The Institute of Biology's
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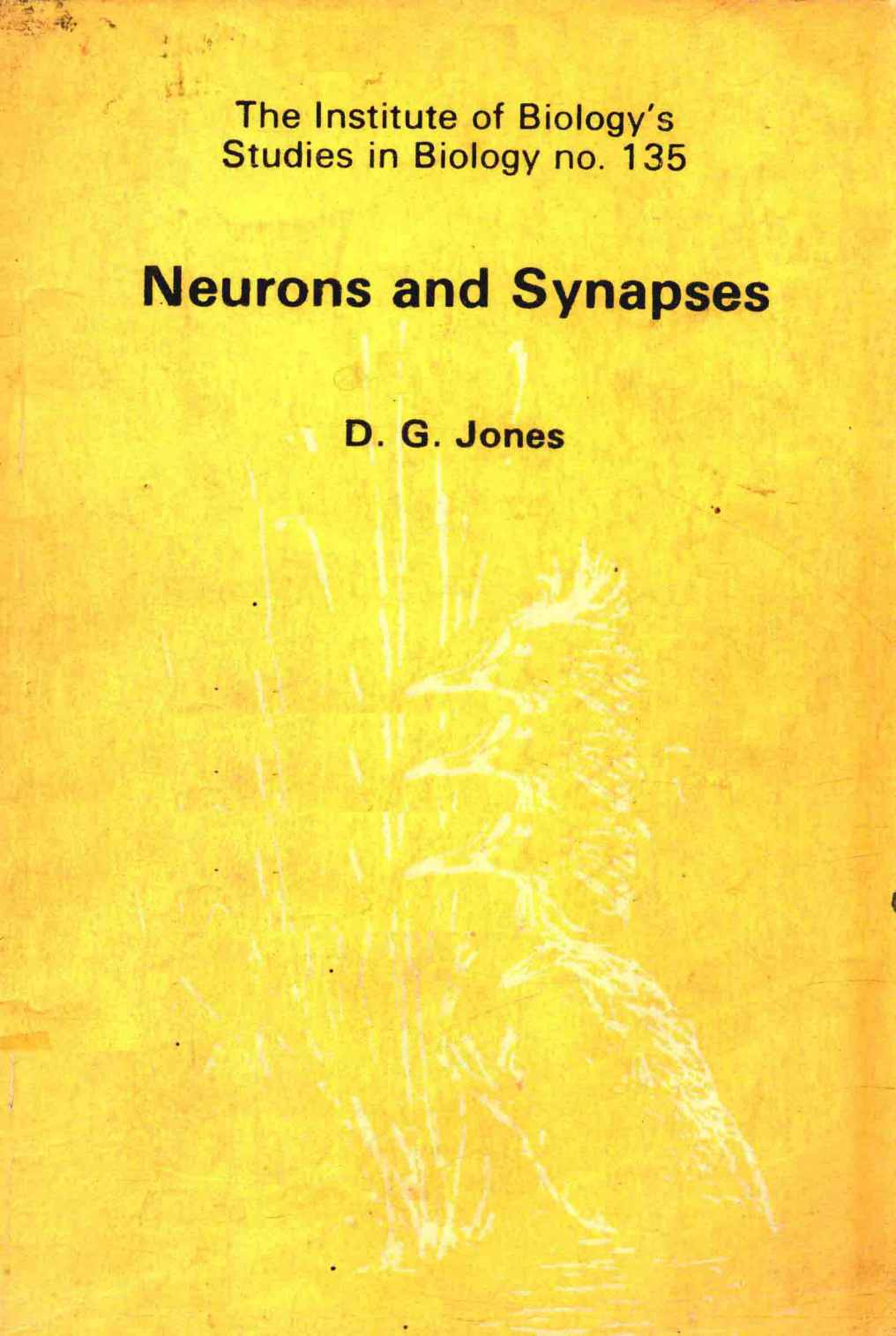
Neurons and Synapses

D. G. Jones



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General Preface to the Series

Because it is no longer possible for one textbook to cover the whole field of biology while remaining sufficiently up to date, the Institute of Biology proposed this series so that teachers and students can learn about significant developments. The enthusiastic acceptance of 'Studies in Biology' shows that the books are providing authoritative views of biological topics.

The features of the series include the attention given to methods, the selected list of books for further reading and, wherever possible, suggestions for practical work.

Readers' comments will be welcomed by the Education Officer of the Institute.

1981

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Preface

Few areas of modern biology are in such ferment as neurobiology, and few areas are as forbidding to the non-specialist as neurobiology. The success of research endeavours in this burgeoning area has tended to make the subdisciplines into which it is divided inaccessible to outsiders. The present book is an attempt to overcome this obstacle by viewing two of the basic components of the nervous system – neurons and synapses – within the perspective of the nervous system as an entity. To accomplish this the topics considered range from the macroscopic to the ultrastructural and encompass morphological and biochemical approaches.

Issues and problems are raised whenever necessary; some currently-accepted interpretations are critically analyzed. Ideas expressed here should not be regarded as final. Many will undoubtedly undergo considerable revision within the coming years. Nevertheless, present concepts are important because they are the only ones we have; they are to be bettered rather than glibly discarded. My hope is that the reader will be prepared to question interpretations as a prelude to constructive thinking.

I am grateful to Mrs Barbara Telfer and Ms Donna Redl for help with the diagrams, to Mrs Susan Dyson for providing the electron micrograph and to TVW Telethon Foundation (Western Australia) for support with aspects of this and other neurobiological projects.

Perth, 1981

D.G.J.

Contents

1 Organization of the Central Nervous System

The focus of this book is the neuron, with particular emphasis on the synaptic connections between neurons. Nevertheless, it would be unwise to limit attention prematurely to these specific components of the nervous system, because to do so would obscure the role of the neurons and synapses in making the nervous system such an immensely complex and refined instrument. Indeed, an understanding of the organization and connectivity of neurons is essential for an understanding of brain function as a whole.

The transition from the level of neurons to that of consciousness and all that is characteristic of human thought, human values and human culture is an immense one. Moreover, it would be grossly misleading to suggest that the bridging of this transition had been accomplished; it has only just commenced. Nevertheless, the neurons and their environment provide a perspective within which many features of brain organization can be usefully approached. In particular, the nature of brain plasticity can be profitably explored against a background of neuronal and synaptic plasticity. Movement between the microscopic and macroscopic levels of organization is essential therefore, if the full potential of the explanatory power of neurons and synapses is to be realized. Hence the need for an initial introduction to the general features of the nervous system in its entirety.

1.1 Overview

Together, the brain and spinal cord constitute the *central nervous system* (CNS), which is kept in contact with the receptors and effectors of the rest of the body by the *peripheral nervous system*. The nerves of the latter convey messages to and from the spinal cord. Afferent nerves run towards the cord and have a sensory function, whereas efferent nerves run away from it and are motor. Afferent nerves carry information about sensations at the surface of the body in to the spinal cord, while efferent nerves bring about the movements of muscle groups, thereby bringing the limbs and trunk into action.

The peripheral nerves are subdivided into two groups: spinal nerves connected to the spinal cord, and cranial nerves connected to the brain.

Spinal nerves are arranged segmentally, one pair to each body segment. Each nerve is connected to the spinal cord by a dorsal and ventral root, and contains both sensory and motor fibres. There are twelve pairs of cranial nerves, all of which originate from the brain and leave the cranial cavity to be distributed to structures principally in the head and neck region. The nerves have sensory and motor components of somatic (bodily), visceral (organs) and special visceral fibres.

A third component of the nervous system is the *autonomic nervous system*, which is concerned with controlling the body's involuntary activities. These include such functions as the beating of the heart, movements of the gastrointestinal tract, and the secretion of sweat. Although these activities have traditionally been regarded as involuntary ones, this may be a misnomer, as biofeedback research indicates that it is possible for individuals to exert some conscious control over them.

The autonomic nervous system is subdivisible into two parts: sympathetic and parasympathetic. The fibres of both systems arise from neurons of the visceral columns of the brain and spinal cord, and synapse with ganglion cells in the periphery before reaching the organs they supply. The respective fibres, however, leave the CNS at different sites, those of the sympathetic system in the thoracic and upper lumbar regions of the spinal cord and those of the parasympathetic system at the cranial (head) and sacral (lower) ends of the CNS. In general, the fibres of the two systems have opposing effects on the organs they innervate, most organs being supplied by both systems. The sympathetic system, for instance, accelerates the heart, constricts arteries, slows gastrointestinal movements and contracts various sphincters. The fibres of the parasympathetic system exert precisely opposite effects.

1.2 Spinal cord

Information entering the spinal cord via afferent (sensory) nerves generally passes to the butterfly-shaped grey matter of the spinal cord (Fig. 1–1). Here the incoming nerve fibre usually synapses with a second fibre, which transports the information upwards within the white matter of the cord to the thalamus. A further synaptic connection occurs in the thalamus, and a final neuron conveys the information to the sensory part of the brain's cerebral cortex. Most ascending tracts, as these are called, cross from one side of the spinal cord to the other somewhere along their course. The major ascending tracts are the anterior and lateral *spinothalamic tracts* (Fig. 1–1), carrying pain, touch and temperature sensations; the *posterior columns*, responsible for conscious position sense, vibration, and size and shape discrimination; and the anterior and posterior *spinocerebellar tracts*, carrying information on unconscious position sense.

Once an appropriate response has been determined within the brain, information is sent back to the spinal cord via another set of tracts. These are the *descending tracts*, which are again found in the white matter of the brainstem and spinal cord. The major one is the corticospinal (pyramidal) tract, responsible for conveying commands for voluntary movement from the motor cortex of the brain (§ 1.3) to the spinal cord (Fig. 1–1). This subdivides into two constituent tracts – lateral and anterior – in the lower part of the brainstem. Most of the corticospinal fibres cross over from one side of the CNS to the other, with the result that the left side of the brain controls movements of the right side of the body, and *vice versa*.

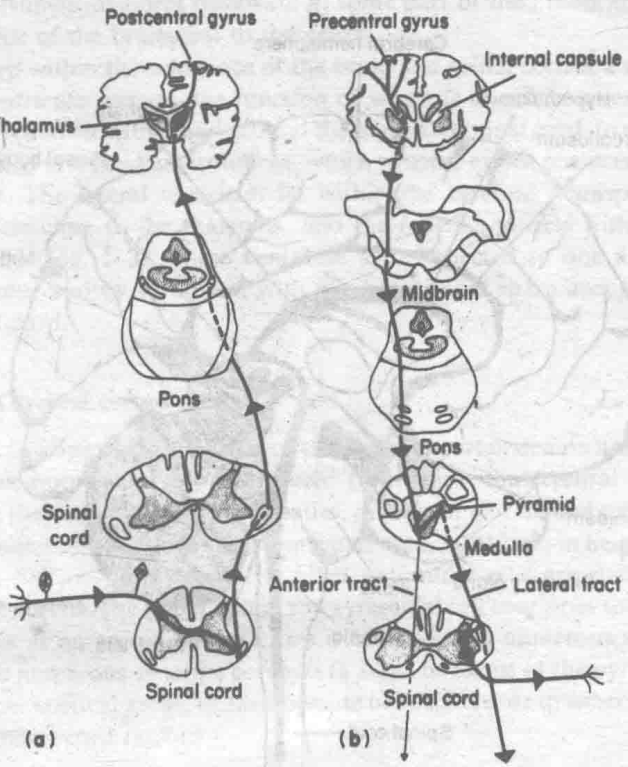

Fig. 1–1 Diagrams illustrating (a) lateral spinothalamic tract, and (b) corticospinal tract. The lateral spinothalamic tract originates from temperature and pain receptors of the skin, and terminates in the sensory cortex. The corticospinal tract originates from the motor cortex and descends to the spinal cord.

1.3 Brain

The human brain can be subdivided into three principal regions: *forebrain*, *midbrain* and *hindbrain*. The forebrain can be further subdivided into the cerebral hemispheres and the more deeply-situated thalamus, while the hindbrain consists of the pons, medulla and cerebellum (Fig. 1–2).

The cerebral hemispheres are joined together across the midline by a bundle of fibres, the *corpus callosum*. Each hemisphere consists of a core of white matter and a 3–4 mm thick enveloping rind of grey matter, the cerebral cortex. The surface of the hemispheres is characterized by numerous fissures (sulci) between which are folds (gyri). The purpose of this irregularity is to increase the surface area of the hemispheres and hence the area of the cerebral cortex. From the side each cerebral hemisphere displays frontal, occipital, parietal and temporal lobes, separated by sulci (Fig. 1–3). Functionally-distinct regions within the cerebral hemispheres include motor, sensory, visual, auditory and olfactory

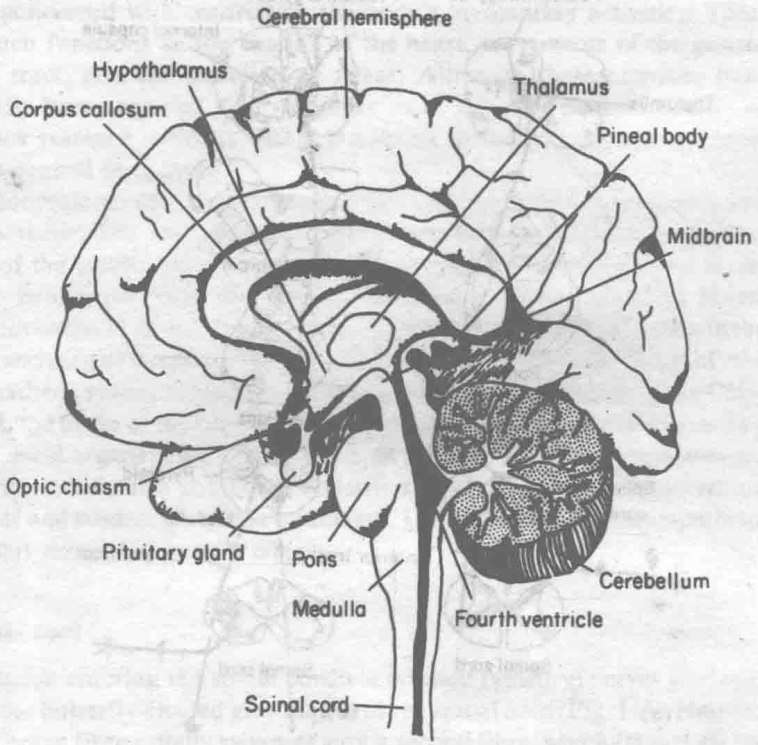

Fig. 1–2 Vertical section of the human brain in the midline, displaying medial views of brain regions.

areas, plus Broca's and Wernicke's speech areas (generally in the left hemisphere).

Deeply embedded within each cerebral hemisphere are the nuclei of the *basal ganglia*, which are intimately involved in the execution of voluntary movements. In the vicinity of the basal ganglia is the *thalamus*; one of the chief functions of this intricate structure is to act as a final relay station where ascending, sensory influences are processed before transmission to the sensory region of the cerebral cortex. It is also implicated, with the cerebellum, basal ganglia and motor cortex, in motor control. The *hypothalamus* lies alongside the thalamus (Fig. 1–2) and plays an important role in the regulation of the autonomic nervous system as well as of various endocrine glands.

The *midbrain* is by far the smallest subdivision of the brain, consisting of various nuclei and fibre tracts. The latter are made up of nerve fibres on their way to the forebrain or hindbrain. The functions served by these structures include control of visual and auditory reflexes.

The *hindbrain* is continuous with the upper end of the spinal cord, and consists of the *pons*, the *medulla oblongata*, and on either side of these the *cerebellum* (Fig.

1–2). Numerous fibres decussate in some part of the hindbrain, running from one side of the brainstem to the other.

Deep within the substance of the brain and spinal cord is a series of cavities, the *ventricular system*, the function of which is to produce cerebrospinal fluid and circulate it within and around the brain and spinal cord. In this way the CNS is bathed in a fluid environment, which to some extent protects it from external injury. The lateral ventricles lie within the cerebral hemispheres, the third ventricle close to the thalamus, and the fourth ventricle within the pons and medulla (Fig. 1–2). These ventricles are connected to one another by small channels, and by foramina, with a subarachnoid space around the brain and spinal cord.

1.4 Cerebral cortex

Microscopical examination of the cerebral cortex demonstrates that neurons are not homogeneously distributed throughout the cerebral cortex. Furthermore, they are of two major varieties, *pyramidal* and *stellate* cells (Fig. 1–4). The pyramidal cells range in size from small ones, 10–12 μm in height, to large ones, up to 100 μm high. The latter giant pyramidal cells are characteristic of the motor cortex. The upper end of the pyramidal cell continues toward the cortical surface as an apical dendrite; this is covered with numerous spines and hence makes numerous synaptic contacts (§ 2.2) The axons of the pyramidal cells pass to other cortical areas, to the opposite hemisphere, or to subcortical, brainstem and spinal cord regions.

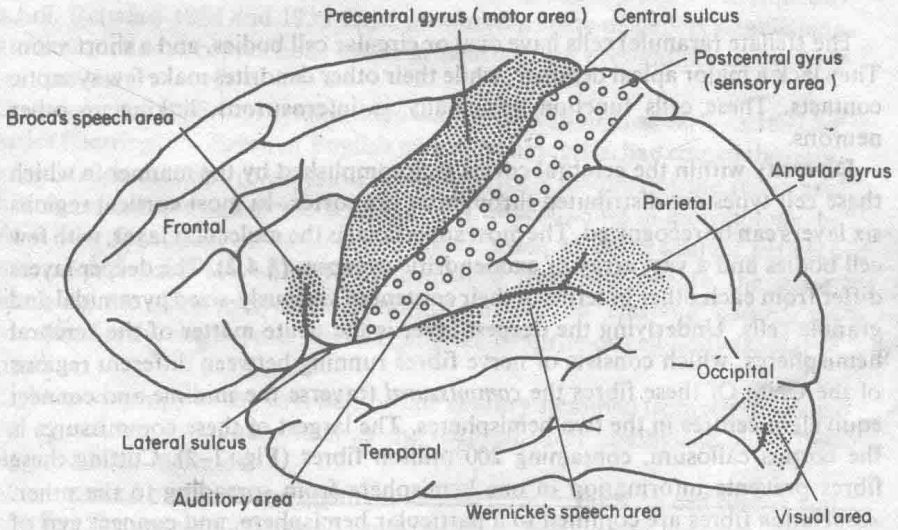

Fig. 1–3 Left cerebral hemisphere of the human brain showing the major lobes into which it is divided, plus the localization of functionally-distinct areas.

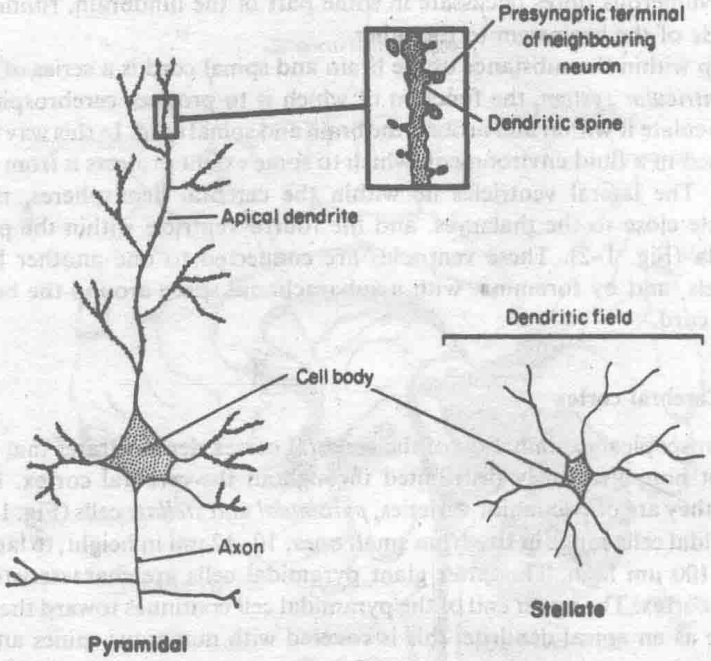

Fig. 1–4 Pyramidal and stellate neurons in Golgi-stained preparations. The inset shows enlarged dendritic spines. The dendritic field refers to the spread of the dendrites of each neuron.

The stellate (granule) cells have oval or circular cell bodies, and a short axon. They lack a major apical dendrite, while their other dendrites make few synaptic contacts. These cells function principally as interneurons, linking up other neurons.

Diversity within the cerebral cortex is accomplished by the manner in which these cell types are distributed throughout the cortex. In most cortical regions six layers can be recognized. The most superficial is the molecular layer, with few cell bodies and a vast array of axodendritic synapses (§ 4.2). The deeper layers differ from each other in terms of their content of variously-sized pyramidal and granule cells. Underlying the deepest layer is the white matter of the cerebral hemispheres, which consists of nerve fibres running between different regions of the CNS. Of these fibres the *commissural* traverse the midline and connect equivalent centres in the two hemispheres. The largest of these commissures is the corpus callosum, containing 200 million fibres (Fig. 1–2). Cutting these fibres prevents information in one hemisphere from spreading to the other. *Association* fibres are confined to a particular hemisphere, and connect gyri of the same hemisphere. Lesions of them give rise to deficits in memory and speech. *Projection* fibres either arise in the cerebral cortex and end in subcortical regions, brainstem and spinal cord, or run in the opposite direction.

2 Neurons

2.1 Neuron doctrine

One of the greatest obstacles encountered by neurobiologists in their study of the mammalian brain has been its complexity. For morphologists this has entailed the arduous task of wading through entangled networks of neuronal processes, in an attempt to bestow order and pattern on the seemingly disordered. It was the neurohistologists of the latter part of the nineteenth century who did precisely this, as they attempted to decide whether neurons were discrete entities or simply part of an extensive network of fibres and processes. These two possibilities were known, respectively, as the *neuron* and *reticular* theories, and each had its ardent champions. Perhaps the best-known of these were Santiago Ramon y Cajal, the main protagonist of the neuron theory, and Camillo Golgi with his insistence that the neurons constitute an integral part of a continuous network or reticulum.

The anachronism of this controversy lay in the fact that it was Golgi's new staining methods, coupled with Cajal's brilliant concepts, that led to the triumph of the neuron theory. The advent of Golgi's silver staining method in 1873 placed neurohistology on a new footing by providing it with vastly superior preparations. It was left to Cajal and a few others to utilize Golgi's techniques to the full. Between 1888 and 1933 Cajal produced a spate of papers establishing that the functional connections between neurons are brought about by their close contact.

So it was that the era of synaptology was born, although as early as 1897 Sir Charles Sherrington, doyen of English neurophysiologists, had coined the term, *synapse*, in an attempt to explain the characteristic features of the reflex arc. While Sherrington's use of the term had a firm grounding in morphology, he used it in a functional sense to denote those areas of close contact between neurons specialized for effective transmission from the one to the other. Underlying the word itself is the notion of one neuron 'clasping' another or, more specifically, the axon of one clasping the dendrite or cell body (soma) of another.

Light microscopy in the first half of this century stemmed from the development of staining techniques such as the reduced-silver, methylene-blue-vital, Golgi and Nissl methods.

Silver-stained preparations highlight axonal terminations on cell bodies and dendrites. The terminations stand out as synaptic boutons on account of their content of either mitochondria or neurofilaments, depending on the stain used. *Boutons* are characterized as ring-, bulb- and club-shaped profiles (Fig. 2–1);

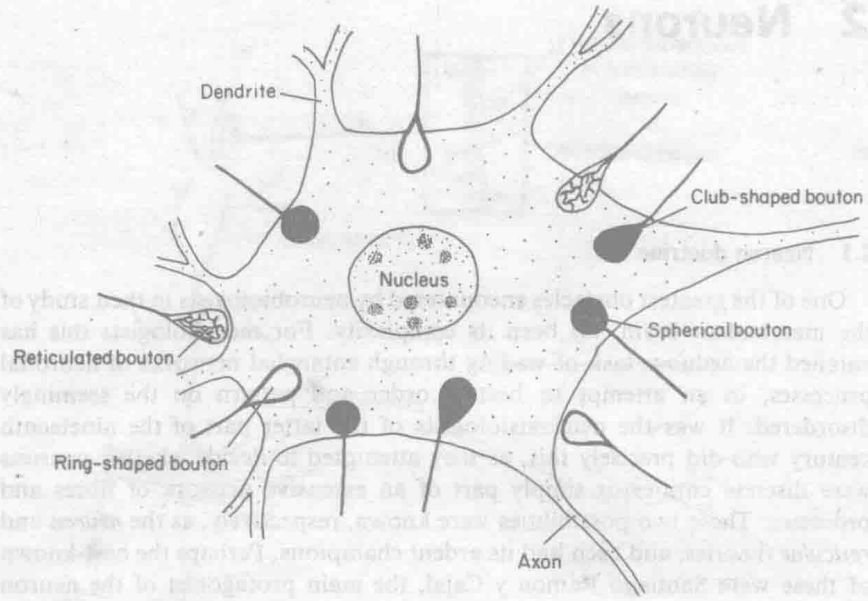

Fig. 2–1 Neurofibrillar boutons on a spinal cord ventral horn cell. Note the different shapes of the boutons, although there is little indication of their substructural organization. This is a diagrammatic representation of a silver-stained preparation, which stains the neurofilamentous bundles in the boutons.

hence the position and number of synaptic contacts can be determined, but little can be said about internal structure.

Of greatest interest in contemporary terms are Golgi preparations, in which some complete neurons, including their cell body and processes, are stained. These were brilliantly exploited by Cajal at the turn of the century, and it was his use of this range of techniques that enabled him to lay the basis of so much CNS circuitry, and opened the way to the classification of neuronal types. At higher magnifications, numerous spines can be recognized over dendritic surfaces (Fig. 1–4), and these mark the sites at which synaptic contacts occur between the dendrites of one neuron and the axons of adjacent ones.

In the 1870s Du Bois-Reymond suggested that neurotransmission may be either chemical or electrical in nature, but it was left to Elliott and later to Dixon in the early 1900s to suggest that a chemical transmitter might be released at the nerve endings, sympathetic nerve impulses liberating adrenaline and parasympathetic impulses a muscarine-like substance.

In 1914 Sir Henry Dale discovered acetylcholine (ACh). He speculated that it may have physiological significance because of its resemblance to the actions resulting from parasympathetic stimulation. At this stage there was no evidence for the liberation of either ACh or adrenaline at the nerve endings, a gap which was partially filled by Otto Loewi when he demonstrated the release of ACh

during stimulation of the vagus nerve with subsequent inhibition of the heart. The sympathetic side of the story was provided ten years later by Cannon and Bacq in 1931.

Further work by Dale and others led to the extension of the chemical transmitter hypothesis to sympathetic ganglia and neuromuscular junctions with ACh as the transmitter. In 1935 Dale proposed that the chemical transmitter hypothesis also be applied to synapses of the CNS, an event of great significance for subsequent neurochemical and neuroanatomical studies.

2.2 Neuronal morphology

Neurons show a considerable degree of diversity depending on the number and arrangement of the dendrites. The result is multipolar, bipolar, unipolar and apolar neurons.

Multipolar neurons are the most frequently encountered and are characterized by the possession of a single axon and a number of dendrites. Arrangements vary, and include some cells with a symmetrical spread of dendrites around the cell body, and others with dendrites confined to specific regions above and below the cell body. *Bipolar neurons* have two processes – an axon and a dendrite – arising from the cell body. They are sensory in function, and are found in the retina, nasal passages and receptors of the inner ear. *Unipolar* neurons are characterized by a single process, serving as axon and dendrite; they are far more common in the invertebrate than the vertebrate nervous system, where they occur in sensory ganglia. Neurons lacking any process at all, *apolar neurons*, occur during early development.

Neurons are sometimes distinguished on the basis of axon length. Golgi type I neurons have long axons and Golgi type II short ones (Fig. 1–4). Of these two varieties, the Golgi type II are the more common constituting the internuncial (connecting) cells of the CNS. The long axons of the Golgi type I neurons form the tracts and commissures of the CNS.

In most vertebrate neurons the dendrites conduct impulses towards the cell body, while the axon conducts impulses away from it. The axon often possesses a myelin sheath as insulation, the dendrites never do.

In general, dendrites of adult neurons are fairly short processes with a length of about 1 mm. In multipolar neurons the dendrites branch repeatedly as they move away from the cell body giving to the dendrites a tree-like appearance – the dendritic field (Fig. 1–4). The branching of dendrites is consistent for many types of neuron, so that the number and distribution of first-, second- and third-order dendrites are consistent for a given type of neuron at a particular age. As a result, they provide clues to the state of maturity of the neurons; since these are readily quantifiable features, they are proving of value in experimental studies dealing with, for instance, the effects of malnutrition, sensory deprivation and hypothyroidism on normal brain development.

Dendritic spines consist of a neck and terminal swelling, and constitute the postsynaptic component of axodendritic synapses (§ 4.1). They are generally

found on dendritic branches, but are absent from the more proximal part of dendritic trunks. In some neurons they account for almost half the total neuronal surface area, reaching lengths of 1–5 μm and occurring in numbers of 40 000–100 000 per cell. Dendritic spines lack microtubules and neurofilaments, although they frequently contain an enigmatic spine apparatus (§ 4.1).

The axon is the thinnest and longest process of a neuron, the length varying from 200 μm to at least one metre depending on the type of neuron under consideration. The profuse branching of the dendrites does not occur in axons, although a few collateral branches may be present (Fig. 1–4). Most axons arise directly from the cell body, the region of origin being the axon hillock (Fig. 2–2). This, in turn, merges with the initial segment of the axon, which is distinguished from the remainder of the axon by its lack of a myelin sheath. Within the axonal cytoplasm are numerous mitochondria, as well as profiles of smooth endoplasmic reticulum, microtubules and neurofilaments. Situated at intervals along myelin-ensheathed axons are nodes of Ranvier, where the myelin lamellae terminate, leaving an exposed section of axon.

The axon transports proteins and neurotransmitter materials from the cell body toward the terminal. There is movement of the axoplasm itself (axonal flow), of the order of 1 mm per day. Besides this, axonal transport within the axoplasm takes place, representing a much more rapid means of conveying substances along the axon. For instance, some light protein particles travel up to 150 mm per day. Such fast intra-axonal transport is probably brought about by the microtubules, a phenomenon made possible perhaps by a sliding-vesicle mechanism.

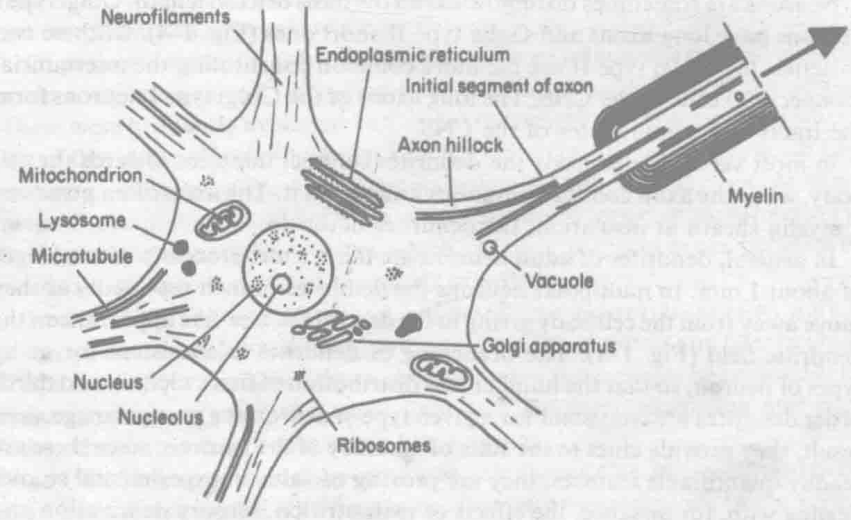

Fig. 2–2 Diagram of a neuron showing its major cytoplasmic constituents, and the component parts of an axon. Arrow indicates direction of nerve impulse.

Within the neuronal cell body is a centrally-located nucleus (Fig. 2–2). Typically, this is large and ovoid, with a single spherical nucleolus that stains strongly for RNA and DNA. The cytoplasm contains organelles that provide the metabolic requirements of the cell. These organelles include Nissl substance, Golgi apparatus, mitochondria and various inclusions. The bulk of the neuronal cytoplasm is produced in the cell body, and from here is distributed to the axon and dendrites.

The Nissl substance is a light microscope phenomenon demonstrated using basophilic stains. With the electron microscope it appears as parallel rows of endoplasmic reticulum plus associated ribosomes (Fig. 2–2). The Nissl substance is most concentrated in the cell body and adjacent parts of dendrites. Besides the ribosomes associated with endoplasmic reticulum, others lie free in the cytoplasm scattered throughout the cell body, dendrites and the initial part of the axon closest to the cell body. Since ribosomes are the principal sites of protein synthesis, much of the protein is produced in the cell body from where it is transported along the axon to its synaptic termination.

The Golgi apparatus is demonstrated at the light microscope level with osmium and silver stains. Ultrastructurally, it appears as a series of stacks of smooth membranes, located in the cell body and proximal regions of dendrites (Fig. 2–2). The protein secretion from the Nissl substance is transferred to the Golgi apparatus, where a carbohydrate component is added before release as secretory vesicles.

Additional structures present in the neuronal cytoplasm include mitochondria, lysosomes, various inclusions, microtubules, neurofilaments and microfilaments. Of these, the mitochondria are responsible for the energy production required for metabolic functions, while the lysosomes have a role to play in the digestion of macromolecules. The inclusions include pigment, glycogen and lipid droplets.

Microtubules are long tubes along the length of the neuron, traversing the dendrites and axon (Fig. 2–2). They are 25 nm in diameter and appear to function as a skeleton for the neuron, thereby maintaining the characteristic shape of the different cell types. In addition, they probably serve a transport role by providing a means by which materials may be transported along the axon and dendrites from the cell body towards their terminations, and also in the opposite direction. Microtubules consist principally of the protein, tubulin, which binds to drugs such as colchicine and vinblastine.

Neurofilaments are of the order of 10 nm in diameter and are distributed throughout the neuron. They occur in some dendritic spines, where they have a ring-like orientation. They also increase in number and may largely fill terminals which are degenerating. The function of neurofilaments is not clear, although it has been suggested they help form the neuronal skeleton.

Microfilaments are slightly smaller than neurofilaments, with a diameter of around 6 nm. They predominate in the developing neuron, and are probably responsible for neuronal movements.

2.3 Neuroglia

A discussion of the architecture of the nervous system is incomplete without reference to the neuroglia or supporting cells, which bind together the neuronal material. However, in spite of the fact that there are as many as 6–10 neuroglial cells for each neuron in the CNS, the neuroglia are easily overlooked. This may, in part, be accounted for by the difficulties sometimes experienced in distinguishing between neurons and neuroglia at the ultrastructural level.

The neuroglia of the CNS can be divided into three types: astrocytes, oligodendrocytes and microglia (Fig. 2–3). Their counterpart in the peripheral nervous system is a single cell type, the Schwann cell. They constitute a dynamic system of functional significance in fluid and respiratory interchange between the neurons and their environment. They form the structural matrix of the CNS

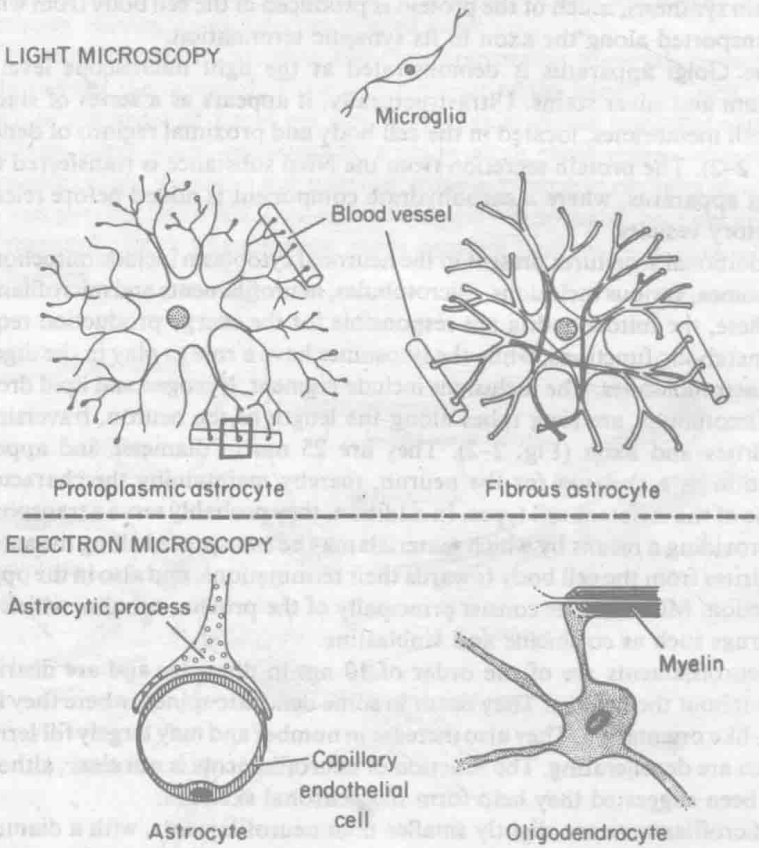

Fig. 2–3 Neuroglial cells of the CNS. The astrocyte processes and capillary at the electron microscope level (lower left) are enlargements of the boxed-in area of the protoplasmic astrocyte (upper left).