Nerves and Nerve Injuries

NERVES AND NERVE INJURIES

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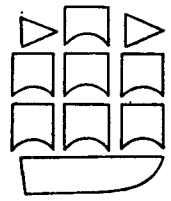

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Foreword

It will be clear to the reader of his monumental work on 'Nerves and Nerve Injuries' that its author, Professor Sydney Sunderland, is uniquely and formidably equipped to write it. His anatomical studies on the internal constitution of nerves and nerve trunks and his other original contributions to the study of the peripheral nervous system have been considerable and important, both to anatomists and to those who have to treat nerve injuries, and to his wide experience in this field he has also added a comparable experience in the study of nerve injuries. Thus his work has a double significance.

His anatomical researches in their immense detail and scope recall the great days of human morphological study when this was regarded as the essential field of the professor of human anatomy and the primary subject of his teaching. These days are long past, and it has become widely, if tacitly, assumed that human morphology is a completed and closed book, and the subject a pedagogic burden to be passed by the professor to his assistants, while the holder of the chair follows his fancy in the realms of comparative anatomy and physiology with occasional dangerous incursions into the field of philosophy. Professor Sunderland's book reveals that our knowledge was not complete nor the chapter ready for closing.

The last world war has provided the author with the further opportunity for a prolonged clinical and pathological enquiry into the phenomena of nerve injuries and of the associated changes in tissues innervated by injured nerves. This double experience gives his present work a unique, authoritative quality, and it will long remain for anatomist, physiologist, clinical neurologist and surgeon a quite indispensable work of reference.

Ever since Weir Mitchell published his remarkable studies on nerve injuries after the American Civil War, every war has renewed these grim opportunities, but it is fair to say that hitherto no single contribution has equalled in scope and magnitude this volume of Professor Sunderland's. The very exhaustive treatment of every aspect of the subject is revealed in the Table of Contents. In so rich a selection it is not easy to single any out for special mention, but the author provides a new and needed classification of nerve injuries, and his treatment of the baffling problems of causalgia and of the phantom limb reveals the content and the present limitations of our understanding of these enigmas. Finally the chapters on diagnosis and treatment are practically very valuable. Nothing relevant is left out of this work which combines the author's own contributions and an admirable account of all that is known and thought upon its subject.

This volume has clearly been a labour of love of many years for its author, and its completion lays us under a heavy debt to him. It takes its place among the many outstanding contributions to medicine and biology that continue to come from Australia and it can well stand comparison with any of them. It is also a tribute to the Melbourne University School of Anatomy over which the author presided for so long with distinction.

London, 1968 F. M. R. WALSHE

Preface

For most tissues, once some sort of mechanical repair has been effected, the body takes care of the return of function. In the peripheral nervous system the surgeon may anticipate no such reward for his services, for here the restoration of function involves far more than the simple restoration of nerve trunk continuity. While it is the quality of the recovery which is the principal objective of nerve repair, both the pathological basis of the injury and the limits of surgery are, as we shall see, anatomical. Nowhere else are anatomy, physiology, and pathology more intimately related or more mutually interdependent. These considerations involve biological and technical issues of great complexity which tend to escape attention, or fail to stimulate enquiry, so long as patients with nerve injuries are dispersed in small numbers over many hospitals where they are, in turn, scattered through general surgical, neurosurgical, orthopaedic and plastic units.

Interest only quickens under the special conditions of war when the incidence of nerve injuries increases dramatically and the permanently crippling effects to which they only too often give rise become more obvious. Furthermore, it is only when patients are concentrated in large numbers in selected centres, under conditions which encourage and permit intensive and uninterrupted study by specially qualified personnel, that many of the problems associated with nerve injuries become apparent, and begin to challenge the imagination and experimental initiative.

The work which forms the basis of this book is the outcome of laboratory and clinical investigations on nerves, nerve injuries and nerve repair which were commenced in 1940 when the author was Professor of Anatomy in the University of Melbourne and visiting consultant on peripheral nerve injuries to the 115th Australian General Military Hospital and the Commonwealth Repatriation Department, Melbourne. Over the war years and subsequently, thanks to the kind offices of the Repatriation Department, it was possible to maintain unbroken records by the same observer which, in most cases, extended over a ten-year period. Three hundred and sixty-five patients were seen and investigated in this way. Though the clinical studies relate largely to battle casualties they were supplemented by studies of civilian injuries. The laboratory studies were undertaken in the Department of Anatomy and subsequently the Department of Experimental Neurology of the University.

In general, service men in the Australian Forces who sustained peripheral nerve injuries in the Middle East campaigns were returned as soon as possible to a Service Hospital in Australia for the continued treatment of the nerve injury, and surgical repair when this was indicated. Because of the delay incurred in awaiting transport, together with the time taken on the long voyage home, many of these patients were not seen in Australia until a considerable time after the injury. This series presented some rather unusual and puzzling features that could not, at that time, be explained by human authority or by reference to the literature. The anatomy of nerve trunks and the pathology of nerve injury were clearly ill-understood, and the doctrines and theories relating to nerve injuries and their treatment too incomplete to be trustworthy.

Prolific though earlier work had been, there had, at the same time, been a general tendency to accumulate facts, often of an isolated and unrelated character, in such a way that principles were obscured in a mass of confusing detail. Anatomists had largely come to think only in terms of structure, physiologists to become preoccupied with function, and those called upon to treat nerve injuries were often

unaware of the existence and implications of certain anatomical and physiological findings that were not readily accessible because they were widely scattered over studies that were unrelated to a common point of interest. This was partly a product of twentieth century specialisation.

The twentieth century has seen an almost unrestrained growth of medical knowledge due, in no small measure, firstly to the fact that every advance in the physical sciences has had its influence on medical research, and secondly to the spectacular development and refinement of instrumental methods and experimental procedures. The pressure of expanding knowledge, the vast literature that has grown up about it, and the special skills required for the use of high precision equipment have led to increasing specialisation and the partitioning of medicine into many special branches. Though this specialisation has brought a rich harvest of rewards it is not without some dangers.

The inability of the individual to keep pace with advancing knowledge on all fronts has meant the eclipse of those allrounders who could encompass, and maintain an active interest in, several scientific disciplines under conditions where knowledge could be integrated in the most orderly and fruitful way, namely within the mind of a single individual. As specialisation increases and the advance of knowledge further outstrips the capacity of the mind to keep pace with it, the threads of science gradually become tangled and disconnected, perspective becomes blurred, and enquiries come to lack design and purpose. This results in knowledge taking on a patchwork form rather than a continuous and meaningful design woven into the fabric of medicine. If new information is to be fully effective it will be necessary to preserve the closest possible integration of knowledge against those forces that are tending to destroy it.

The Second World Wa., with its greatly increased incidence of nerve trauma, not only resurrected many of the old problems but also uncovered a host of new ones. On this occasion the urgent need for achieving a better understanding of the problems involved gained early recognition and, to this end, centres for peripheral nerve research were established in many countries. In general, the overseas approach to the problem showed a distinct preference for planning programmes around the efforts of teams of experts working separately, and often independently, in different but related fields. The publication of the Medical Research Council Special Report Series 'Peripheral Nerve Injuries' under the joint authorship of several British collaborators is an outstanding illustration of the valuable contributions which can be made by such a 'division of labour'.

In the present study the approach has been different, for the author was compelled, both by inclination and local circumstances, to tackle the central theme of nerve injury and nerve repair on a broad, but co-ordinated, front by resorting to anatomical, physiological, pathological and clinical investigation as the occasion demanded.

Attention was first directed to the lessons which could be learnt in the ward where each lesion was regarded as a providential experiment from which every possible advantage should be taken. When clinical observation posed questions to which no satisfactory answers could be given, the emphasis shifted to anatomical, physiological and pathological studies. Morphological details were sought and studied only in so far as they shed light on physiological and pathological processes, for only then do such investigations become purposeful and can full value be derived from the information they provide. Moreover, wherever possible, observation and investigation were confined to patients and human material, recourse being made to animal experiment only when the nature of the problem excluded any other approach.

The elucidation of these fundamental features of the anatomy and physiology of nerve fibres and nerve trunks leads logically to an understanding of the pathology of trauma and, finally, to the formulation of general principles that govern diagnosis and treatment. A guiding principle throughout the study has been the need to keep the total picture of nerve injury and repair constantly in perspective for, as Wilfrid Trotter has so aptly reminded us, ' Even the most assiduous workman will from time to time stand back to get a more general view of his work and to contemplate its wider relations. Indeed, such intermissions are necessary if he is to escape the tyranny of detail '.

Concerning the text itself some points call for comment. In order to achieve the widest possible coverage, some repetition is inevitable because many anatomical and pathological features have relevance to different sections and not necessarily always in the same context. Unless otherwise qualified by reference to the relevant literature, the views expressed are based on the published or unpublished observations of the author. Relevant material from world literature has been reviewed and the extensive bibliography will be useful to those seeking further detail. So that some finality could be reached in the preparation of the text, literature published after 1966 has not been included. Descriptions of operative procedures have been omitted, the intention being to concentrate on establishing the scientific criteria for the techniques employed to repair the damaged nerve.

This, then, is an account of the thoughts, experience and investigations of one individual examined and analysed against the background of existing knowledge and, as such, it represents 25 years of personal endeavour in this field. While an objective approach to the subject has been attempted, it is clear that some expression of personal convictions is inevitable. There is the further problem of deciding what to include and what to omit and such decisions must be largely a matter of personal judgment.

Some problems remain unsolved, and some even unformulated. Nevertheless, such a synthesis as has been attempted is desirable if only to provide some definite points of view from which to see and plan new and, perhaps, more fruitful lines of investigation. In this respect it is hoped that it will prompt the reader to further study and investigation in an area where much remains to be done.

In conclusion, the material has been presented in a manner designed to emphasise the importance of maintaining at all times the closest possible integration between the findings of anatomical, physiological, pathological and clinical studies, for it is integrated knowledge that rationalises our understanding of nerve injuries and the management of patients in clinical practice.

Melbourne, 1968 SYDNEY SUNDERLAND

Acknowledgements

As mentioned in the preface, this book is the result of activities in the laboratory and the clinic spread over the years 1940 to 1957. The actual task of preparing the manuscript was also commenced several years ago. Owing to staff changes over such a long period, the mechanical task of preparing the material for the book has been shared by many different hands so that the number to whom some acknowledgement is due is inevitably increased. The author wishes to take this opportunity to record his thanks to the many persons who, in one way or another, have assisted in the preparation of this book for publication.

The laboratory studies were conducted in the Department of Anatomy and subsequently the Department of Experimental Neurology, University of Melbourne, with the aid of grants from the University and the National Health and Medical Research Council of Australia. This assistance is gratefully acknowledged. The clinical studies were undertaken while the author was visiting consultant on peripheral nerve injuries to the 115th Australian General Military Hospital and the Commonwealth Repatriation Department, Melbourne. I am indebted to the Australian Army Medical Services and to the Repatriation authorities for the facilities and assistance placed at my disposal which enabled me to combine patient care and clinical investigation. With these I associate the servicemen of the Australian forces who cooperated so helpfully in the investigations. The association became such that examinations could be conducted at regular and frequent intervals over long periods and, after their discharge, ex-servicemen would willingly travel great distances to assist in the completion of the study. These men are, in fact, the backbone of the book for the problems that came to the laboratory bench originated in the wards where questions were posed to which, at that time, there were no answers. At this point I also take the opportunity to express my indebtedness to the late Mr. Hugh Trumble, the consultant surgeon at the 115th Australian General Hospital over the war years, with whom I was associated and who was responsible for the surgical side of the relationship. His interest and encouragement were an inspiration in those early days. My thanks are also due to Mr. B. K. Rank and his colleagues who kindly referred patients with civilian injuries for study.

Miss V. Purmalis, Miss C. Hill, Mrs. I. J. Chapman and Mrs. D. A. Harvey Williams have been more directly associated with the laborious and tiresome task of typing, retyping and checking the manuscript. Secretarial help throughout the preparation of the book has been ably and willingly supplied by Miss Purmalis. Mr. L. Preston, despite the difficult conditions and inadequate facilities and materials in this country during the war years, managed to obtain photographs which have survived and are reproducible. In preparing the line drawings I have had the assistance of Mr. A. Wigley and many of the completed figures are from his pen. To all these I extend my sincere thanks. My thanks are also due to Professor W. Hare for kindly providing the radiographs from which Fig. 188 was prepared, to Dr. P. Bladin for the electromyograms shown in Fig. 67 and to Dr. P. Colville for his helpful comments on electrical testing and the data from which Figures 63, 64 and 65 were prepared.

I am also grateful to the Editors and Publishers of the Journals enumerated below for their permission to use data and to reproduce figures from my articles published in their journals over the past 25 years. References to the source of such

material are given in the appropriate sections of the text. Figures have been reproduced from the following Journals: The Journal of Neurology, Neurosurgery and Psychiatry, B.M.A. House. Tavistock Square, London, W.C.1. (Figs. 48 to 59 and 68 to 72); Acta Anatomica, S. Karger, Basel/New York (Figs. 3, 4, 6); Australian and New Zealand Journal of Surgery, Royal Australasian College of Surgeons, Melbourne (Figs. 73, 78, 83 to 93, 96 to 99, 132, 133, 134, 150, 152, 154, 156, 157, 170, 171, 174); British Journal of Surgery, Royal College of Surgeons, London (Figs. 13, 40, 103, 104, 105); Brain, London (Figs. 23, 74, 107, 108, 111, 112, 126, 141, 165, 166, 190 to 193, 195); Archives of Neurology and Psychiatry, American Medical Association, Chicago, U.S.A. (Figs. 9, 18, 19, 21, 29, 38); Journal of Comparative Neurology (Figs. 24, 25, 26, 123, 139, 140, 163, 164, 189), Anatomical Record (Figs. 100, 101, 183) and the American Journal of Anatomy (Figs. 158, 169, 175, 177, 178), Wistar Institute, Philadelphia, U.S.A.

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Sir Francis Walshe has kindly written the Foreword but my debt to him for honouring the book in this way goes much further. His own writings have always been a source of inspiration to the author and his interest, advice, and encouragement during the long and tedious task of completing the manuscript are gratefully acknowledged.

My warm thanks are due to the publishers, Messrs. E. and S. Livingstone, for the manner in which the manuscript has been converted into a book. The concluding stages of the preparation of a book for publication are never straightforward but when 12,000 miles separate author and publisher the difficulties are greatly multiplied. I am indebted to Mr. Charles Macmillan, Mr. W. Henderson and, in particular, to Mr. A. D. Lewis for their courtesy and assistance at all stages of the production.

Finally, without the devoted interest and assistance of my wife this book would have been much longer in the preparation than has been the case and without her astute and helpful criticism it would contain even more obscurities and inadequacies than it undoubtedly still does. No one has spent more time checking and rechecking typed copies of the manuscript and galley proofs and for a non-medically qualified person I can only regard her contribution as exceptional. Her continued sacrifices and encouragement made it possible for the book to be written. That it is dedicated to her is indeed a totally inadequate recognition of her remarkable services.

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PART I

ANATOMICAL AND PHYSIOLOGICAL FEATURES OF PERIPHERAL NERVE FIBRES AND NERVE TRUNKS

Chapter 1

Peripheral Nerve Fibres

1. HISTOLOGICAL CONSIDERATIONS

Histologically, peripheral nerve fibres may be divided into myelinated and non-myelinated varieties on the basis of the presence or absence of a readily demonstrable sheath of myelin. Studies, however, on birefringence in relation to fibre size have failed to confirm a sharp distinction between the two, myelination being the consequence of increasing amounts of lipid in the protein matrix of the nerve sheath. This lipid becomes demonstrable by staining techniques at about 2μ which is approximately the dividing line between the two varieties (Duncan, 1934; Schmitt and Bear, 1937, 1939). Despite this it is convenient to retain the subdivision into myelinated and non-myelinated fibres.

Nerve fibres are composed of a central core of axoplasm surrounded by a multilayered sheath (Fig. 1).

I. THE AXOPLASM

The perinuclear cytoplasm of some nerve cells extends beyond the central nervous system as a filamentous process of variable length and thickness. Those processes from the neurons of sympathetic ganglia and the anterior horn of the spinal cord are axons; those connected with the posterior root

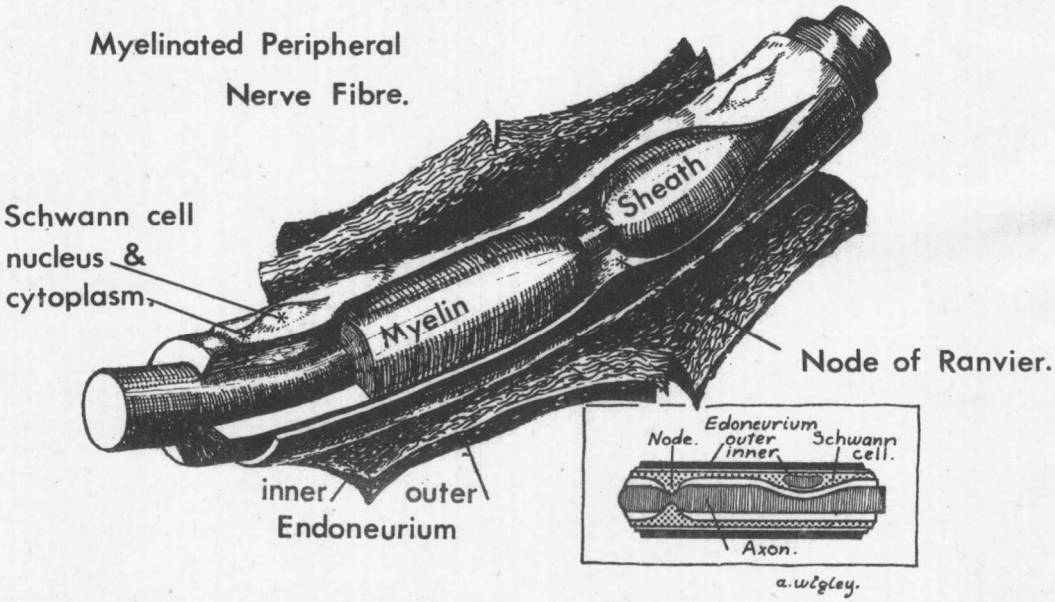

FIG. 1
Diagrammatic reconstruction of the essential histological features of a myelinated nerve fibre.

ganglion neurons are dendrites. Both these processes are histologically indistinguishable and for this reason the general term axon will be applied to all such processes.

Axons vary from a few millimetres to a metre in length. They have the form of a cylinder that tapers gradually towards the periphery and on this are superimposed variations in diameter represented by a slight constriction at the nodes, and random variations elsewhere (Sunderland and Roche, 1958; Robertson, 1962). Excluding these local variations the axons of fibres vary from $0{\cdot}5\mu$ to 20μ in diameter.

The axoplasm is a viscous fluid in which molecules are organised to form neurofibrils which extend along it from the cell body.

Connection with the cell body is a prerequisite on which the life of the axon depends. This vital relationship appears to be associated with an intracellular pressure which promotes a proximo-distal flow of the axoplasm. That this pressure is appreciable is suggested by the outflow of the axoplasm which occurs when the nerve fibre is severed (Young, 1945), by the behaviour of nerve fibres subjected to circumferential pressure (Causey, 1948), by the swelling which appears proximal to the constriction of a fibre (Weiss, 1943; Weiss and Davis, 1943; Weiss and Hiscoe, 1948; Weiss and Cavanaugh, 1959; Weiss, 1961), and by the asymmetry of the bulbous enlargements of the axon on both sides of a node (Lubińska, 1954; Lubińska and Lukaszewska, 1956). The nucleus and perinuclear territory of the neuron are known to contain important energy-producing mechanisms which involve, inter alia, the breakdown and synthesis of nucleoproteins. It is conceivable that materials which are essential for the survival and efficient functioning of the axon are provided from the cell body by this centrifugal flow.

A proximo-distal gradient along axons has been found for phosphoproteins after the administration of labelled phosphate (Samuels *et al.*, 1951), for P^{32} after its injection into the spinal cord (Grande and Richter, 1950; Ochs and Burger, 1958), and for P^{32} phospholipids (Miani, 1962). Grande and Richter (1950) interpreted the results of their study of the effect of electrical stimulation on the transport of radio-active phosphorus in the frog sciatic nerve as being consistent with an increased flow of cytoplasm from the cell bodies into the axons during the activity of the system. This finding was confirmed by Droz and Leblond (1963) who, from a radioautographic study of the distribution of labelled amino acids after injection, concluded that proteins are synthesised in the nucleus and perikaryon of nerve cells and then move along the axon at a rate of the order of 1·5 mm a day to replace the proteins broken down in the axoplasm. After nerve section or axonal interruption, the fate and behaviour of certain enzymes such as choline acetylase (Sawyer, 1946; Krause, 1955; Hebb and Waites, 1956; Hebb, 1957; Hebb and Silver, 1961), lipolytic esterase (Lumsden, 1952), cholinesterase (Dale, 1955; Lubińska *et al.*, 1961, 1962), succinic dehydrogenase, DPN diaphorase and TPN diaphorase (Friede, 1959, 1961), also suggest enzyme transport mechanisms that operate in a proximo-distal direction though apparently at different rates. Such a gradient is not common to all enzymes, however, for no changes have been reported in pseudocholinesterase (Sawyer, 1946), acetic thiokinase and cholinekinase (Berry and Rossiter, 1958; Berry *et al.*, 1958). Furthermore, cholinesterase activity recovers in a distoproximal direction (Clouet and Waelsch, 1961a, b, c) while axonal cholinesterase forms independently from that in the cell body (Koenig and Koelle, 1960, 1961).

The generalisation of a proximo-distal flow, while essentially true, is clearly an oversimplification of a very complex process. The recent and informative studies of Lubińska (1964) on the migration of radioactive tracers and the movement of some morphological and physiological disturbances along axons suggest 'the existence of a continual migration of the neuronal cytoplasm from the perikaryon to the nerve endings and from these back to the perikaryon ensuring the metabolic unity of the nerve cell'. This implies a pattern of streaming in the axons that is bidirectional. The rate of this movement is

given as about 30 to 70 mm a day which is much greater than the centrifugal flow of 1 mm a day reported by Weiss and Hiscoe (1948), 1·5 mm a day by Droz and Leblond (1963), 3 mm a day by Samuels *et al.* (1951), 4·5 mm a day by Ochs *et al.* (1962) and 2 to 11 mm a day by Koenig (1958).

II. THE SHEATH

Surrounding the axon is a multilayered sheath which presents more complex features in myelinated fibres.

(*a*) The Sheath of Non-Myelinated Nerve Fibres

In the case of non-myelinated fibres this consists of a chain of Schwann cells external to which is an encircling connective tissue covering, the endoneurium. The boundaries between Schwann cells are indistinct and the relationship to the axon is one in which the cytoplasm of individual Schwann cells surrounds, to a varying degree, one, or more commonly several, axons (Gasser, 1952, 1955, 1958; Geren and Raskind, 1953; Hess and Lansing, 1953; Geren, 1954; Causey and Hoffman, 1956; Hess, 1956; Terry and Harkin, 1957; Causey, 1960, 1962; Robertson, 1962; Porter and Bonneville, 1963). The endoneurial wall differs in no significant respects from that investing the myelinated fibre and will be described with it. One significant difference, however, is that, whereas the endoneurial tube of a myelinated fibre contains only one axon, that associated with non-myelinated fibres may contain several axons.

(*b*) The Sheath of Myelinated Nerve Fibres

In the case of myelinated nerve fibres, the multilayered sheath consists of a Schwann cell-myelin complex internally and a connective tissue layer externally.

Immediately surrounding the axon is a layer of myelin which, longitudinally, is broken into segments. This segmental arrangement outlines the nodes and internodes of the nerve fibre. The internodes vary in length depending on the thickness of the fibre and the increase in fibre length which occurs during postnatal growth. In general, the length increases with the diameter of the fibre (Key and Retzius, 1876; Boycott, 1904; Takahashi, 1908; Hatai, 1910; Kubo and Yuge, 1938; Hiscoe, 1947; Vizoso and Young, 1948; Thomas and Young, 1949; Thiel, 1957). Internode length may, however, vary greatly in fibres of the same diameter while successive internodes in the same fibre may have different lengths (Boycott, 1904; Takahashi, 1908; Vizoso and Young, 1948; Thomas and Young, 1949; Lehmann, 1951; Thiel, 1957). The number of internodal segments remains constant throughout development so that the length of the internodes increases as the nerve fibre elongates during growth (Vizoso and Young, 1948; Siminoff, 1965). For this reason internode lengths are greater where elongation takes place rapidly and for great distances (Ranvier, 1872, 1875; Boycott, 1904; Takahashi, 1908; Hatai, 1910; Vizoso and Young, 1948; Thomas and Young, 1949; Vizoso, 1950). In contradistinction, the remyelination of regenerated nerve fibres in the adult produces internodes that are short and of about the same length for all fibres regardless of their calibre (Leegaard, 1880; Young, 1945; Sanders and Whitteridge, 1946; Hiscoe, 1947; Vizoso and Young, 1948).

Investing the myelin, and intimately related to it in a manner to be described, is a single layer of flattened Schwann cells which, at each node, reaches and embraces the axon which is constricted at this site. The outlines of individual Schwann cells can not be precisely defined in the normal adult state so that this layer has the appearance of a cytoplasmic wrapping in which are embedded conspicuous ovoid nuclei. Each internode, however, carries only one Schwann cell nucleus which is situated approximately midway between adjacent nodes and indents the subjacent myelin. The complex junctional arrangement of the Schwann cytoplasm at the nodes, with one nucleus to an internode, justifies the conclusion that in myelinated nerve fibres there is one Schwann cell to each myelin segment.

(*c*) Schwann Cell-Myelin-Axon Relationships

The myelin sheath is composed of a complex lipoprotein system. Polarisation microscopy, X-ray diffraction studies, and electron microscopy have established the laminated nature of the sheath in which concentrically arranged bimolecular mixed lipid leaflets alternate with thin monolayers of protein. The long axis of the lipid molecules is oriented radially in relation to the axon and the composition of the myelin can be represented by the ratio 2:2:1 for phospholipid:cholesterol:cerebroside. The protein molecules are distributed tangentially around the circumference (Schmitt *et al.*, 1935; Schmidt, 1936; Schmitt and Bear, 1939; Schmitt and Palmer, 1940; Bear *et al.*, 1941; Schmitt *et al.*, 1941; Elkes and Finean, 1949, 1953; Fernández-Morán, 1950; Finean, 1953, 1954, 1958, 1960; Sjöstrand, 1953, 1960, 1963; Fernández-Morán and Finean, 1957; Uzman and Nogueri-Graf, 1957; Engström and Finean, 1958; Finean and Robertson, 1958; Elfvin, 1961). Ultramicroscopic studies of nerve fibre development and myelination are unravelling the true nature of Schwann cell-myelin relationships and the basis of the complex laminated structure of the myelin sheath of the adult fibre (Geren, 1954, 1956; Robertson, 1955, 1957, 1960, 1962; Honjin, 1957; Peters and Muir, 1959).

During development the axon indents the Schwann cells with which it is associated along its course. In the case of the myelinated nerve fibre to be, each Schwann cell establishes a relationship with only one axon. These cells gradually envelop the axon, the encircling lips of cytoplasm finally meeting to constitute a mesentery for the axon which is appropriately called the mesaxon (Fig. 2). The layers of the mesaxon, which are but the inturned cytoplasmic surfaces of the Schwann cell, outline a narrow channel containing material which is continuous with that around the axon internally and with the extracellular basement material applied to the exposed surface of the Schwann cell. The axon, though now embedded in the Schwann cell, remains a distinct entity, being surrounded by a sub-

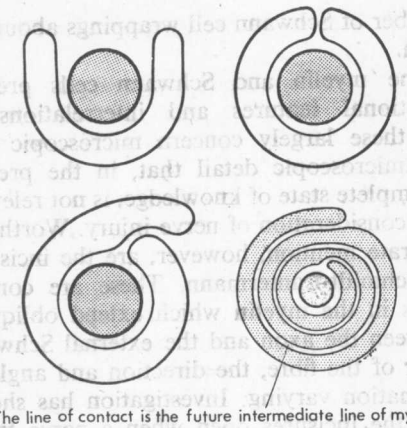

FIG. 2

Diagrammatic representation of the changing axon-Schwann cell relationship leading to the development of the myelinated nerve fibre.

microscopic space which still communicates with the exterior.

The subsequent development of the nerve fibre involves the repeated folding of one lip of the Schwann cell around the system so that the mesaxon becomes wrapped around the axon in an increasing number of turns as the process continues (Fig. 2). In this way a series of double concentric laminae is formed successively around the axon, a thin continuous spiral extension of Schwann cell cytoplasm alternating with the interval between the layers of the mesaxon which is also drawn out in a helical fashion as the mesaxon elongates. The enlarging axon ultimately forces the laminae together so that the cytoplasm in the layers of the Schwann cell wrapping is greatly thinned by being displaced to the surface, and the interval between the leaves of the mesaxon is obliterated. In this way the several layers of the system become packed closely together. The lipid protein membranes of the cytoplasmic surfaces, which are now tightly compressed together, constitute the myelin sheath of the nerve fibre and give to it a characteristic laminated structural organisation. The final arrangement is also one in which the myelin has become incorporated in Schwann cell territory. Increasing myelination during development proceeds by an increase in the

number of Schwann cell wrappings about the axon.

The myelin and Schwann cells present additional features and interrelationships but these largely concern microscopic and ultramicroscopic detail that, in the present incomplete state of knowledge, is not relevant to a consideration of nerve injury. Worthy of separate mention, however, are the incisures of Schmidt-Lantermann. These are conical clefts in the myelin which extend obliquely between the axon and the external Schwann layer of the fibre, the direction and angle of inclination varying. Investigation has shown that the incisures open when a nerve trunk is stretched (Glees, 1943), their behaviour under these conditions suggesting that they function to prevent abnormal distortion and fracturing of the myelin segments.

The Schwann cell layer has been called the Schwann sheath by some and the neurolemma (neurilemma) by others while these two terms are sometimes used synonymously.

(*d*) The Connective Tissue Sheath

External to the Schwann cell layer is a thin and delicate, but complex, investment of connective tissue which is the endoneurium. This forms the outer limiting sheath of the nerve fibre, and also the wall of what is conveniently referred to as an endoneurial tube which is occupied by a cylinder of tissue composed of the axon and the Schwann cells together with the myelin when this substance is present. The nature and functional properties of this endoneurial sheath are described with the connective tissues of peripheral nerve trunks in Chapter 2.

III. THE NERVE FIBRE

Myelinated nerve fibres vary from 2μ to 30μ in diameter. These variations in thickness are reflected in both the axoplasm and myelin. Axon-myelin relationships in peripheral nerve fibres have been investigated and reviewed in detail by Sunderland and Roche (1958) but only the following findings are relevant to the subject matter of this text.

1. The smallest fibres have myelin sheaths with a cross-sectional area exceeding that of the axon, but with axon diameters in excess of 8μ the axon area is larger than the myelin area; the difference between the two becomes rapidly greater as groups of progressively larger axons are considered. The decline in the proportion of the total cross-sectional area occupied by the myelin is steep at first and then becomes more gradual so that the largest fibres have myelin sheaths whose areas are a little less than half that of the entire fibre.

2. Generally the absolute myelin thickness is greater in larger axons but a more obvious feature of the relationship is the great range of variation in the thickness of the myelin sheath around axons of the same diameter. It is not possible, therefore, to predict accurately the amount of myelin that would surround an axon of any particular diameter, so that there is no ground for the belief that the myelin thickness is constant for axons of the same diameter.

3. Variations in Structure along Individual Nerve Fibres: Peripheral nerve fibres are conventionally regarded as smooth cylindrical structures. There is, however, convincing evidence that along their length they show frequent irregular changes in total fibre diameter, in the amount of both axon and myelin and in the area ratio between these two components. It is not practicable to record all the measurements made on serial sections of individual nerve fibres but representative findings are summarised in Tables 1 and 2 (See also Figs. 3 to 7).

(i) The precise status of an overall tapering of the nerve fibre rests on Schwalbe's (1882) observations on living nerves and a mass of indirect evidence that is somewhat offset by data indicating the contrary.

(ii) The Schwann cell nuclei are large and, where they are related to the myelin sheath, always decrease its thickness. Furthermore, they often cause a local reduction in the diameter of the axon.

(iii) Constriction of the axon at the nodes of Ranvier has been frequently reported and illustrated. De Renyi (1929, 1932) claims that the diameter at the nodes is reduced to 50 per cent of its average internodal size. Similar findings are reported by Ramon y Cajal