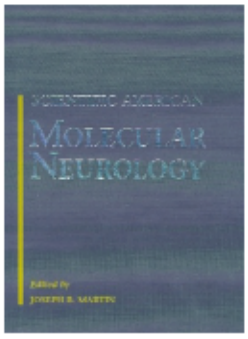
Scientific American Molecular Neurology

Edited by Joseph B. Martin

Scientific American Library, $85.95, 321 pp.
ISBN 0-894-54030-0, 1998

REVIEWED BY SOLOMON H. SNYDER
Johns Hopkins University School of Medicine
Department of Neuroscience
725 North Wolfe Street
Baltimore, Maryland 21205 USA

The most dramatic advances of scientific medicine in the last decade of the century involve molecular biologic inroads into the cause and treatment of important diseases. A new field of 'molecular medicine' has emerged, with associated journals, university departments and graduate programs. To focus on these issues, *Scientific American* has established the series *Introduction to Molecular Medicine*. Previous volumes have dealt with oncology, cardiovascular medicine and an overview of molecular medicine. This volume, *Molecular Neurology*, reviews how molecular neuroscience has impacted neurologic diseases. The editor, Joseph Martin, Dean of Harvard Medical School, is a molecular neuroscientist and clinical neurologist.



The book begins with a chapter on the principles of neurogenetics, co-authored by James Gusella and Martin. It provides to the nonspecialist a lucid yet thorough coverage of the principal strategies employed in finding abnormal genes in diseases. Of the subsequent chapters, half deal with 'genetic' diseases, and the others involve non-genetic conditions for which sophisticated molecular strategies provide insights into new therapy.

The important role of the clinician in genetic diseases is well illustrated by the chapter on Huntington disease authored by Anne Young. Young and Nancy Wexler made many trips to Venezuela, assiduously characterizing families with an extraordinarily high incidence of Huntington disease, work that was indispensable for identification of the abnormal gene. The gene codes for a large protein, called huntingtin. In patients with Huntington disease, huntingtin has extensive repeats of the amino acid glutamine, coded for by the nucleotides CAG. Several other neurodegenerative diseases also have increased numbers of CAG repeats. Identifying huntingtin and the repeats did not clarify the genesis of disease symptoms, the massive degeneration of the caudate nucleus, which controls motor behavior, leading to the characteristic choreiform movements. Huntingtin is not concentrated in the caudate, or even in the brain, but is distributed uniformly throughout the body. Despite massive efforts by many laboratories, no one so far has linked the abnormal gene to the disease process, a disturbing theme that recurs in various genetic diseases.

The chapter on Alzheimer disease by Rudolpho Tanzi, a pioneer in elucidating molecular abnormalities of this disease, emphasizes an important principle, increasingly appreciated in various neurologic disorders. For most patients, Alzheimer disease is not associated with an obvious genetic determinant. In a minority of patients, the genetics have been well worked out and molecular causes have been identified. One group of patients shows abnormalities in the amyloid precursor protein, whose degradation gives rise to the amyloid β-peptide, which accumulates in the plaques and tangles that are diagnostic of the disease. Other patients have mutations in a completely different group of proteins called the presenilins. No one knows exactly how disorders in presenilin give rise to the plaques. At autopsy, the microscopic abnormalities are essentially the same, whether the patient has the 'nongenetic', sporadic form of the disease or one caused by abnormalities in amyloid precursor protein or the presenilins. Thus, the same phenotype arises from disparate causes.

The chapter on stroke by Frank Sharp and colleagues illustrates how molecular techniques can address seemingly recalcitrant physical abnormalities. As a medical student, I was taught that stroke is simple: brain tissue dies immediately after occlusion of a cerebral artery, so treatment is only palliative. We now know that the main neural damage in strokes evolves gradually over a period of a day or more after massive release of the excitatory neurotransmitter glutamate as well as the formation of oxygen free radicals from inefficient mitochondria. Although there have been no revolutionary advances in dealing with the causes of stroke, an army of researchers has made inroads into dealing with the excitotoxicity of glutamate and brain damage caused by free radicals. Glutamate leads to excess production of nitric oxide, which combines with superoxide to form the highly toxic agent peroxynitrite. Peroxynitrite and other free radicals are the main culprits. Drugs that block glutamate receptors or interfere with actions of free radicals have therapeutic effects in animal models, and such drugs are moving towards clinical trial.

Nobel laureate Stanley Prusiner provides a magnificent exposition of how prions give rise to various disorders ranging from scrapie in animals to Creutzfeldt-Jakob disease in humans. Whereas most modern research begins with molecular analysis, which is later applied to diseases, Prusiner, trained as a clinical neurologist, began with a fascination for one of his patients dying of Creutzfeldt-Jakob disease. After years of purifying brain extracts and tediously injecting them into animals to reproduce scrapie symptoms, Prusiner isolated prions, cloned them and then established their role as replicating proteins. Besides the importance of this research for disease, he enunciated a new principle of biology, which has overturned the dictum that only DNA can self-replicate.

Besides these disorders, the book contains chapters dealing with the fragile X syndrome, epilepsy, brain tumors, HIV, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, peripheral neuropathies, ion channel defects and mitochondrial diseases. The chapters are uniformly well presented. The editing is so well done as to be transparent. All of the chapters are well balanced rather than presenting a single, prejudicial perspective. Finally, the book incorporates the *Scientific American* tradition of crystal-clear, user-friendly illustrations. All in all, this treatise is a 'must' for basic researchers and clinicians in the neurosciences.

Viruses and Human Cancer

Edited by J.R. Arrand & D.R. Harper

Bios Scientific Publishers, $35, 200 pp.
ISBN: 1-872-74844-9, 1998

REVIEWED BY HARALD ZUR HAUSEN
Vorsitzender des Stiftungsvorstandes
Deutsches Krebsforschungszentrum,
Im Neuenheimer Feld 280,
69120 Heidelberg, Germany

Viruses and Human Cancer presents a general overview of all viral infections now known