Principles and Practice of Medical Genetics

Volume 1

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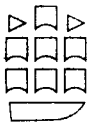

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Foreword

The six years since the first edition of *Principles and Practice of Medical Genetics* has seen the full-flowering of molecular clinical genetics. As discussed in my foreword for the first edition, medical genetics as a clinical speciality has been further strengthened by the new molecular diagnostic armamentarium.

It was in 1983, as the first edition was appearing, that the gene for Huntington disease was found to be linked to a DNA marker on the end of the short arm of chromosome 4. This was followed in relatively rapid succession by the linkage of other genetic disorders to markers at specific chromosome sites. The list now includes adenomatous polyposis of the colon (5q), childhood spinal muscular atrophy (5q), cystic fibrosis (7q), multiple endocrine neoplasia type II (10q), multiple endocrine neoplasia type I (11q), Wilson disease (13q), myotonic dystrophy (19q), polycystic kidney disease (16p), von Recklinghausen neurofibromatosis (17), bilateral acoustic neuroma (22q), Duchenne muscular dystrophy (Xp21), and many others. Each of these discoveries was welcomed with great enthusiasm by both the lay and the professional media and justly so: all of these conditions shared – at least at the time the linkage was determined – the characteristic that the nature of the fundamental defect was completely unknown, therefore no diagnostic test based thereon could be devised and rational management was hampered. Knowing the 'map location' of these disease genes meant that one could hope to test for the presence of the mutant gene by the linkage principle, i.e., by the company it keeps. It also meant that the basic gene defect might be elucidated by the approach of 'reverse genetics' – moving in on the segment of DNA altered in the mutation, determining how it differs from the normal, and most importantly, the nature and function of the normal gene that is changed. Definition of the precise genetic lesion makes it possible to do direct DNA diagnosis, by a process that might be called 'diagnostic biopsy of the genome'. Also, the improved understanding of pathogenesis is likely to enhance management by methods directed at the steps between gene and phene, i.e., without resort to gene therapy.

Remarkable indeed is the extent to which, since 1983, molecular methods have come into routine use in prenatal diagnosis, preclinical (premorbid or presymptomatic) diagnosis, and carrier detection of many of the above mentioned disorders as well as others. Cystic fibrosis and Duchenne muscular dystrophy are cardinal examples of diagnostic usefulness of molecular information, and in the case of DMD reverse genetics has been played out in full with identification of a muscle protein dubbed dystrophin as the site of the abnormality. The second edition of *Principles and Practice of Medical Genetics* is marked particularly by advances in this area of clinical molecular genetics.

A second area of remarkable advance since 1983 is that of somatic cell genetic disease. Traditionally, we employ the rather arbitrary but nonetheless useful three-way classification of diseases as to the role of genetic factors: monogenic (Mendelian) disorders, multifactorial disorders, and chromosomal disorders. Another large category of genetic disease is that caused by mutations in somatic cells. Cancers are prime examples. The chromosome theory of cancer, as advanced by Boveri in 1914 and others, has been massively corroborated in the last six years by the demonstration of many specific chromosomal aberrations in association with specific neoplasms, by the discovery of oncogenes, and by the correlation of the two approaches. Even cancers as intimately related to an environmental factor as small cell cancer of the lung is to cigarettes can be shown to have specific genetic changes that are responsible ultimately for the malignant change.

Obviously the new information on somatic cell mutation is valuable not only for understanding the malignant process but also for specific tumour diagnosis. Increasingly, we will depend on demonstration of specific DNA changes in the tumour rather than the relatively crude morphologic characteristics. Prognostication and management will be enhanced thereby. The

role of somatic cell mutations in congenital malformations and autoimmune disease is also under exploration.

All these developments augur well for the future of medical genetics, and are discussed in detail in this new edition by contributors who are themselves internationally recognised authorities in their respective fields. This new edition will therefore be welcomed by all concerned in this rapidly advancing and exciting subject.

Baltimore, Maryland, 1990 Victor A. McKusick

Preface to the second edition

Since the first edition of this book appeared in 1983 considerable changes have taken place in many aspects of medical genetics. These have been very largely due to the application of recombinant DNA techniques. This technology has helped our understanding of the fine structure of genes and is also beginning to unravel the molecular pathology of many inherited disorders. But perhaps of more immediate and practical importance, the technology has introduced novel and precise methods for detecting female carriers of X-linked disorders, pre-symptomatic cases of dominant disorders of late onset and in the prenatal diagnosis of genetic disease. These changes are reflected in most of the contributions to this new edition and their relevance will be apparent in almost all aspects of the subject.

As in the first edition we have enlisted the cooperation of internationally recognised experts to review developments in their respective fields. With no less than 116 chapters with 154 contributors there have been inevitable concerns about delays. But all have responded to our harassment and we believe that this new edition presents an up-to-date picture of the more important aspects of this rapidly growing subject.

Besides thanking our contributors we feel we must also acknowledge the invaluable help we have received from Mrs Isobel Black and the editorial team of Churchill Livingstone in Edinburgh, and Sheilah Levin and Susan Lane in Los Angeles. Finally we must also thank Dr Victor McKusick, in many ways the father of present-day medical genetics, for writing a Foreword to this new edition which we fervently hope will provide an important reference work for all those involved in this exciting field.

Edinburgh and Los Angeles, 1990 A.E.H.E.
D.L.R.

Preface to the first edition

Medical genetics has come of age as a unique speciality in medicine. All practitioners of medicine regardless of their individual speciality, encounter numerous patients with genetic disorders or conditions strongly influenced by hereditary factors and must be aware of their aetiology, pathogenesis, natural history and prognosis, as well as current approaches to their treatment and prevention. Unlike most other medical specialities, which are limited to a body system, age range or diagnostic modality, medical genetics has no such limits, involves all bodily systems and utilizes all manner of diagnostic and therapeutic modalities. In addition, the recent spectacular advances in cellular, biochemical and molecular genetics have been quickly translated into clinical applicability, and thus there are unique diagnostic tools available in modern genetics to which most practitioners of medicine have never been exposed.

There is a vast array of information available relating to genetic disease, which is found not only in genetics or general medical journals but appears throughout the many speciality and subspeciality medical journals and basic science journals as well. Although there are excellent textbooks and reference books dealing with the basic principles of medical genetics, or specific areas of medical genetics and broad catalogues of syndromes, inherited diseases and chromosomal diseases, there is no up-to-date reference source which attempts to cover all areas of medical genetics, from basic principles, to specific diseases, to therapy and prevention. Since most medical geneticists will encounter patients with a wide variety of genetic diseases and since most medical speciality textbooks do not pay a great deal of attention to the principles of genetics or genetic diseases, it was felt that a broad reference book in medical genetics, ranging from basic principles to applied genetics would be useful. The editors have undertaken the difficult task of trying to compile all of this information under one cover.

This task might have been easier 20 years ago when both of the editors were fellows and doctoral students at the Moore Clinic at Johns Hopkins Hospital with Dr Victor McKusick. At that time medical genetics was a relatively new speciality and the number of authors who could have contributed to this text was quite limited. The explosion of knowledge in genetics has been so great over the last two decades that complete coverage of all aspects of medical genetics is clearly impossible. Rather than ask relatively few individuals to contribute sections covering broad areas, such as the genetics of ophthalmology or the genetics of the endocrine glands, we have elected to conscript over 100 authors, each of whom has been asked to contribute to a relatively well defined area related to their own field of expertise. Thus each of the chapters is written by an individual who has had personal experience in the area in which he has been asked to write. The danger of this type of compilation is that there will be areas of medical genetics that have been excluded because they fell between the lines of the individual experts. We hope that our readers will bring these areas of omission to our attention so that they can be corrected in the next edition. We feel that we have included an outstanding group of international experts who have attempted to bring their current area of expertise to this readership in a relatively brief but complete form, with much of the information in useful tabular form and a fairly complete bibliography. We wish to thank these many individuals for their excellent contributions and apologize for the harassment they may have received from us.

In addition we would like to thank the individuals who contributed in a clerical and editorial fashion to this book including Margaret Fairbairn, Rita Anand, Dorothy Rivera, Toni Armstrong and Elena Hanson. We should also like to thank the publishers themselves especially Andrew Stevenson and Claire McLeod for their encouragement and much helpful advice. Finally, we should especially like to offer our gratitude to Dr Victor McKusick, who kindly agreed to write the foreword to this book. Dr McKusick's teaching, inspiration and encouragement were the prime factors in the development of both of our careers in medical genetics and thus we are doubly grateful to him.

Edinburgh and Los Angeles, 1983

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