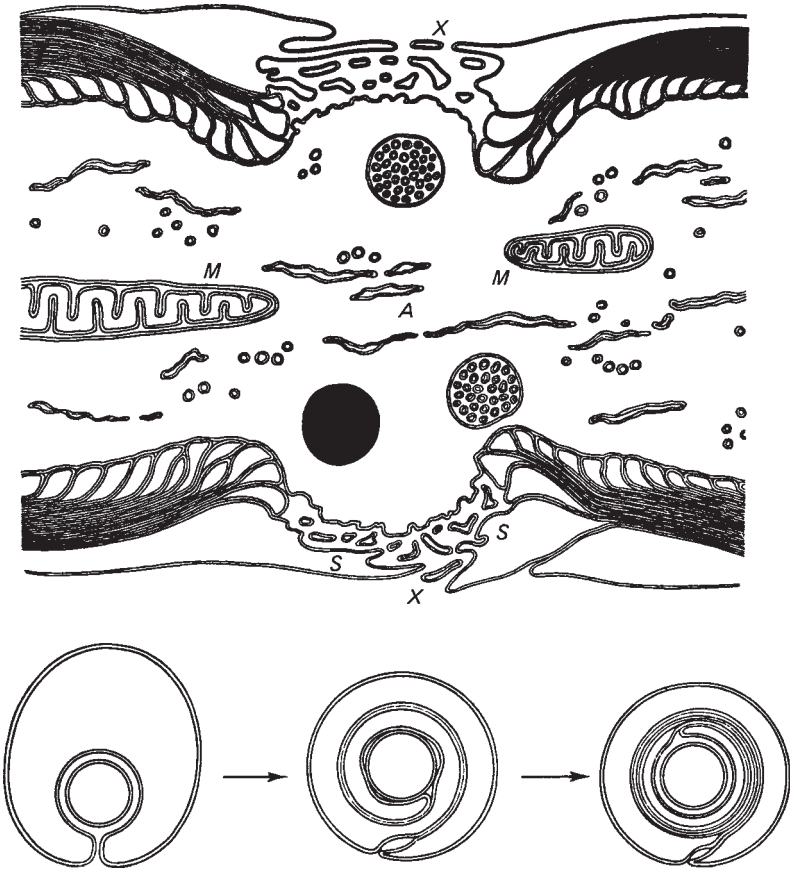

Figure 1.7 Drawing of a node of Ranvier made from an electron micrograph. The axis cylinder *A* is continuous through the node; the axoplasm contains mitochondria (*M*) and other organelles. The myelin sheath, laid down as shown below by repeated envelopment of the axon by the Schwann cell on either 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.)

refractive index, and in unstained preparations 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, as contrasted with the central core of *grey matter*, which is mainly 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 non-myelinated fibres.

At the node of Ranvier, the closely packed layers of Schwann cells terminate on either side as a series of small tongues of cytoplasm (Figure 1.7), leaving a gap about 1 μm in width where there is no obstacle between the axon membrane and the extra-cellular 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 (see Section 6.2), which enables them to conduct impulses some 50 times faster than a non-myelinated fibre of the

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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 usually described as being covered by a thin, apparently structureless basement membrane, the *neurilemma*. The nuclei of the Schwann cells are to be found just beneath the neurilemma, at 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 usually said 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 $AgNO_3$.

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Resting and action potentials

2.1 Electrophysiological recording methods

Although the nervous impulse is accompanied by effects that can under especially favourable conditions be detected with radioactive tracers, or by optical and thermal techniques, electrical recording methods normally provide much the most sensitive and convenient approach. A brief account is therefore necessary of some of the technical problems that arise in making good measurements both of steady electrical potentials and rapidly changing ones.

In order to record the potential difference between two points, electrodes connected to a suitable amplifier and recording system must be placed at each of them. If the investigation is only concerned with action potentials, fine platinum or tungsten wires can serve as electrodes, but any bare metal surface has the disadvantage of becoming *polarized* by the passage of electric current into or out of the solution with which it is in contact. When, therefore, the magnitude of the steady potential at the electrode tip is to be measured, non-polarizable or reversible electrodes must be used, for which the unavoidable *contact potential* between the metal and the solution is both small and constant. The simplest type of reversible electrode is provided by coating a silver wire electrolytically with AgCl, but for the most accurate measurements calomel ($Hg/HgCl_2$) half-cells are best employed.

When the potential inside a cell is to be recorded, the electrode has to be very well insulated except at its tip, and so fine that it can penetrate the cell membrane with a minimum of damage and without giving rise to electrical leaks. The earliest intracellular recordings were actually made by pushing a glass capillary 50 μm in diameter longitudinally down a 500 μm squid axon through a cannula tied into the cut end (Figure 2.1*a*), but this method cannot be applied universally. For tackling cells other than giant axons, glass microelectrodes are made by taking hard glass tubing about 2 mm in diameter and drawing down a short section to produce a tapered micropipette less than 0.5 μm across at the tip (Figure 2.1*b*). The

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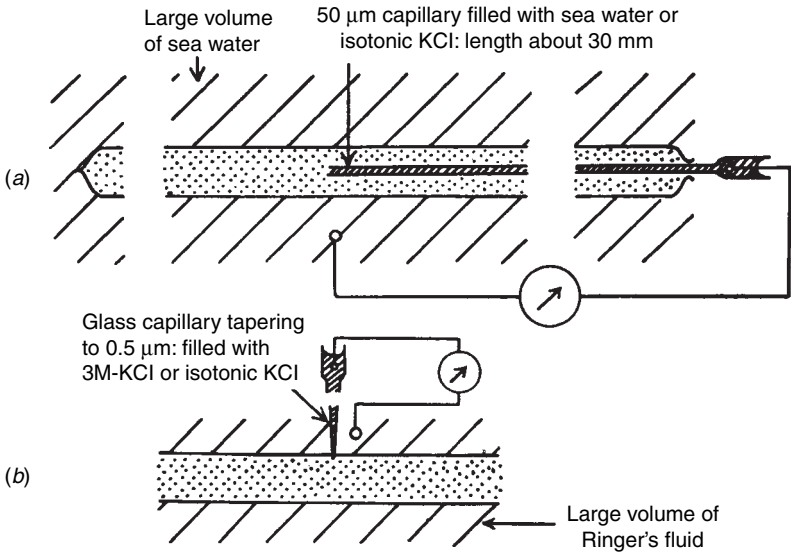

Figure 2.1 Methods for measuring absolute values of resting potential and action potential: (*a*) longitudinal insertion of 50 µm internal electrode into a squid giant axon; (*b*) transverse insertion of 0.5 µm internal electrode used for recording from muscle fibres and other cells. (From Hodgkin, 1951.)

microelectrode is then filled with 3 M KCl, and an Ag/AgCl electrode is inserted at the wide end. With various refinements, microelectrodes of this type have been used for direct measurement of the membrane potential not only in single neurons, but also in many other types of cell.

The potentials to be measured in electrophysiological experiments range from 150 mV down to a few µV, and in order to record them faithfully the frequency response of the system needs to be flat from zero to about 50 kilohertz (1 Hertz = 1 cycle/s). In addition to providing the necessary degree of amplification, the amplifier must have a very high input resistance, and must generate as little electrical noise as possible in the absence of an input signal. Now that high-quality solid-state operational amplifiers are readily available, there is no difficulty in meeting these requirements. The output is usually displayed on a cathode-ray oscilloscope, ideally fitted with a storage tube so that the details of the signals can be examined at leisure. To obtain a permanent record, the picture on the screen may be photographed. Direct-writing recorders yielding a continuous record on a reel of paper are convenient for some purposes, but cannot generally follow high frequencies well enough to reproduce individual action potentials with acceptable fidelity. A recent development for experiments involving close examination of the time course of the signals is to convert them into digital form, and to use an online computer both for storage and analysis of the data (Figures 4.12, 4.13).

A technique that since its introduction by Hodgkin and Huxley in 1949 has played an ever more important role in investigations of the mechanism of excitability in nerve and muscle is *voltage-clamping*. Its object, as explained in Section 4.3, is to enable the experimenter to explore the relationship between the potential difference across the membrane and its permeability to Na^+ and K^+ ions, by

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