Edited by
Abel Lajtha

Handbook of Neurochemistry

SECOND EDITION

10

PATHOLOGICAL NEUROCHEMISTRY

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Preface

More than for any other volume of the *Handbook of Neurochemistry*, the chapters in this volume on *Pathological Neurochemistry* deal with the interface of the laboratory bench with the patient's bedside. Most of the chapters reflect the confluence of basic scientists, clinical investigators, and physicians. Considered here are many of the more important disorders that afflict the nerves, muscles, spinal cord, and/or brain of mankind throughout the world. There are well over 500 such disorders. And our understanding of their nature and of measures for effective prevention or treatment depends significantly on application of the biochemical disciplines that characterize neurochemistry.

Before World War II, any attempt to compile a volume on pathological neurochemistry would have been largely descriptive and very rudimentary, as such "handbooks" by Hans Winterstein (1929), Irvine Page (1937), and others demonstrate. But thanks to the many major advances in research and technology in the postwar decades, we now stand at the threshold of understanding how to manage many of the major neurological disorders, and we may expect more such delineations in the immediate decades ahead. Neurochemistry, defined broadly, has played a central role in this extraordinary turn of events, progressing from what J. L. W. Thudichum in 1884 called objects of anxious empiricism to his anticipation of the proud exercise of chemical precision. Indeed, over the next decades we may reasonably expect future editions of this *Handbook* to devote progressively greater space to the pathological and less to the physiological aspects of neurochemistry.

In the present volume, there are notable examples of successful or promising interfaces between the laboratory bench and the clinical bedside. One major advance has been among the genetically determined disorders of the nervous system—in the groups of lipid and mucopolysaccharide storage diseases. The recognition that these disorders arise as consequences of deletions or attenuations of specific lysosomal hydrolases has made possible the development of relatively simple diagnostic and screening procedures and effective prenatal counseling, so that what were once baffling and hopelessly fatal conditions are now susceptible to clinical management and many may soon prove to be treatable by enzyme replacement or analogous therapies.

Major advances have also taken place in the field of movement disorders. The discovery of the neurochemical lesion in Parkinson's disease—the failure of dopamine transmission in nigral neurons—led to the introduction of therapy

with L-DOPA and congeners and the rescue of a sizable adult population group from progressive disability and isolation. In a different way, the even larger problem of epilepsy has been significantly diminished: first, by the devising of practical clinical methods for measuring the circulating levels of anticonvulsant drugs to enhance greatly the clinical management of seizure patients; and second, by the application of the positron-emission tomographic (PET) technique with ^{18}F-labeled 2-deoxyglucose to evaluation of seizure patients *in vivo*. The latter studies have uncovered significant differences between ictal and interictal periods and between seizure foci and adjacent normal brain areas that could not have been anticipated or indeed studied in any other way. The observations of a relatively depressed glucose uptake in areas of seizure foci suggest new research directions for one of the most complex of neurological disorders, epilepsy.

The isolation and purification of receptors for acetylcholine and the exploitation of immunochemical techniques have now provided us with a solution to the problem of myasthenia gravis and with a more rational therapy. Myasthenia gravis may now be clearly classified as an autoimmune disorder. Other potential candidates such as multiple sclerosis seem likely to follow. Surely, the resort to immunochemical techniques carries much promise for many basic and clinical problems of the nervous system. Yet there are challenges as well in such examples as the neurotropic and slow and latent viruses. Not only do viruses or viral particles conceal themselves in neural cells (e.g., the herpesviruses), but others, like the viruses of poliomyelitis and rabies, may elude general bodily defenses by entering axonal terminals and utilizing axonal transport systems to invade and destroy nerve cells. These are special but important facets of the relevance of newer knowledge about axonal transport to clinical problems. And the analogies provided by such neurotropic viruses seem to point to one of the major trophic mechanisms responsible for the maintenance of connective integrity between pre- and postsynaptic elements.

Another most fruitful area of research concerns the neuropeptides. Here, almost from the beginning, the interface between basic and clinical was clearly perceived. On the one hand, the opiate receptors, enkephalins, drug addiction, and pain mechanisms provided an obvious example that continues to intrigue us with its expanding complexities. We ought not to overlook the fact that pain (its mechanisms and their management) represents one of the most prevalent and important clinical and public health problems facing the world today. On the other hand, there are such examples as the hypothalamic–pituitary systems in which a neurotransmitter such as dopamine regulates the elaboration of certain hypothalamic peptide releasing factors, which in turn control the release of specific pituitary hormones. Moreover such hormones are now known to exhibit significant feedback and other modulatory effects on the central nervous system itself. Thus, the triad of neurotransmitter, neuromodulator, and neurohormone in tandem or even in combination (in one molecule) begins to provide the neurochemical perspective with which to comprehend neuroendocrine, behavioral, and other complex phenomena of central processing.

In fact, the whole problem of central processing still poses many fundamental challenges. Sensory input from specialized receptors for touch, position

sense, pain, light, sound, and the like must be transduced by mechano-, chemo-, photo-, and other specialized receptors into encoded nerve signals that can be centrally analyzed, stored in and recalled from memory, and responded to appropriately. Much more research must be accomplished before we can adequately contend with such disorders of central processing as autism, learning and language disabilities, deafness, blindness, and perhaps even the dementias of the Alzheimer type.

One final area deserves particular attention because of its socioeconomic importance and our as yet rudimentary understanding of the nature of such disorders. Included are cerebrovascular disorders or strokes (the third leading cause of death, after heart disease and cancer, in the United States) and trauma to the central nervous system, primarily head and spinal cord injuries (which afflict the young adult male in particular and are major factors in nearly three-fourths of the fatal accidents in the United States). In fact, these are universal, worldwide problems of a magnitude comparable to that for the United States. For the clinician, and for the neurochemist as well, much of the problem concerns the consequences of these insults to the central nervous system: edema and coma in particular are persisting challenges in terms of mechanisms and of clinical management.

With respect to stroke, recent promising research approaches include the role of prostaglandins in aggregation of platelets, in the control of the caliber of blood vessels, and in the effects of acetylsalicylic acid to inhibit the initial cyclooxygenase step of prostaglandin synthesis from arachidonic acid—all focused on the puzzling problem of pathological mechanisms and prophylaxis in cerebral ischemia and thrombosis. Additionally, more knowledge is needed concerning unique neurochemical aspects of cerebral vessels, which are embryologically and pharmacologically distinct from blood vessels elsewhere in the body.

With respect to central nervous system trauma, a major unsolved problem is why the brain and spinal cord fail to repair damaged areas to achieve spontaneous restoration of function. The tragedy of the wheelchair-bound paraplegic paralyzed below the level of spinal cord injury and unable to regenerate functional connections across the injury gap is the dramatic example. But there are comparable situations for patients with head injury, stroke, multiple sclerosis, and the like. In all cases, the original developmental potential of central axonal outgrowth and establishment of appropriate functional connections among central neurons does not operate when mature brain or spinal cord tissue is damaged. Yet peripheral nerves do regenerate under like circumstances, central connections in nonmammalian species regrow, and in mammals the potential in the central machinery remains. Thus, the neurochemical events and factors involved in developmental and regenerative processes in the mammalian and especially the human central nervous system pose an unusually urgent challenge. In such types of research investigators at the laboratory bench may be involved without realizing the clinical implications and needs.

It seems appropriate to conclude this Preface with a brief review of the dimensions of such clinical problems in the United States today (data for other

countries would be quite comparable). Developmental disorders of the nervous system affect one out of every ten children; there are some one-half million new strokes each year, with 2.5 million Americans continuing to be disabled by stroke; 2 million are legally deaf (and another 12 million have significant hearing impairment); 2 or more million have epilepsy; more than 1.5 million elderly are demented (and account for nearly one-half of all nursing home patients in this country); about 0.5 million have Parkinson's disease; there are 400,000 new cases of head trauma and 10,000 new cases of spinal cord injury each year (with some 100,000 continuing paraplegics); and much more. For example, we have yet to comprehend or to begin to contend with the immense problem of neurotoxicology, especially in the industrial sector. In all, one out of every five persons, or 50 million Americans, are afflicted with neurological or communicative (hearing, speech, language) disorders. The cost to the United States in terms of care, lost income, and the like exceeds 65 billion dollars each year. And the costs to patients in terms of quality of life and to their families in terms of disruptions of home life as well as financial hardship or outright disaster are incalculable. In the case of stroke alone, only 10% of all survivors can return to full activity, whereas fully one-half are so severely disabled that full-time home or institutional care is required.

Yet the expenditures for research by the public and private sectors together amount to considerably less than 400 million dollars annually, or only about 0.5% of the annual cost to society of these disorders. Clearly, a modest increase in the support of research, particularly in the Federal and industrial sectors, would allow us to capitalize on the current upsurge in the neurosciences, as new knowledge and new technologies continue to impinge on us. Two aspects in particular warrant special support and encouragement. One is the training of new investigators (with a special attention to those with clinical orientation) to fill the gaps created by attrition, new fields and technologies, and new academic teaching institutions. The other is the provision of research funding at the interface between the laboratory bench and the patient's bedside. Human research is extraordinarily difficult, demanding, and expensive, and it does not compete well with nonclinical or basic research. Both types are needed, but research on man deserves special attention.

In all of these considerations there is a continuing and vital central role for neurochemistry. Physiological phenomena—electrophysiology, if you will—depend on membrane structure, on ionic gradients and conductance, and on energy metabolism in their support; and on specific transmitters, receptors, and intracellular interactions to generate and display the observed functional phenomena. The same may be said by analogy for pharmacological, immunological, toxicological, endocrinological, and especially behavioral disciplines. In this and preceding volumes in this *Handbook* series, many chapters underscore the central importance of neurochemistry for our understanding of the nervous system, for the management of its disorders, and, indeed, for man himself. For it is his nervous system that makes man human; and it is in its composition, circuitry, awareness of the surrounding world from sensory in-

puts, storage and recall of such experiences, and responses appropriate to its central processing that the human nervous system operates primarily as a chemical entity of marvelous design and superb performance. May careful perusal of this volume bring such understanding and appreciation.

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Contents

Chapter 8

Adrenoleukodystrophy

Yasuo Kishimoto, Hugo W. Moser, and Kunihiko Suzuki

Chapter 9

Brain Edema

Pak Hoo Chan and Robert A. Fishman