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THE PERIPHERAL NERVE

Edited by

D.N. LANDON



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CONTRIBUTORS

- G. Allt Department of Anatomy, The Middlesex Hospital Medical School, Cleveland Street, London W1P 6DB.
- L. H. Bannister Department of Biology, Guy's Hospital Medical School, London Bridge SE1 9RT.
- A. J. Buller Department of Physiology, The Medical School, University Walk, Bristol ES8 1TD.
- S. Conradi Neurologiska Kliniken, Karolinska Sjukhuset, Fack, 1041 Stockholm 60, Sweden.
- G. Gabella Department of Anatomy and Embryology, University College, Gower Street, London WC1E 6BT.
- H. J. Gamble Anatomy Department, St. Thomas Hospital Medical School, London SE1 7RH.
- Geraldine F.
Gauthier Wellesley College, Wellesley, Massachusetts 02181, U.S.A.
- N. A. Gregson Department of Anatomy, Guy's Hospital Medical School, London SE1 9RT.
- Susan Hall Department of Anatomy, Guy's Hospital Medical School, London SE1 9RT.
- J. F. Hallpike Wessex Neurological Centre, Southampton General Hospital, Tremona Road, Southampton SO9 4XY.
- J. J. B. Jack Physiology Laboratories, Parks Road, Oxford OX1 3PT.
- D. N. Landon Institute of Neurology, Queen Square, London WC1N 3BG.
- A. R. Lieberman Department of Anatomy and Embryology, University College, Gower Street, London WC1E 6BT.
- F. N. Low Department of Anatomy, University of North Dakota, Grand Forks, North Dakota 58201, U.S.A.
- J. Ochoa Division of Neurology, Dartmouth Medical School, Hanover, New Hampshire 03755, U.S.A.

PREFACE

"Our aim will be to make propositions about nerve-fibres which shall express as many aspects as possible of our experience of them, without allowing any to remain special or unrelated. We shall try to answer the question 'What is a nerve fibre?' in such a way as to relate the information about it to as wide a range of ideas as we can, and shall resolve not to be disquieted if the search leads us to some of the grandest questions of creation."

— J. Z. Young, from 'The History of the Shape of a Nerve Fibre' in *Essays on Growth and Form*, presented to D'Arcy Wentworth Thompson, 1945.

In the late 19th and early part of this century studies of the peripheral nerves and their distal terminations occupied a prominent place in accounts of the vertebrate nervous system, largely as a consequence of their accessibility for both microscopic examination and experimental manipulation. Thereafter the development of improved staining methods and electrophysiological techniques led to an increasing preoccupation with the integrative functions and internal connections of the central nervous system. Interest in the peripheral nervous system was renewed in the war, and early post-war, years as a result of concern for peripheral nerve injuries and their repair, and the structural bases responsible for the differing modalities of peripheral sensibility. However fashions change in biology, as in other fields of intellectual endeavour, and in many respects study of the peripheral nervous system has latterly become a poor relation to the more fashionable, and ostensibly more philosophically challenging, study of the structure and function of the central nervous system.

None-the-less the peripheral nervous system continues to offer many advantages to the experimenter concerned with the biology of nervous tissue and its functional behaviour, as well as the potential for greater and more immediate rewards in terms of the understanding and treatment of human pathology. Much has indeed been done in these fields within the last twenty years, but the information obtained is disseminated through a wide range of specialist publications and is not readily accessible to newcomers to the study of the nervous system, or to workers in other fields of biology and medicine. This book is intended to fulfill the need felt to exist at the time of its gestation for a

PREFACE

concise yet well documented survey of present knowledge concerning the structure and function, and development and pathology of the mammalian peripheral nervous system.

The time has long since passed, however, when a genuinely comprehensive account of the peripheral nervous system could be contained within one volume, and emphasis has thus been placed upon recent advances in knowledge, particularly in the field of fine structure, and upon the nature of the biological interrelationships which exist between the neuron and its supporting cells, end organs, and other surrounding tissues. Extensive references are provided to more detailed accounts of the individual topics discussed. Successive chapters deal with the myelinated and unmyelinated peripheral axons and their relationships to their satellite cells and connective tissue sheaths; with the cells of origin of such axons, both in the spinal cord and in the peripheral somatic and autonomic ganglia; and with their peripheral sensory and motor terminals. Further chapters are concerned with the structure and chemistry of myelin; with the histochemical reactions of peripheral nerves; with a review of the cytological phenomena associated with degeneration and regeneration in the peripheral nervous system; and with the physico-chemical processes underlying the initiation and conduction of the nerve impulse.

I am very grateful to the Medical Research Council and the Institute of Neurology, Queen Square, for the use of the research facilities needed for some of the work described in Chapter 1; to my wife Karen for her encouragement and support, and for much tedious typing; and to the contributors to this volume for the effort and care they have put into their individual chapters. I am sure that it is their hope, as much as it is mine, that this book may provide a useful foothold on the path towards a more complete understanding of the structure and function of the mammalian nervous system.

D.N.L.

July, 1975

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1 THE MYELINATED NERVE FIBRE

D.N. Landon and Susan Hall

1.1 Introduction

The fundamental functional unit of the nervous system is the *neuron*, a remarkable cell which possesses the capacity to receive, conduct, process in the context of other incoming information, and subsequently transmit onwards, coded stimuli which converge upon it from a variety of central and peripheral sources, and is able to make functional contact with other neurons and with effector and receptor mechanisms via specialized sites of intercellular contact. The vertebrate neuron is a mononucleate, diploid cell which, for descriptive purposes, is usually subdivided into a cell body, the *soma* or *perikaryon*, and a population of fine cytoplasmic processes, collectively termed *neurites*, which are extensions of the soma into the surrounding tissues, and, like the soma, are covered with an excitable plasma membrane. By convention, a neurite that conveys information towards the soma is called a *dendrite*, and one that conveys information away from the soma, an *axon*. This division implies that conduction is unidirectional, as indeed is the case *in vivo*, although experimental studies have shown that axons can in fact conduct in either direction.

A neuron typically possesses but one axon, and a variable number of dendrites, arranged so as to form a *dendritic tree*, whose shape is often characteristic of the neuron. In some smaller neurons, the structure of the dendritic tree is relatively simple, but in the larger neurons, particularly in the higher centres, the dendrites branch more or less dichotomously many times, so that the resultant distribution of dendrites is an elaborate network in which the area of membrane surface available for the reception of stimuli is correspondingly increased, e.g., the cerebellar Purkinje cell. Although there is enormous variation in both the shape and dimensions of neurons in different loci, a morphological classification applicable to all vertebrate neurons is available, based upon the spatial relationships between a soma and its neurites: thus a neuron may be *unipolar* (e.g., dorsal root ganglion cells, granule cells of the olfactory bulb); *bipolar* (e.g., cells of the cochlear and vestibular ganglia), or, more commonly, *multipolar* (most of the cells of the central nervous system). In some rather rare instances the axon is absent — examples of such *anaxonic* neurons are the retinal bipolar cells and retinal amacrine cells.

Neurons may be located either wholly within the central nervous system, or,

as in the case of cranial and sensory ganglia and dorsal root ganglion cells, cranial and spinal motor neurons and pre- and post-ganglionic autonomic neurons, their peripherally-directed axonal processes may lie wholly or partially within the peripheral nervous system, and are thus external to the pial envelope which covers the central nervous system.

An axon arises from its parent soma at the *axon hillock*, whence it continues into a short unmyelinated *initial segment* (see Chapter 5), distal to which it may extend for considerable distances before terminating in some specific site at the periphery. Though single throughout the initial segment and much of its subsequent course, an axon typically divides as it nears its termination, producing a terminal arborization of delicate *telodendria*. Between initial segment and terminal arborization, all axons are associated with a population of satellite cells; in the vertebrate central nervous system these are the *oligodendroglia*, and in the peripheral nervous system the *Schwann cells*.

1.1.1 *The organization of a peripheral nerve trunk*

In the peripheral nervous system, the functional unit constituted by an axon and its Schwann cells is termed a *peripheral nerve fibre*; and this unit may be further categorized as being either *non-myelinated* or *myelinated*, according to the nature of the structural relationship which obtains between the axon and its satellite. In the vertebrates, a major nerve trunk, e.g., one containing the nerve supply to part of a limb, is composed of many thousand non-myelinated and myelinated peripheral nerve fibres. In its proximal parts, where it is commonly incorporated in a limb plexus, it is a mixture of motor, sensory and post-ganglionic sympathetic fibres, having a plurisegmental derivation from the spinal cord. As the nerve trunk is traced distally, there is a gradual functional segregation of this initially heterogeneous population of fibres into bundles or *funiculi*, within which the majority of fibres are either motor or sensory. Repeated fasciculation (division of the funiculi), in conjunction with interchange of fibres between fascicles via numerous intraneural plexuses, continues the process of segregation according to destination, until ultimately small groups of fibres appear, each providing specific connections for a particular effector or receptor mechanism (see Sunderland, 1968).

A typical histological section through a peripheral nerve trunk would, therefore, contain numerous fibres, some emanating from anterior horn cells and conveying motor impulses to neuromuscular junctions, others the peripheral dendrites of dorsal root ganglia carrying pain, pressure, temperature and stretch impulses from either free endings in the skin or a number of specialized end-organs in skin, muscle, tendons, joints, connective tissue and bone. A more extensive functional classification of this spectrum of fibres has been derived from analyses of total fibre diameter and conduction velocity, parameters which show a direct proportional relationship in myelinated fibres (Hursh, 1939; Rushton, 1951). A fibre in any mixed peripheral nerve trunk may thus be

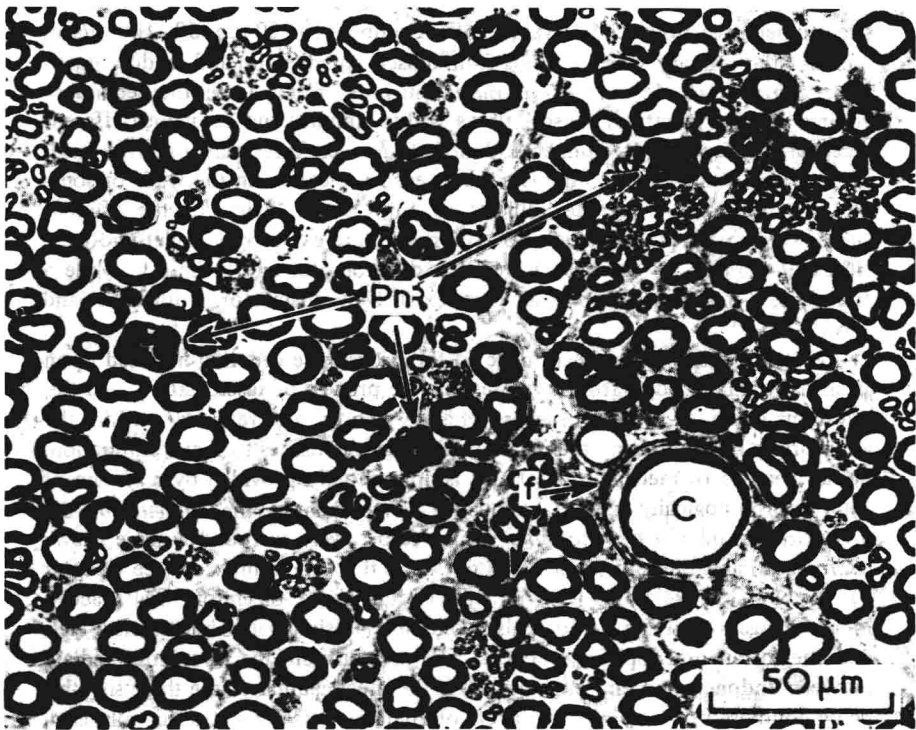


Fig. 1.1 A 1 μ m transverse section through a resin embedded peripheral nerve from a baboon, stained with toluidine blue. Large and small diameter myelinated nerve fibres can be seen embedded in a matrix of longitudinally running collagen fibres. Also visible are endoneurial capillaries (C), fibroblasts (f), and crenated paranodal myelin sheaths (Pn).

allotted to one of three groups, A, B and C, originally defined by Erlanger and Gasser (1937), by comparing the shape of the compound action potential obtained from frog sciatic nerve with the fibre size histogram for that nerve. Group A comprises the largest fibres with the fastest conduction velocities, i.e., the myelinated somatic afferent and efferent fibres; group B contains the myelinated pre-ganglionic fibres of the autonomic nervous system, and group C is composed of the smallest-diameter, slowest-conducting, fibres, the unmyelinated visceral and somatic afferent fibres and the post-ganglionic autonomic efferents. Furthermore, as a result of numerous combined histological and electrophysiological studies of chronically de-afferented and de-efferented preparations, group A has been subdivided into groups I, II and III (all afferent fibres), and α , β and γ (all efferent fibres). In the following description of these subgroups, the values given in parentheses are respectively the diameter range and conduction velocity for the nerve fibres of the adult cat: it should be remembered however, that absolute values vary according to the species and the

site studied (see Boyd and Davey, 1968). Group I (10–20 μm , 50–100 m/sec) includes the primary sensory fibres from muscle spindles (Ia) and tendon organs (Ib); group II (5–15 μm , 20–70 m/sec) includes fibres from the secondary endings on the intrafusal muscle fibres within spindles and cutaneous afferent receptors; group III (1–7 μm , 5–30 m/sec) includes fibres which convey nociceptive impulses, afferent impulses from sensory plexuses in the walls of some blood vessels and from the follicles of fine 'down' hairs. In the efferent subdivision, α fibres (9–20 μm , 50–100 m/sec) are exclusively skeletomotor, β fibres (9–15 μm , 50–85 m/sec) are both skeletomotor and fusimotor, while γ fibres (4.5–8.5 μm , 20–40 m/sec) are exclusively fusimotor, both 'fast' and 'slow'.

Reference has already been made to the progressive ordering imposed upon an initially mixed population of fibres, by the process of fasciculation, and the question arises as to the means whereby fibres are retained within the appropriate bundle during their passage through the tissues to their termination. Some measure of mechanical restraint is undoubtedly provided by a system of three morphologically-distinct connective tissue sheaths, the *epineurium*, the *perineurium* and the *endoneurium*, which respectively surround a nerve trunk, its funiculi, and the individual fibres of which they are composed (see Chapter 3). Peripheral nerve fibres lie within the endoneurium, or endoneurial space, a loose collagenous matrix, which also contains occasional fibroblasts, mast cells and the intraneural capillary network. The perineurium, the layer intermediate between endoneurium and epineurium, is the most cellular of the three sheaths, being composed of a number of layers of characteristically flattened cells, each covered by a basal lamina and exhibiting evidence of considerable pinocytotic activity. As will be seen in a later chapter, many workers have demonstrated the effectiveness of the perineurium as a diffusion barrier responsible for the isolation of the peripheral nerve fibres it encloses from potentially noxious materials in the surrounding connective tissue spaces. The epineurium constitutes the adventitial coat of a nerve trunk, and consists of irregular, dense connective tissue, which is largely collagenous. These three components of the connective sheath of the peripheral nerve are described and discussed at length in Chapter 3.

1.1.2 The basic organization of a myelinated peripheral nerve fibre

In a normal mammalian myelinated peripheral nerve fibre, the Schwann cells, which are responsible for the elaboration and subsequent maintenance of the myelin sheath, are arranged in longitudinal sequence along the axonal surface, every Schwann cell territory defining the extent of an *internode*. In both immature and mature fibres, there is only one Schwann cell, and, hence, one Schwann cell nucleus, per internode, and when fibres branch this invariably occurs at a node. Internodal length is an easily measured dimensional parameter that is frequently employed in quantitative analyses of fibre populations, and it

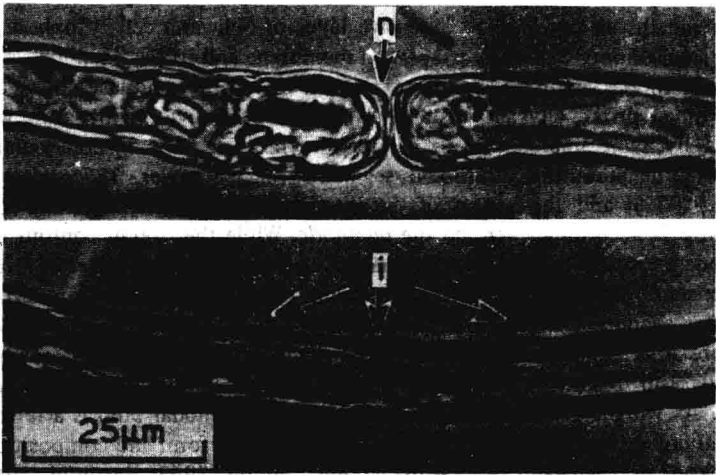


Fig. 1.2 Large myelinated nerve fibres from a mouse teased in saline, showing a node of Ranvier (n) with its paranodal bulbs, and a myelin sheath containing incisures of Schmidt-Lanterman (i).

bears a positive but variable correlation to external fibre diameter (e.g., Thomas and Young, 1949). In mammalian myelinated fibres, internodal length ranges from c. 300 μm in the smallest diameter fibres to c. 1500 μm in the largest (e.g., Vizoso and Young, 1948).

Every internode, irrespective of its length, and whether it is observed microscopically *in vivo* or *in vitro*, appears to be subdivided into a variable number of *cylindrico-conical segments* whose boundaries are delimited by a series of zones within the myelin sheath, the *incisures of Schmidt-Lanterman*. For over a century the latter were considered by the majority of histologists to be artefacts, but they are now known to be inclusions of Schwann cytoplasm within the myelin which pursue a spiral course across the sheath, and connect the external and internal layers of Schwann cell cytoplasm (Section 1.23). The cylindrico-conical segment becomes more apparent in the acute stage of Wallerian degeneration (Chapter 14), when it forms the basis of a primary degeneration ovoid; however, in the normal fibre, it has, as yet, no functional connotation, and thus remains merely a descriptive 'unit'.

The distribution of compact myelin and cytoplasm within a Schwann cell is such that an internode is organized internally into a series of concentric subcellular compartments which surround the axon, and insulate it, both morphologically and physiologically, from the endoneurium (Ranvier, 1878). The axon consists of a central core of cytoplasm or *axoplasm*, bounded by a continuous plasma membrane, the *axolemma*; this is surrounded in turn by a narrow peri-axonal space, the Schwann cell plasma membrane and a thin inner layer of Schwann cell cytoplasm, the numerous membranous lamellae of the

myelin sheath, an outer more extensive layer of Schwann cell cytoplasm, and finally a continuous Schwann cell plasma membrane and its basal lamina.

All internodes, with the obvious exception of the first and last along a fibre, are bounded proximally and distally by a *node of Ranvier*, a structure which appears by light microscopy to be narrow transverse interruption seemingly separating neighbouring internodal segments (e.g., Ranvier, 1875; Hess and Young, 1952), and the region of the internode immediately adjacent to the nodal gap is accordingly termed the *paranode*. While the overall contour of an internode is usually envisaged to be that of a smooth-walled cylinder of more or less constant diameter, there is in fact considerable and consistent deviation from this shape in the region of the paranode and node of larger fibres, where the fibre first expands dramatically into a *paranodal bulb*, before narrowing at the nodal gap to a diameter which is considerably less than that of the internode (Fig. 4). As will be seen later (Section 1.24), the paranodal bulb is a region at which there exist complex reciprocal alterations in the form and composition of both axon and Schwann cell (Williams and Landon, 1963; Berthold, 1968a). Unlike the incisure of Schmidt-Lanterman, which has been little investigated, and whose function is at present unknown, the nodal region has been the subject of numerous studies. The importance of the node in the propagation of the action potential has been recognized since the early 1940's (Tasaki and Takeuchi, 1941), and it is generally accepted that the nerve impulse is conducted along the fibre by saltation from node to node, and that this process involves rapid ionic fluxes across successive nodal axon membranes (see Chapter 14).

1.1.3 *The development of ideas about the structure of the peripheral nerve fibre*

The process by which ideas are evaluated is a complex one, greatly influenced by previous experience, and therefore the ways in which our knowledge of the structure of the peripheral nerve fibre has developed will be briefly traced prior to describing current views concerning its morphology and functional activities.

The fibrous nature of the components of the peripheral nervous system has been recognized for almost two centuries, since the writings of Fontana (1781), who described in detail semi-transparent nervous cylinders within teased fibre bundles. During the first half of the last century, Remak described the unmyelinated nerve fibres which still bear his name, and recognized that the fibres of the organic (sympathetic) nervous system differed from those elsewhere in the body in that they lacked a white outer layer. Moreover, he was aware that within each nerve fibre in the peripheral nervous system, there was a thin-walled tube containing a flat ribbon (primitive Band), which corresponded to the whole grey fibre of the organic system, and he gave what is probably the first account of the maturation of peripheral nerve fibres (Remak, 1836, 1837).

During the nineteenth century, the shape of the peripheral nerve fibre, the nature of the myelin sheath, the physical consistency of the axon and the