PATHOLOGY OF PERIPHERAL NERVE

ASBURY • JOHNSON

Volume 9 in the Series

MAJOR PROBLEMS IN PATHOLOGY

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This Book is Dedicated to:

DR. E. PEIRSON RICHARDSON, JR.
DR. RAYMOND D. ADAMS
DR. J. RICHARD BARINGER
DR. SURL L. NIELSEN

who taught us,

and to our wives

PAT AND MARYANN

who forebear.

EDITOR'S FOREWORD

Our knowledge of the structure and function of the peripheral nerve dates back to the first report of myelinated nerve fibers by Ranvier in 1878. In the 100 years since this report, tremendous progress has been made in elucidating the histology, physiology, and chemistry of the normal peripheral nerve through technologic advances and the combined efforts of investigators from many fields. These contributions have provided the basis for the many recent advances in our understanding of the pathology of the diseased peripheral nerve.

Although clinical diseases that produce histopathologic alterations in peripheral nerves—including the various forms of neuropathy, motor neuron degeneration, infectious disorders, trauma, and neoplasms—are encountered regularly, most pathologists have had little experience with biopsies of the peripheral nerve except for those taken for diagnosis of neoplasms. However, with our increased understanding of the disease processes that involve the peripheral nerve, clinicians have become more and more aware of the potential of biopsy as a means of accurate diagnosis and classification of peripheral nerve disease.

Inasmuch as the tools for histopathologic diagnosis of the peripheral nerve biopsy, i.e., histology, histochemistry, and electron microscopy, are widely available, it is essential that pathologists develop proficiency in this emerging area of diagnostic pathology. In their *Pathology of Peripheral Nerve*, Drs. Asbury and Johnson have provided a beautifully written, concise, and systematic approach to the pathologic diagnosis of peripheral nerve disease. All who must wrestle with the problem of diagnosis of peripheral nerve disease, whether it be the pathologist, neurologist, neurosurgeon, or neurophysiologist, will find this monograph an invaluable guide and reference source.

JAMES L. BENNINGTON, M.D.

Consulting Editor

PREFACE

Several years ago, it became apparent to us that there was no general reference volume for pathology of peripheral nerve. Our book is an attempt to fill the void. For the most part, we have had in mind the general pathologist and the surgical pathologist, but we hope that others will find the volume useful as well.

This book was begun in San Francisco in 1971, when Dr. Johnson served for a time during his neuropathology training as a Fellow in the Neurology Research Laboratory with Dr. Asbury at the San Francisco Veterans Administration Hospital. Work continued sporadically over the next six years as our careers diverged, and there were times when we feared that this would always remain an unfinished project, but our common interest in the subject overcame the obstacles of geographic distance and the press of other duties.

Creation of a monograph such as this requires the contributions of many others. We take great pleasure in acknowledging these. First, we offer our thanks to our many friends and colleagues who lent us illustrations, some of which have not been published previously. These individuals include Professor Albert Bischoff, Dr. Peter J. Dyck, Dr. Pamela LeQuesne, Professor W. Ian McDonald, Dr. Claire Payne, Dr. John Prineas, Dr. Michael Rasminsky, Dr. Herbert Schaumburg, Dr. Peter Spencer, Sir Sydney Sunderland, Professor Peter K. Thomas, Dr. Javad Towfighi, Dr. Betty Uzman, and Dr. Henry deF. Webster. We are also indebted to Dr. Mark J. Brown for providing some of the pathologic material and for writing Chapter 2 and part of Chapter 22. Dr. Jack Layton, Chairman of the Department of Pathology at the University of Arizona School of Medicine, deserves our special thanks for his support of the project. Many persons helped with the gathering and printing of the illustrations, including Ms. Susan C. Barbano, Ms. Midori Yoshimura, Ms. Sandra Radich, Mr. John Burgess, Mr. Cliff Pollack, Ms. Carol Kerr, Mr. Arthur Siegel, and Ms. Kay Dalton. Endless typing was involved in the manuscript, and for this we thank Ms. Chris Dodson, Ms. Linda Boyle, and Ms. Judy Smith.

Mr. John Hanley, Ms. Susan Hunter, and their editorial and publishing staff at W. B. Saunders Co. have been unflagging in extending expert guidance, aid, and encouragement.

Arthur K. Asbury
Peter C. Johnson

HOW TO USE THIS BOOK

Our purpose is to provide the generalist in anatomic pathology with a frame of reference to enable an approach to problems in the pathology of peripheral nerve in a systematic and knowledgeable manner. To this end, we have tried to keep the point of view of the general pathologist constantly in mind and to use illustrative material that would strike a familiar note. Photomicrographs of paraffin-embedded tissue stained with conventional dyes have been used wherever possible, often in conjunction with semithin plastic sections that are in general more illustrative of neuropathic processes. Even in this age of the electron microscope, paraffin-embedded preparations are still the cornerstone of microscopic pathology, and we felt obliged to use them as frequently as we could. Electron micrographs also are employed, but primarily to illuminate specific points not otherwise demonstrable.

The layout of illustrations was arranged for ease of reference. By and large, all the illustrations appear on the right-hand pages, and a rapid survey may be made simply by letting the pages flip past the thumb. For those unfamiliar with abbreviations used in the legends for various stains, a table of abbreviations appears on page 279 at the end of Chapter 22 on Histopathologic Techniques.

Peripheral nerve has a number of unique histologic features, all of which are dealt with in the first chapter on normal nerve. For the pathologist, it is important to avoid confusing these features with pathologic change. Also in the first chapter, standard histologic preparations using a variety of stains and techniques are depicted, along with some of the common preparative artifacts.

Chapters 4 through 19 deal with specific diseases of peripheral nerve. Although we are concerned primarily with the pathology of nerve, brief summaries of clinical considerations and correlations are included in the text. When unsettled points are discussed, we have not hesitated to voice our own opinions, but have tried to indicate which opinions are ours and which are those of others.

Literature references deserve a special comment. Brief lists of references are appended to each section or chapter, but in addition there is a cumulative bibliography at the end of the volume, in which the page numbers of the text on which a particular reference is cited are also listed. This feature allows the accumulated bibliography to be used in the same fashion as the Index.

For readers unfamiliar with the everyday clinical aspects of peripheral nerve disorders, Chapter 20 is designed to provide a simple background. The clinically sophisticated will not find much that is new in this chapter. The final three chapters are intended to be practical how-to-do-it sections. Attention is drawn particularly to Chapter 23 on the microscopic analysis of nerve pathology. Here we set forth a method by which diagnostic evaluation of a given sample of peripheral nerve tissue may be carried out.

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PATHOLOGY OF PERIPHERAL NERVE

Chapter One

Normal Nerve

THE CONCEPT OF THE PERIPHERAL NERVOUS SYSTEM

The peripheral nervous system (PNS) is all those parts of primary sensory neurons, lower motor neurons, and autonomic neurons that lie outside the confines of the central nervous system (CNS). Put in another way, the peripheral nervous system includes the dorsal and ventral roots, dorsal root ganglia, spinal nerves and plexuses, distal motor and sensory endings, cranial nerves including the sensory ganglia lying outside the brain stem, and the autonomic nervous system including autonomic ganglia, postganglionic fibers, and all the preganglionic fibers lying outside the spinal cord and brain stem. A corollary to this last statement is that all parts of these neuronal systems that lie outside the CNS are associated with Schwann cells or their ganglionic analogues, satellite cells.

From a neural standpoint, the notion of the peripheral nervous system is merely a construct, a conceptual artifice imposed on a complex system for purposes of simplification. Most neurons with peripheral projections lie partly within the peripheral and partly within the central nervous system, and thus are vulnerable to disease processes that affect either. Our concern in this volume is with those disorders that produce visible patterns of pathologic change primarily in the peripheral portions of these neuronal systems.

When one considers some of the other anatomic peculiarities of primary sensory and lower motor neurons, it is small wonder that they seem at times to be selectively vulnerable to disease. For instance, a large sensory neuron, the cell body of which lies in the fifth lumbar dorsal root ganglion, has a peripheral projection that ends distally in the foot, and a central process that synapses in the gracile nucleus at the level of the base of the skull. This is a linear extent of some 170 cm in a man 6 feet tall. Thus, we are dealing with a cell process that is 10 microns in diameter on the average, and 1,700,000 microns in length, discounting collateral branches in the spinal cord and terminal branching in the periphery. This cell and its processes are associated with literally thousands of supporting cells, both Schwann cells and oligodendrocytes, but the main source of metabolic support is the perikaryon of the nerve cell body. The perikaryon is a veritable protein factory, the products of which may be transported as far as a meter away. What is surprising is that this system fails as infrequently as it does.

CONCEPT OF THE PERIPHERAL NERVOUS SYSTEM

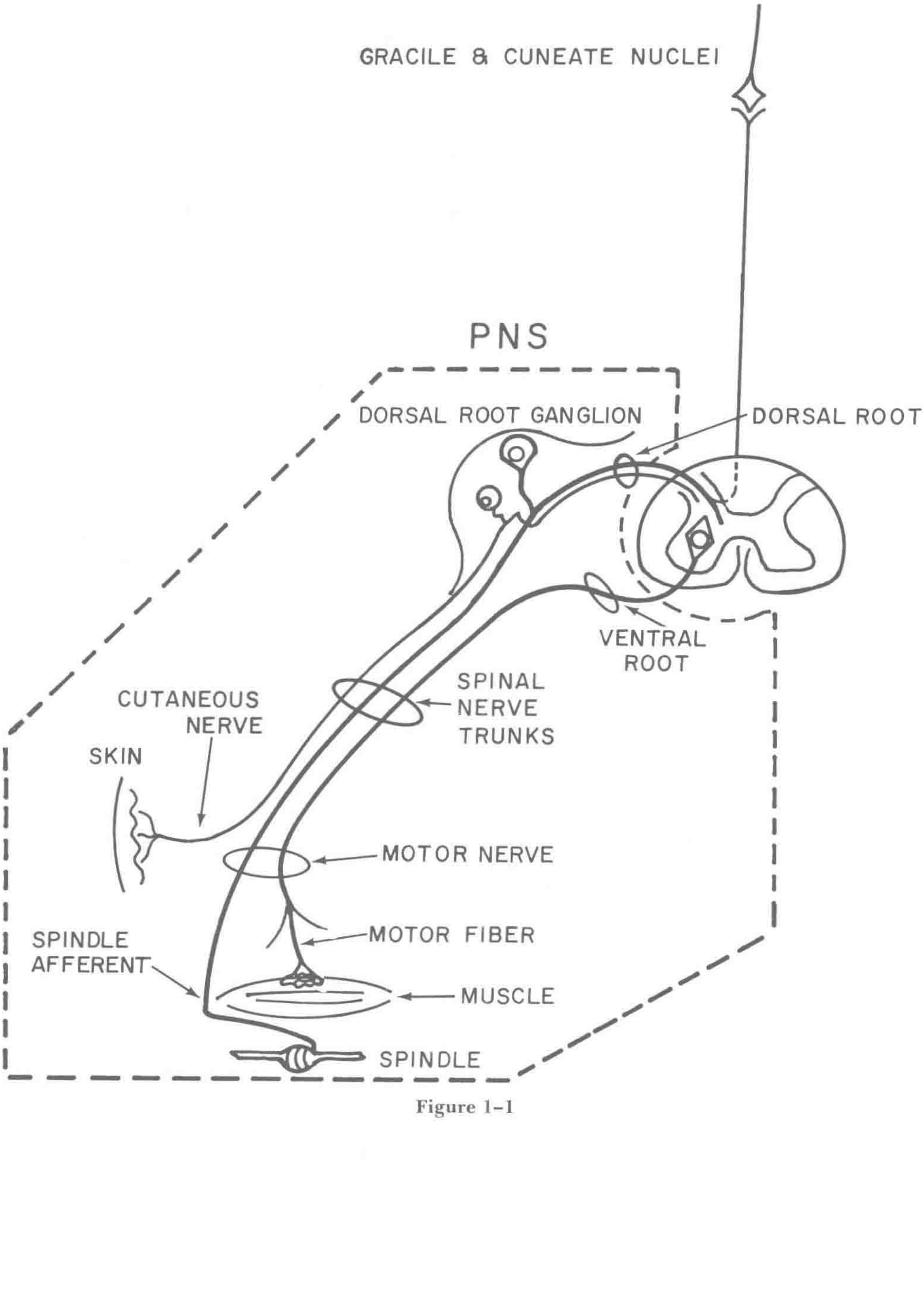

Figure 1-1

PERIPHERAL NERVE TRUNKS

Upon gross examination, spinal nerve trunks are seen to be wrapped in sheaths of connective tissue. If the enveloping layers of connective tissue are dissected away, the nerve may be separated into individual bundles or fascicles numbering up to 20 or more, depending on the size and site of the nerve. Each fascicle is itself closely invested with a sheath of tough connective tissue. In transverse section, the large amount of extrafascicular connective tissue is readily appreciated, and may comprise anywhere from 35 to 70 per cent of the cross-sectional area of the nerve trunk, once again depending on the particular nerve and the particular site at which it is sampled. Fat within lipocytes is prominent within extrafascicular nerve sheath, especially in the proximal sciatic trunk and the lumbosacral and brachial plexuses (Sunderland, 1945a).

Intraneural arrangements of fascicles is variable, both as to size and number, not only from one nerve to another, but also from one side of the body to the other in a given nerve (Sunderland and Bradley, 1949). Considerable fascicular rearrangement takes place from centimeter to centimeter along the course of a nerve trunk, with small groups of nerve fibers shifting from one larger fascicle to another in bridging interfascicular bundles (Sunderland, 1945b). Over moveable joints, the number of fascicles and the proportion of extrafascicular connective tissue increases (Sunderland, 1965), presumably as a natural protection against stretch injury that could result from increased mobility of the nerve at such sites.

Peripheral nerve trunks possess a certain amount of elasticity, by which is meant the ability to return to their previous length after release of stretch. In an elaborate series of studies, Sunderland and Bradley (1961a,b) found that the elasticity of human peripheral nerve trunks varies from 8 to 20 per cent of the original length. Nerve roots have the same elastic properties, but much less tensile strength than peripheral nerve trunks. Most of the tensile strength in peripheral nerve resides in the connective tissue nerve sheaths and not in the nerve fibers, as shown by a comparison of normal nerve and nerve undergoing wallerian degeneration (Sunderland and Bradley, 1961c). Tensile strength was the same in both.

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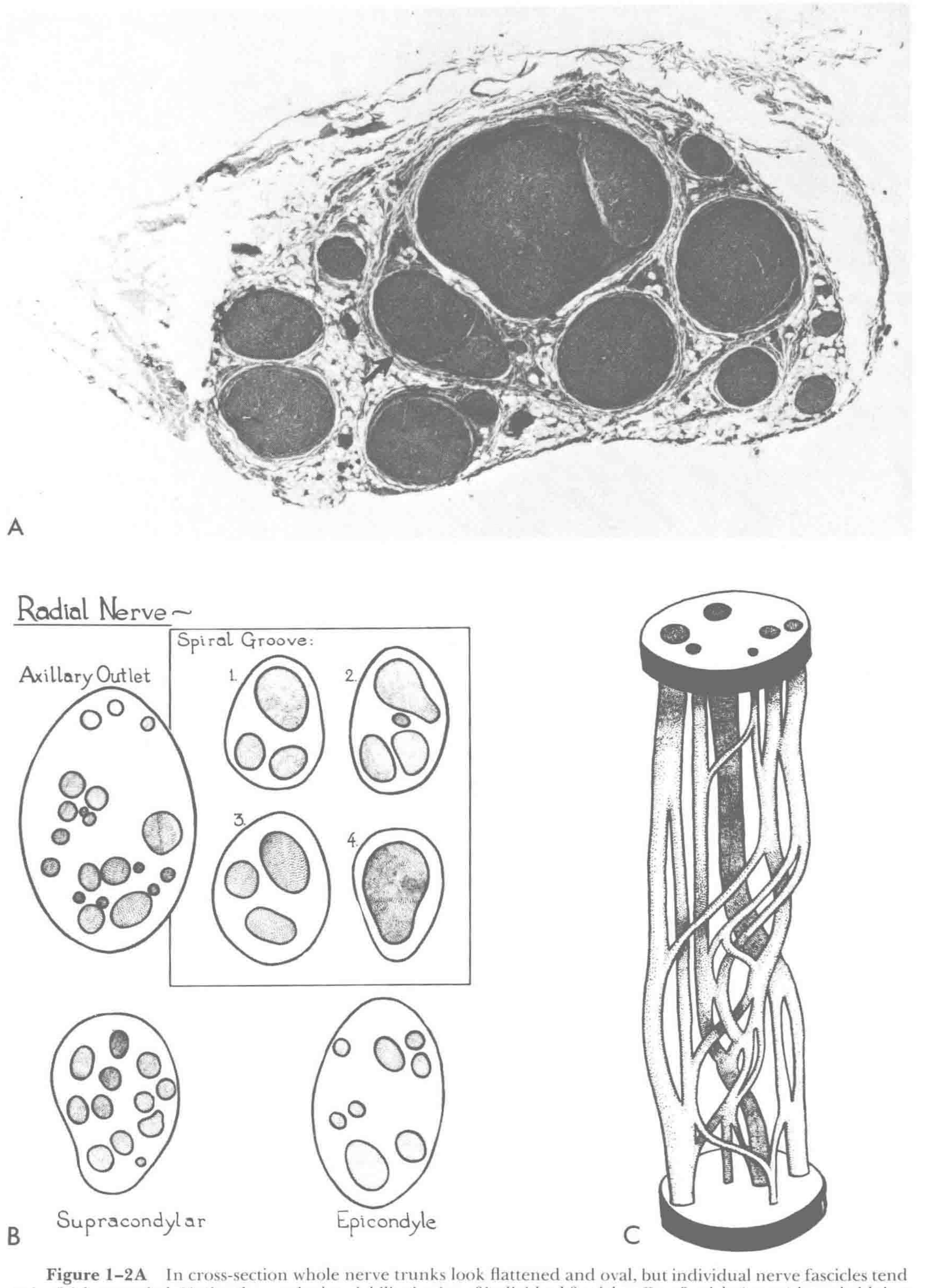

Figure 1–2A In cross-section whole nerve trunks look flattened and oval, but individual nerve fascicles tend to be fairly rounded. Notice the marked variability in size of individual fascicles. One fascicle (*arrow*) has a bridging bundle emerging from it. Fascicles are bound together by dense epineurial collagen, but the outer coats of connective tissue are looser in texture. H & E, 30×.

B and C Fascicular rearrangement takes place continuously throughout the length of every nerve trunk. This is apparent in diagrams B and C. (*From* Sunderland S: Nerve and Nerve Injuries. Churchill Livingstone, London, 1968.)

NERVE SHEATHS

EPINEURIUM, PERINEURIUM, AND ENDONEURIUM

The term "epineurium" refers to the relatively loose connective tissue that binds fascicles into a single nerve trunk; the term "perineurium" indicates the circularly arranged tissue that invests each fascicle; and the term "endoneurium" specifies the delicate connective tissue stroma and fibroblasts that lie in septa and between individual nerve fibers within fascicles.

EPINEURIUM. Epineurium is composed primarily of collagen fibers and the fibroblasts from which they are formed. Most epineurial collagen is longitudinally oriented, as is the occasionally encountered elastic fiber. Near the outer surface of perineurial coverings of fascicles, epineurial collagen is arranged more compactly. Fat cells, when present within the epineurium, exhibit no unusual characteristics, and look like fat cells in any other locus.

PERINEURIUM. Perineurium is circularly oriented, and consists of flattened cells arranged concentrically in layers numbering from one to a dozen or more, depending on the size of the fascicle. Each layer of perineurium is one cell thick with basement membrane on its inner and outer surfaces (Fig. 1–3). Each layer is separated from the adjacent one by longitudinally oriented collagen and an occasional fibroblast. Within a given layer, adjacent perineural cells attach to each other by tight junctions. Organelles are relatively sparse except for pinocytotic vesicles in large numbers. The perineurium is discussed in more detail on page 10.

ENDONEURIUM. This term usually refers to the interstitial connective tissue within fascicles, but at times "endoneurial contents" is used to specify all tissue elements including nerve fibers bounded by the perineurium of a given fascicle. Fibroblasts, recognizable by their angular shape, long sinuous processes, and absence of basement membrane, are scattered between nerve fibers, in septa, and in the subperineurial space. They number less than 5 per cent of the cellular constituents within a fascicle. Endoneurial collagen fibers are longitudinally or obliquely oriented. The remainder of the endoneurial space is filled with granular or finely fibrillar material.