Preface to the Eighth Edition

This Eighth Edition of *Basic Neurochemistry: Principles of Molecular, Cellular and Medical Neurobiology* encompasses 40 years of progress in neurochemistry since its first edition, entitled *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*. This seems an appropriate time to consider the progress of neurochemistry and of this book. To make this brief, we will consider only two topics, both featured prominently in this edition: neurodegeneration and neuroimmunology. When the first edition was being written, the neurochemistry of neurodegenerative disease was in its infancy, while neuroimmunology didn't exist as a discipline.

In 1972, the major neurodegenerative diseases were familiar to clinicians and pathologists, having been described in heartbreaking detail by neurologists and pathologists: including Alzheimer's disease (AD) (1906), Parkinson's disease (1817), amyotrophic lateral sclerosis (1869), Huntington's disease (1872), and Charcot-Marie-Tooth disease (1886), among others. Recognizable descriptions of some of these diseases can be found in writings of antiquity in many parts of the world. These early descriptions focused on describing the distinctive symptoms of each disease and even then recognized the inability of physicians to cure these diseases. With the twentieth century, came detailed neuropathological descriptions that identified affected brain regions and the hallmark histopathology for each. This era was epitomized by the work of Alois Alzheimer in his initial description of plaques and tangles associated with the disease that bears his name, subsequently validated by Solomon Carter Fuller's demonstration that these pathological hallmarks were observable in many aged patients with dementias.

The next 50 years revealed pathological hallmarks for other neurodegenerative diseases, such as Lewy bodies in Parkinson's disease. Descriptions of each neurodegenerative disease grew more detailed with respect to which neurons were lost, the order in which different brain regions were affected. Subtle variations were noted, such as differences in age of onset and rate of progression. Still, we knew little or nothing about the causes of these diseases or of their underlying biochemistry. In that first edition, the neurochemistry of neurodegenerative diseases barely existed.

With each subsequent edition, additional clues and insights accumulated and could be incorporated into the text. Twelve years after the first edition, in 1984, the Aβ peptide was isolated from the brains of patients with Alzheimer's disease and Down syndrome and sequenced , thus uniting these two disparate conditions at the biochemical level and leading to determining the major component of amyloid plaques in AD. The Aβ peptide appeared in Basic Neurochemistry with the 4th edition, as the neurochemistry of the amyloid precursor protein (APP) and of Alzheimer's disease began to take form. A few years later in 1988, the microtubule associated protein, tau, was shown by immunochemical methods to be the major constituent of neurofibrillary tangles, showing up in the 5th edition. The discovery of prions in 1982 led to a completely different view of how proteins and neurodegeneration were linked in prion diseases in the 5th edition, eventually meriting a chapter on prion diseases starting with the 6th edition.

As protein components were identified, molecular genetics played an increasing role in our understanding of neurodegeneration, starting with the cloning of the APP in 1985 and of pathogenic mutations in APP in 1990. Mutations in additional genes leading to familial forms of Alzheimer's were identified in 1995, providing insights into the generation of Aβ and amyloid. The genetic bases for additional neurodegenerative diseases were found. The huntingtin protein was identified as the gene product mutated in Huntington's disease in 1993 and found to be associated with expansion of a polyglutamine repeat (5th edition). That same year, mutations in superoxide dismutase type 1 were shown to cause some cases of familial amyotrophic lateral sclerosis. Synuclein was identified as the major constituent of Lewy bodies in 1997, thus providing a connection to Parkinson's disease that was reinforced by the concurrent identification of mutations in the α−synuclein gene that gave rise to a familial form of Parkinson's disease. As genes were identified, we added information eventually leading to inclusion of chapters on the use of transgenic animals in studying inherited diseases in the 6th and the genetics of neurodegeneration and of polyglutamine repeat diseases in the 7th editions.

As our understanding of the biochemical, cellular and molecular components of these diseases increased, new information was added to *Basic Neurochemistry* and the chapters devoted to the topic grew in size and number. In the current edition, ten different chapters consider aspects of different neurodegenerative diseases. This transformation of our understanding of these diseases is providing insights into the specific molecular mechanisms for pathogenesis and with these insights comes hope for treatments or cures that will finally solve the challenges of these devastating conditions. We would like to think that *Basic Neurochemistry* has not only chronicled these advances in our understanding, but has contributed to the training and shaping of researchers who will provide the key to cures and treatments to some of the most difficult challenges in contemporary medicine. To emphasize this connection of basic neurochemistry to understanding disease, this 8th edition incorporates a new feature, namely, Translational Neurochemistry, consisting of a special box in each chapter in which a selected recent or emerging basic concept, or discovery is related to its potential significance

in understanding translational neurochemical principles. To emphasize that this exchange between basic and clinic neurosciences is two-way street, boxes in basic neuroscience chapters provide an example of a disease mechanism or therapy related to the topics covered in the chapter, while chapters focusing on disease feature a box discussing a basic neuroscience issue related to the disease pathogenesis.

In contrast, when *Basic Neurochemistry* first appeared in 1972, immunology and neuroscience occupied different worlds. Little overlap was seen beyond the damage to neurons during inflammation due to infection and autoimmune episodes such as multiple sclerosis. Indeed, the brain was thought to be isolated from the immune system by the blood brain barrier, creating an immunologically privileged domain. When this barrier was breached, the nervous system was inevitably damaged. As described in one of the new chapters added to this edition, we now understand that the nervous system plays an important role in regulating the immune system and immune responses. Many gene products originally identified as regulating immune responses may also have functions in the nervous system. Similarly, behavioral and cognitive changes can be related to alterations in immune function. As a result, the latest edition features a chapter on neuroimmunology that provides a framework for understanding the complex interrelationships between the nervous and immune systems along with expanded discussions of inflammatory mechanisms and shared transcriptional factors. In the coming years, we expect to see this area expand like the study of neurodegeneration as we understand more about the fundamental cell and molecular biology of the nervous system.

The preface of the 1972 first edition of *Basic Neurochemistry* stated the "unifying objective" for the book:

"Its central, unifying objective is the elucidation of biochemical phenomena that subserve the characteristic activity of the nervous system or are associated with neurological diseases. This objective generates certain subsidiary ... goals ... (1) isolation and identification of components; (2) analysis of their organization ... and (3) a description of the temporal and spatial relations of these components and [of] their interactions to [produce] the activity of the intact organ. A comprehensive description ... should be continuous from the molecular level to the most complex level of integration."

This initial goal continues to inform the creation of each new edition. As we understand more of the fundamental principles and ideas of molecular, cellular and medical neurobiology, *Basic Neurochemistry* will continue to provide a foundation for exploring and understanding the critical ideas.

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For the Editors