Scientific American Molecular Neurology

Edited by Joseph B. Martin

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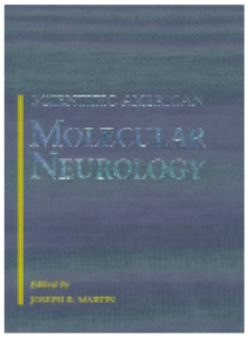
The most dramatic advances of scientific medicine in the last decade of the century involve molecular biologic inroads into the cause and treatment of important diseases. A new field of 'molecular medicine' has emerged, with associated journals, university departments and graduate programs. To focus 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

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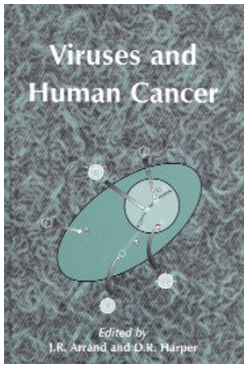
Viruses and Human Cancer presents a general overview of all viral infections now known

to be linked with human cancers. After a preliminary chapter about the general biological characteristics of viruses and cancer growth, the reader is introduced to the association between primary liver cancer and hepatitis B virus, cancer and human papillomaviruses, Epstein-Barr virus, Kaposi's sarcoma and human herpesvirus-8, as well as human onco-retroviruses. A final chapter on antiviral vaccinations and virus-mediated therapies summarizes clinical applications in this field.

In the introduction, Robin Weiss competently outlines some historical aspects, selectively discusses some epidemiological aspects of tumors associated with viral infections and evaluates the role of immunosurveillance in this form of carcinogenesis. Not surprisingly, these few paragraphs are not enough to present in detail all the mechanisms underlying viral carcinogenesis or all the experimental work done by different groups with a variety of tumour viruses. This nonetheless very informative chapter ends with a positive outlook of the general expectations for the prevention and control of viral infections dangerously associated with tumor development.



Tim Harrison summarizes what is now known of the role of hepatitis B and C viruses in the induction of hepatocellular carcinomas. This is a well-written and informative section, which ends with useful hints for further reading, but the following chapter about the association between human papillomaviruses and cancer is far less rewarding. Although the discussion of the interactions of E6 and E7 with p53 and Rb is extensive and satisfactorily covered, there is a significant lack of information about the natural history of papillomavirus infections, which would help to shed light on the mechanisms of progression of human papillomavirus precursor lesions to cancer. Similarly, the reader is left unaware of the large body of experimental data indicating the importance of human papillomavirus in anogenital and other cancers, as well as of the epidemiological and immunological implications.

John Arrands' contribution on Epstein-Barr virus is interesting to read and covers most of the recent developments in Epstein-Barr virus research. My only criticism here is that the as-yet unknown functions of the BamA RNAs (for example, the BARF0 open reading frame), expressed consistently in latency conditions, might deserve more emphasis, given its expression in almost all tumors carrying Epstein-Barr virus. The most recent discovery of genetic changes underlying the X-linked lymphoproliferative syndrome was published too late for inclusion in this book. In this disease, the absence of SAP, a specific inhibitor of B- and T-cell interactions, results in an immunologic inability to control Epstein-Barr virus infections.

The role of human herpesvirus-8 in the etiology of Kaposi's sarcoma is analyzed here by Denise Whitby and colleagues. This chapter represents a good summary of the recent findings and also addresses some clinical aspects of Kaposi's sarcoma. In contrast to some of the other sections, it also contains an excellent compilation of references. Unfortunately, in the overview of human oncoretroviruses by Graham Taylor and Myra McClure, the historical analysis refers mainly to Gallo's contributions to human retrovirology, and I feel that a somewhat less-biased analysis of the critical findings reported in the 1970s would have contributed to a more balanced view of the historical developments in this field. However, the characteristics and consequences of HTLV-1 infections are presented with a clear and in-depth analysis. I wish that this section had served as an example for Chapter 3.

The final part of the book is devoted to antiviral vaccinations and virus-mediated therapies. After a long discussion about vaccines against hepatitis virus, the recent developments in the design of new vaccines to human papilloma virus infections are mentioned only relatively briefly. For example, the most exciting animal model for preventive papillomavirus vaccination, the canine oral papillomavirus, described by Suzich and colleagues, is not mentioned. Because papillomaviruses produce most of the virus-linked cancers known today, the preventive and therapeutic potential of the respective vaccines could significantly influence the global cancer rate. Overall, however, this chapter is very useful, as it describes ongoing efforts for vaccine development against all human oncoviruses now known, and provides, at the same time, a brief overview of the more experimental attempts at virus-mediated cancer therapy.

It would have been interesting to also find in this book chapters on potential human tumor viruses, like BK, JC and SV40-like polyoma viruses (all potent inducers of tumors after inoculation in newborn rodents), and other human tumors suspected to have a viral etiology, such as leukemias and lymphomas. Given that tumor virology had its roots in studies of animal systems, a brief introduction of the *in vivo* experimental models established so far would have been helpful in dissecting the mechanisms underlying host cell transformation by oncoviruses. Despite of the shortcomings mentioned, I find this book a useful and interesting introduction to virus-associated human tumors for undergraduates and postgraduates in biomedical disciplines.

The Molecules Within Us

by Charles A. Pasternak

Plenum, $28.95, 275 pp.

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REVIEWED BY JENNIFER FOSMIRE
Nature Medicine

The preface and forward of *The Molecules Within Us* state its purpose well: to bring molecular medicine to the lay public in lay terms, explaining the science behind how the body works. The author, Charles Pasternak, is an expert on health and the body with a strong background in cancer and infectious disease. He is also the founder and director of the Oxford International Biomedical Centre. Given these credentials, he would seem the ideal author for such a book, and indeed, the book generally succeeds in its aim of providing easily digested scientific information for the public. The text is well illustrated, including 'mug shots' of many of the scientists being discussed, the imaginative use of other artwork, including, for example, festive flamenco dancers to demonstrate atomic bonds, and helpful line drawing diagrams throughout. Useful features of the book are the summaries at the end of each chapter, a very short bibliography and a helpful glossary.

A book of this kind must strike a balance between being too simple, possibly leaving out important information, and too complex, thereby losing the interest of non-scientific readers. Moreover, the amount of ground to be covered risks overwhelming readers. The second chapter illustrates how difficult it is to reach this balance. Whereas