MYELIN

SECOND EDITION

MYELIN

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PREFACE TO THE SECOND EDITION

My colleagues and I have been gratified by how rapidly the first edition of *Myelin* has been accepted as a standard reference work by myelin researchers. This is undoubtedly the primary factor accounting for the high rate of recidivism among the authors with respect to preparation of a second edition; eleven of the original twelve contributors were again involved. Four new authors (Wendy Cammer, Marjorie Lees, Ute Traugott, and Seymour Greenfield) have also contributed to the present volume. This new edition retains many aspects of the format of the original, even including use of the same chapter headings. Thus, comments in the preface to the first edition concerning the level at which material is presented and the relationships between chapters covering the “basic” and “clinical” material are still applicable.

Despite certain similarities in overall organization, comparison of the present edition with the original demonstrates that our efforts to restrict expansion in the length of the text were not notably successful; the new edition is much lengthier than the original. Nevertheless, the increase in text length is modest relative to the increase in information in the seven years separating the preparation of the two editions. Most of the material in the individual chapters has had to be completely redone in order to include this new information. For example, our view of the metabolism of myelin increasingly must take cognizance of a very rapidly turning over pool of certain of its components. These data, and new information concerning enzyme activities intrinsic to myelin, imply that myelin is more than just an “insulating sheath,” its traditionally ascribed function. Myelin may be actively involved in certain dynamic processes, possibly even including ion or water transport. New protein sequence information is now available, leading to a better understanding of the molecular structure of myelin. Tissue culture methodology is referenced through the book as various laboratories increasingly turn to this sophisticated methodology to study problems which were previously intractable when the whole organism had to be used. Many advances have been made in understanding of the immunological, neurophysiological, and other aspects of the pathophysiology of the disease state in disorders involving myelin. Control of the expression of the genome for myelin proteins is under investigation at the level of assaying specific messenger RNA species by *in vitro* translation systems.

Some very recent advances have not yet reached the stage where they can be detailed extensively. For example, the era of recombinant DNA has reached the field of myelin research (e.g., Roach, A., Boylan, K., Horvath, S., Prusiner, S. B., and Hood, L. E., 1983, Characterization of cloned DNA representing rat myelin basic protein: Absence of expression in brain of Shiverer mutant mice, *Cell* 34:799–806). When the first edition was being prepared the thought that gene cloning would help us to understand myelin or its disorders seemed to be relevant only to the distant future. This work is illustrative of progress being made through the use of animal models of genetic myelin disorders. It appears likely that within a few years we will know the details (in terms of DNA deletion or base sequence change) of

several inborn errors directly affecting the metabolism of myelin of other mouse mutants. I suspect that the genetic lesion in one or more human disorders will also be elucidated; metachromatic leukodystrophy seems like a prime candidate in this regard. These projected achievements will redefine the starting point for the question as to what is the course of events relating the genetic lesion to the observed clinical symptoms. In this context, I am confident that interdisciplinary knowledge concerning myelin will be increasingly important to researchers using ever more sophisticated techniques to study the pathophysiology of disorders involving myelin. I hope that this volume will serve as an appropriate starting point for gaining this information.

Pierre Morell

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PREFACE TO THE FIRST EDITION

The division of the mature mammalian brain and spinal cord into regions of “white” matter and “gray” matter is observable upon the most cursory inspection. Microscopic examination indicates that the “white” matter regions are characterized by a multilamellar sheath (myelin) which surrounds the axons. A morphologically similar myelin imparts the white color to tracts of the peripheral nervous system, although as is emphasized throughout the book, there are very significant morphological and chemical differences between central and peripheral myelin. The rapid postnatal accumulation of myelin is temporally associated with increasing functional capacity and presumably indicates some important role related to neuronal activity. The ability of myelinated axons to conduct electrical impulses much more rapidly and with much lower use of energy, relative to unmyelinated axons, is now generally accepted.

As is evident from the above capsule description, a considerable body of information concerning myelin is available. However, as in other areas of research the unknown expands before us more rapidly than we are able to add to our core of knowledge. This is a corollary of the axiom that a good experiment raises more questions than it answers. Among the areas currently under investigation in many laboratories are the following: interaction of myelin-forming cells with neurons, assembly and metabolism of myelin, molecular architecture of myelin, and the details of the functional role of myelin. Furthermore, the clinical significance of lesions of the myelin sheath has served to focus interest on research in pathological processes affecting this structure.

Scientific activity involving the myelin sheath is a miniature of the many types of investigations in the parent field of neurobiology. Investigators trained in traditional scientific areas—morphology, physiology, biochemistry, etc.—conduct research largely within the context of their particular discipline. Most of us become aware rather early in our careers as neurobiologists of the parochial nature of our outlook on the problems we are investigating and try to maintain as broad and innovative a scientific approach as possible. Nevertheless, few of us can gain true competence in more than one or two of the many disciplines whose overlap defines modern neurobiology. The most obvious solution to overcoming our individual limitations as researchers is to establish collaborative investigation with colleagues in other disciplines. This approach has drawbacks, also; the concepts and terminology of investigators in different disciplines may be so different as to present formidable problems in communication.

Being acutely aware of my personal inadequacies with respect to breadth of knowledge, I have attempted to organize this book so as to provide common reference points for researchers from different disciplines who are involved in study of the myelin sheath. Investigators representing various disciplines have presented some of the background necessary to understand how they think about the myelin sheath and oriented us in the flow of research stemming from this view. The charge to each author was to present the material so that a student with a year's background in a graduate or medical curriculum, or a researcher in another field, would be able to follow the presentation. The authors were especially

cautioned not to make the chapters an extensive review of work in their own laboratories. There was also considerable interchange of rough drafts of the various chapters between authors to prevent excessive repetition and insure that all the important topics were covered. Some rather harsh editing on my part (including elimination or transfer of whole sections between chapters) was also done to achieve these goals.

Another feature of the organization of this book is the separation of the basic science material relating to the structure, function, and chemistry of the myelin sheath (Chapters 1 through 7) from material relevant to considerations of the pathology of myelin (Chapters 8 through 14). There is a certain degree of risk involved in such an arrangement, in particular in the setting of arbitrary barriers between research approaches, when in fact the study of a pathological process is based on comparison with the normal course of events. Continuity between the basic science sections and pathology sections in a particular topic has been gained by having the same author, or authors, involved in the writing of both sections. An outline of the relationships between the various chapters follows.

The first section on morphology both is a general introduction and brings us up to date on current work involving direct visualization of myelin by histological and ultrastructural methods. The second chapter discusses physical methods (X-ray diffraction, neutron diffraction, etc.) used in current investigations of the myelin sheaths. Emphasis has been put on giving insight into the type of information obtained by these methods and how it is interpreted, rather than derivations of the physical principles with the attendant mathematical complexity. A chapter on molecular architecture relates ultrastructural, physical, and chemical data to current concepts involving the arrangement of molecules in membranes. The relationship of the structure of myelin to general schemes of membrane structure is emphasized.

The chapter on function of myelin in conduction is designed to give a background for understanding how the neurophysiologist studies the functional significance of this structure. As with the section on physical methods, this chapter emphasizes concepts and experimental strategies rather than rigorous mathematical analysis. The next group of chapters deals with the biochemistry of myelin. There is a chapter on the isolation and chemical characterization of myelin, one concerning the chemistry of myelin proteins, and an introduction to current research in metabolism of myelin.

The second part of the book deals with disorders of myelin metabolism, starting with an outline of human disorders and leading to various experimental approaches to studies of perturbed myelin metabolism in animal systems. The initial section is designed to give us insight as to how the neuropathologist classifies the various disease processes. The chapter on clinical neurology presents to the nonclinician background on how disorders of myelin affect humans. A presentation of work concerning conduction in demyelinated fibers parallels the earlier chapter discussing conduction in myelinated fibers. Chapters on chemical pathology and immunology complement earlier chapters on chemistry of myelin and properties of myelin proteins. A discussion of myelin metabolism in perturbed systems, and how this is relevant to understanding of certain human disorders, complements the corresponding chapter in the first part of the book. A separate chapter on animals with genetic disorders of myelin metabolism provides an introduction into this rapidly growing area of research. The interdisciplinary approach and the separation of material relating to the normal and pathological state are reminiscent of an earlier book in this field (*Myelination*, 1970, A. N. Davison and A. Peters, eds., Charles C. Thomas, Publisher, Springfield, Illinois), and this intellectual debt is gratefully acknowledged.

The reader may note that I have not contributed a chapter to this book. This is not to be taken as a *a priori* proof of my laziness. I wanted to be free to confer with the authors regarding the distribution of the material in the various chapters, and to do editing with as little vested interest as possible in the contents of a particular chapter.

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ABBREVIATIONS

So that this list might be kept short yet informative, it includes abbreviations only for terms that are specific to the subject matter and, with some exceptions, occur frequently throughout the volume. Each abbreviation additionally appears in parentheses following the first occurrence of the term in each major chapter section within which the term is used more than once and thereafter replaces the term throughout that section. Not included in the list are (1) abbreviations for terms that are similarly specific but occur infrequently; (2) abbreviations for common terms; and (3) abbreviations that are used without definition.

AChE	acetylcholinesterase	CT	comput(er)ized tomography
ACTH	adrenocorticotrophic hormone	DCCD	dicyclohexylcarbodiimide
ADE	acute disseminated encephalomyelitis	DM-20	myelin protein of molecular weight 20,500
AETT	acetyl ethyl tetramethyl tetraline	EACA	ϵ -aminocaproic acid
ALD	adrenoleukodystrophy	EAE	experimental allergic encephalomyelitis
AMCA	aminomethyl cyclohexane carboxylic acid	EAN	experimental allergic neuritis
6-AN	6-aminonicotinamide	EEG	electroencephalogram
ATP	adenosine triphosphate	EGTA	ethyleneglycol tetraacetic acid
ATPase	adenosine triphosphatase	EM	electron microscope, e.
AY9944	<i>trans</i> -1,4- <i>bis</i> -(2-chloro-benzylaminomethyl)-cyclohexane		microscopy, e.-microscopic
B cell	bone-marrow-derived lymphocyte	EPG	ethanolamine-phosphoglyceride
BP	basic protein	ESR	electron spin resonance
BSA	bovine serum albumin	GACH	glutaraldehyde-carbohydrazide
CA	carbonic anhydrase	GFAP	glial fibrillary acidic protein
Ca ²⁺ -ATPase	Ca ²⁺ -dependent adenosine triphosphatase	GLD	globoid-cell leukodystrophy
cAMP	cyclic AMP	G _{M1}	monosialoganglioside
CD	circular dichroism	G _{M4}	sialosylgalactosylceramide
CFA	complete Freund's adjuvant	GPDH	glycerol phosphate dehydrogenase
CMI	cell-mediated immunity	HCP	hexachlorophene
CNP	2',3'-cyclic nucleotide 3'-phosphohydrolase	HFA	α -hydroxy fatty acid(s)
CNS	central nervous system	HLA [complex]	human leukocyte antigen [complex]
CPG	cholinephosphoglyceride	HMG-CoA	hydroxymethylglutaryl-coenzyme A
CSF	cerebrospinal fluid	Ia	I-region-associated

IFA	incomplete Freund's adjuvant	PAPS	3-phosphoadenosine 5'-phosphosulfate
Ig	immunoglobulin [with class suffix]	PAS	periodic acid-Schiff
INH	isoniazid (isonicotinic acid hydrazide)	PKU	phenylketonuria
LBP	large basic protein	PLP	proteolipid protein (lipophilin)
LDH	lactate dehydrogenase	P-M	Pelizaeus-Merzbacher (disease)
LGBS	Landry-Guillain-Barre' syndrome	PML	progressive multifocal leukoencephalopathy
LM	light microscope, 1. microscopy, 1.-microscopic	PNS	peripheral nervous system
LPC	lysolecithin (lysophosphatidylcholine)	P _r	basic protein of PNS myelin of certain rodents—similar or identical in sequence to small basic proteins
MAG	myelin-associated glycoprotein	RER	rough endoplasmic reticulum
MBP	myelin basic protein—molecular weight of about 18,500	RIA	radioimmunoassay
Mg ²⁺ -ATPase	Mg ²⁺ -dependent adenosine triphosphatase	RSA	relative specific activity
MGP	myelin glycoprotein	SBP	small basic protein—present in certain rodents related to LBP by deletion
MLD	metachromatic leukodystrophy	SCP	spinal-cord protein
mRNA	messenger RNA	SDS	sodium dodecyl sulfate
MS	multiple sclerosis	SDS-PAGE	sodium dodecyl sulfate-polyacrylamide gel electrophoresis
MSD	multiple sulfatase deficiency	SEP	somatosensory-evoked potential
Na ⁺ ,K ⁺ -ATPase	Na ⁺ - and K ⁺ -dependent adenosine triphosphatase	SER	smooth endoplasmic reticulum
NAWM	normal-appearing white matter	SLD	sudanophilic leuko-dystrophy
NFA	normal (nonhydroxy) fatty acid(s)	SSPE	subacute sclerosing panencephalitis
NMR	nuclear magnetic resonance	STX	saxitoxin
NPGb	<i>p</i> -nitrophenyl guanidino benzoate	TCA (cycle)	tricarboxylic acid (cycle)
ORD	optical rotatory dispersion	T cell	thymus-derived lymphocyte
P ₀	major protein component of PNS myelin	TEA	tetraethylammonium
P ₁	larger basic protein of PNS myelin—similar or identical to MBP of CNS	TET	triethyl tin
P ₂	smaller basic protein of PNS myelin (different from SBP or P _r)	TTX	tetrodotoxin
PAGE	polyacrylamide gel electrophoresis	VEP	visual-evoked potential
		W ₁ , W ₂	Wolfgram proteins
		X	a low-molecular-weight component of PNS myelin
		Y	a low-molecular-weight component of PNS myelin

MYELIN