Neurocutaneous Disorders

'The reader is most definitely in for a treat . . . provides the essential clinical and genetic data which points the way to the future.' *From the Foreword by Roger N. Rosenberg.*

The neurocutaneous syndromes comprise a large group of neurological disorders that feature skin lesions and often eye lesions, central and peripheral nervous system tumors, brain malformations, mental retardation, psychiatric symptoms, or seizures. Neurocutaneous syndromes have been known for centuries, but recent research into their cellular, biochemical and molecular–genetic basis has pointed to an essential need for a genotypic nosology. In this book, a distinguished team of editors and authors provides an authoritative, illustrated, up-to-the-minute review of the current understanding of phenotype–genotype relationships in these disorders, as well as their recognition, investigation and treatment. It will be essential reading for all neurologists as well as for dermatologists, geneticists and pediatricians.

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We dedicate this book to the memory of

Carol F. Zimmerman, MD

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Foreword

Neurocutaneous syndromes have been in the medical literature since at least the third century BC. They include a large group of neurological disorders that feature cutaneous and eye lesions, central and peripheral nervous system tumors, brain malformations, mental retardation, psychiatric syndromes and seizures. They are encountered and treated by physicians in the neonatal nursery, and in pediatric, adult and geriatric neurology practices. The neurocutaneous syndromes represent several classic neurological syndromes including neurofibromatosis type 1 (von Recklinghausen disease), tuberous sclerosis (Bourneville disease), angiokeratoma corporis diffusum (Fabry disease), von Hippel–Lindau syndrome, ataxia–telangiectasia, cerebrotendinous xanthomatosis, xeroderma pigmentosum, kinky hair syndrome (Menkes disease), hyperuricemia – self-mutilation – hypoxanthine–guanine phosphoribosyltransferase deficiency (Lesch–Nyhan disease), Ehlers–Danlos syndrome, Sturge–Weber syndrome, and others.

In *The Neurocutaneous Disorders*, editors Steve Roach and Van Miller have taken a fresh approach to these venerable neurological disorders by emphasizing in the selection of authors and topics what needs now to be emphasized – the cellular, biochemical and molecular genetic basis of these syndromes. 'The Genetics of Neurocutaneous Syndromes' by Au and Northrup sets the positive orientation for the book by comprehensively reviewing the clinical and molecular–genetic basis of these syndromes as autosomal dominant, autosomal recessive, X-linked, genetic heterogeneous, and genetic mosaic disorders in clear and precise terms. They point out the essential need for a genotype nosology in these complex disorders. A single phenotype can sometimes be caused by several genotypes, and one genotype can express several phenotypes. To make clinical sense of these complex multisystem disorders, it is increasingly possible to sort out the specific genotype and provide clarity and understanding of the variable clinical features.

Au and Northrup have done an admirable job in providing the reader with the nosological matrix to understand pathogenesis of disease to explain the clinical variability that is encountered in these syndromes.

Dr Roach, who has made seminal contributions to our understanding of the phenotype–genotype relationships in tuberous sclerosis, provides an authoritative review of this subject. Goldstein and Gutmann present a state-of-the-science review of neurofibromatosis type 1. The molecular basis of function of neurofibromin and its consequences, when mutant, are ideally presented as a model for the final molecular explanation of all the neurocutaneous syndromes forthcoming in the future. William Nyhan describes his observations with Lesch–Nyhan syndrome, the biochemical and molecular genetic features of the syndrome and future prospects for therapy. Dr Roach and the late Dr Carol Zimmerman describe the unique features of Ehlers–Danlos syndrome, type 4, causal of intracranial aneurysms, carotid–cavernous fistulae and arterial dissections, in compelling and graphic terms. Familial dysautonomia is reviewed by one of the major founders of the disorder, Felicia Axelrod, and it is refreshing to obtain a several decade-long experience and to appreciate the progress made in recent years. In modern times, the one neuroscientist who has defined most clearly the clinical and molecular features of X-linked adrenoleukodystrophy has been Hugo Moser. He is Mr ALD to many of us and it is a privilege to read his compelling descriptions of this group of disorders to which he has provided molecular answers and insight.

The reader is, most definitely, in for a real treat in *The Neurocutaneous Disorders*. Credit, of course, for this book's obvious success, goes to the editors, who have breached the wall of clinical descriptions that has dominated prior publications on this subject and achieved a clinical and molecular genetic breakthrough by inviting the leaders in the molecular genetics of these disorders to contribute. The hope now is to capitalize on the recent publication of the initial sequence and analysis of the human genome by the groups led by Francis Collins, the International Human Genome Consortium, and Craig Venter, Celera Genomics, to provide the molecular basis for all of these major disorders, and predict the clinical type and severity of disease from each patient's genome. From the emerging discipline of pharmacogenomics, the prospect is to provide designer drug therapy to reduce gene expression of the autosomal dominant disorders which often express up-regulation of the mutant gene product, and also to provide alternative gene or drug therapy for each neurocutaneous disorder.

Great progress is expected in these well-described clinical disorders to develop new molecular therapies based on the information expressed in the human genome. I predict the next edition of *The Neurocutaneous Disorders* will include chapters written by neuroscientists pursuing neurogenomics with therapies based on a patient's genomic profile, which will predict and prevent disease before the disease process is clinically evident. This edition of *The Neurocutaneous Disorders* provides the essential clinical and genetic data which points the way to the future.

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Preface

Diseases with congenital or hereditary lesions of the skin and nervous system are often considered together as neurocutaneous disorders. The last thorough review of these conditions was Gomez' 1987 book *Neurocutaneous Diseases*. Since then, our knowledge of neurocutaneous disorders has increased dramatically. Detailed information about the natural history and clinical features has clarified many long-standing clinical riddles, and new information about the genetics of these conditions has provided insight into their classification, pathophysiology, and molecular biology.

The concept of neurocutaneous disorders unifies a group of rare neurological disorders whose initial identification depends on simple visual diagnosis. While each of the conditions included in this book is unique, the clinical utility of using cutaneous signs to help identify unusual genetic or congenital disorders is well established. Our aim is to provide readily accessible information about the clinical features and natural history of these rare conditions as well as an understanding of their genetic basis and molecular mechanisms.

We thank the colleagues who provided clinical photographs, radiographs, information, and encouragement. We are also indebted to the medical students, residents, and colleagues whose enthusiasm and eagerness to learn about neurocutaneous syndromes spurred us to complete this book.

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