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**EMERY AND RIMOIN'S  
PRINCIPLES AND PRACTICE OF  
MEDICAL GENETICS AND GENOMICS  
SEVENTH EDITION**

**Clinical Principles and Applications**

Edited by

Reed E. Pyentz, Bruce R. Korf,  
Wayne W. Grody



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# Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics

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## Clinical Principles and Applications

SEVENTH EDITION

### Editors

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# Preface to the Seventh Edition of *Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics*

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The first edition of *Emery and Rimoin's Principles and Practice of Medical Genetics* appeared in 1983. This was several years prior to the start of the Human Genome Project in the early days of molecular genetic testing, a time when linkage analysis was often performed for diagnostic purposes. Medical genetics was not yet a recognized medical specialty in the United States, or anywhere else in the world. Therapy was mostly limited to a number of biochemical genetic conditions, and the underlying pathophysiology of most genetic disorders was unknown. The first edition was nevertheless published in two volumes, reflecting the fact that genetics was relevant to all areas of medical practice.

Thirty-five years later we are publishing the seventh edition of *Principles and Practice of Medical Genetics and Genomics*. Adding "genomics" to the title recognizes the pivotal role of genomic approaches in medicine, with the human genome sequence now in hand and exome/genome-level diagnostic sequencing becoming increasingly commonplace. Thousands of genetic disorders have been matched with the underlying genes, often illuminating pathophysiological mechanisms and in some cases enabling targeted therapies. Genetic testing is becoming increasingly incorporated into specialty medical care, though applications of adequate family

history, genetic risk assessment, and pharmacogenetic testing are only gradually being integrated into routine medical practice. Sadly, this is the first edition of the book to be produced without the guidance of one of the founding coeditors, Dr David Rimoin, who passed away just as the previous edition went to press.

The seventh edition incorporates two major changes from previous editions. The first is publication of the text in 11 separate volumes. Over the years the book had grown from two to three massive volumes, until the electronic version was introduced in the previous edition. The decision to split the book into multiple smaller volumes represents an attempt to divide the content into smaller, more accessible units. Most of these are organized around a unifying theme, for the most part based on specific body systems. This may make the book more useful to specialists who are interested in the application of medical genetics to their area but do not wish to invest in a larger volume that covers all areas of medicine. It also reflects our recognition that genetic concepts and determinants now underpin all medical specialties and subspecialties. The second change might seem on the surface to be a regressive one in today's high-tech world—the publication of the 11 volumes in print rather than strictly electronic form. However, feedback from our readers, as well as the experience of the editors, indicated that access to the web version via a password-protected site was cumbersome, and printing a smaller volume with two-page summaries was not useful. We have therefore returned to a full print version, although an eBook is available for those who prefer an electronic version.

One might ask whether there is a need for a comprehensive text in an era of instantaneous internet searches for virtually any information, including authoritative open sources such as *Online Mendelian Inheritance in Man* and *GeneReviews*. We recognize the value of these and other online resources, but believe that there is still a place for the long-form prose approach of a textbook. Here the authors have the opportunity to tell the story of their area of medical genetics and genomics, including in-depth background about pathophysiology, as well as giving practical advice for medical practice. The willingness of

our authors to embrace this approach indicates that there is still enthusiasm for a textbook on medical genetics; we will appreciate feedback from our readers as well.

The realities of editing an 11-volume set have become obvious to the three of us as editors. We are grateful to our authors, many of whom have contributed to multiple past volumes, including some who have updated their contributions from the first or second editions. We are also indebted to staff from Elsevier, particularly Peter Linsley and Pat Gonzalez, who have worked patiently with us in the conception and production of this large project. Finally, we thank our families, who have indulged our occasional disappearances into writing and editing. As always, we look forward to feedback from our readers, as this has played a critical role in shaping the evolution of *Principles and Practice of Medical Genetics and Genomics* in the face of the exponential changes that have occurred in the landscape of our discipline.

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# Preface to *Clinical Principles and Applications*

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This volume of *Principles and Practice of Medical Genetics and Genomics* presents topics focused on fundamental principles that underlie clinical applications of genetics and genomics. Some of the authors (Robert J. Desnick, John M. Graham, Kenneth Lyons Jones, and Marilyn Jones) have composed and updated their chapters since the first or second editions of this treatise. Due to the recognition of the evolution of genomic, not just genetic, application, a number of new chapters have been added since the sixth edition. The knowledge and perspectives gained from the chapters in this volume provide the foundation for interpreting and applying the information contained in all subsequent volumes.

*Reed E. Pyeritz, MD, PhD*

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# A Clinical Approach to the Dysmorphic Child

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## Abstract

This chapter outlines a clinical approach to the child with structural defects, defines many terms used in dysmorphology, and presents a parsimonious approach to genetic testing.

## Keywords

Malformation; Deformation; Disruption; Dysplasia Single primary defect; Sequence; Multiple malformation syndrome; Etiology; Pathogenesis; Prognosis; Recurrence risk; Chromosome; Comparative genomic hybridization; Whole exome sequencing

## 1.1. Introduction

The purpose of this chapter is to present a clinical approach to the child with structural defects. The approach is predicated on the concept that the nature of the structural defects presents clues to the time of onset, mechanism of injury, and probable etiology of the problem, all of which determine the direction of the evaluation. It presumes that the dysmorphic child represents an experiment in human development, which, if interpreted correctly, can provide

answers regarding the etiology of various structural defects, as well as permit insights into mechanisms of normal and abnormal morphogenesis. The method on which this approach is based has been most articulately set forth by Sir Arthur Conan Doyle's fictional character Sherlock Holmes, who showed "how much an observant man might learn by accurate and systematic examination of all that came within his way" [1]. This chapter adapts this method to the evaluation of the child with structural defects. By sharpening the faculties of observation, the clinician can narrow systematically the diagnostic possibilities so that the laboratory and the literature can be consulted in a rational fashion to arrive at an accurate diagnosis. The precise cause of many malformations and malformation syndromes is not known. However, careful clinical evaluation in combination with an expanded range of cytogenetic, cytogenomic, and molecular testing has allowed the elucidation of the mechanism underlying a growing list of clinical disorders. The separation between genetic and environmental factors as well as cytogenetic (copy number) and single gene abnormalities is somewhat arbitrary. However, the approach is intended to be practical and to facilitate detection and prevention of human malformations. *Gorlin's Syndromes of the Head and Neck* [2] and *Smith's Recognizable Patterns of Human Malformation* [3] are particularly useful. In recent years, computerized databases available online and on CD-ROM have become useful adjuncts to diagnosis (London Dysmorphology Database [Face2Gene]; Possum Web [4]; Online Mendelian Inheritance in Man [5]; and Decipher [6]).

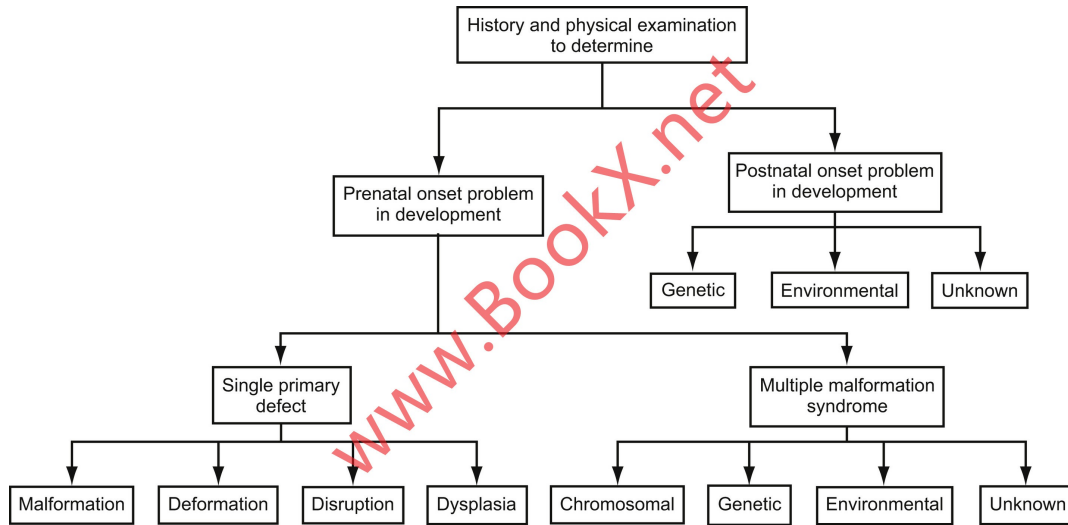
## **1.2. Prenatal Versus Postnatal Onset of Developmental Problems**

A method of approach to children with structural defects is set forth diagrammatically in [Fig. 1.1](#). Although the lists of exceptions is growing, a history and physical examination usually make it possible to determine if the structural abnormality is of prenatal or postnatal onset. In this chapter, "prenatal onset" designates structural abnormalities that are present at birth, and "postnatal onset"

designates structures that have previously developed and differentiated normally. Whereas the genetic alteration responsible for many of the disorders included under postnatal-onset structural defects is present at the time of conception, the structural manifestations of that genetic alteration do not become obvious until postnatal life. On the basis of this distinction, a more rational approach to the problem can be developed, as this determination narrows considerably the diagnostic probabilities and, it is hoped, permits a more judicious selection of adjunctive laboratory tests.

Generally speaking, prenatal-onset problems in development are a consequence of genetic or chromosomal (copy number) alterations that cause programming problems in the development and/or differentiation of structure or are the result of factors unique to the pregnancy itself, such as environmental agents, abnormalities of placentation, or mechanical constraint. Although always evident at birth, most prenatal-onset problems remain static or improve postnatally without evidence of neurologic deterioration. By contrast, postnatal-onset problems in development usually result in deterioration in structure or function that has previously been normal. Deterioration may reflect postnatal accumulation of a toxic metabolic product (as in phenylketonuria), progressive storage of a metabolite (as in Hurler syndrome), deteriorating energy production (as in mitochondrial myopathies), or ongoing infection (as in deafness from cytomegalovirus). Children with postnatal problems usually appear to have thrived in utero. The structural and functional consequences of the problem manifest after the newborn period.





**FIGURE 1.1** Approach to a child with structural defects.

Certain historical information can be particularly helpful in determining onset of the problem. Structural defects of prenatal onset are frequently associated with the following abnormalities noted by the mother during pregnancy and at the time of delivery, whereas, by contrast, with postnatal-onset structural defects, the pregnancy and delivery usually are normal.

Alterations of pregnancy associated with prenatal onset of developmental problems are as follows:

1. Alterations in gestational timing (prematurity or postmaturity).  
As discussed in several other chapters, the majority of

conceptuses do not survive to be born at 40 weeks' gestation.

Much of this loss occurs in the very early part of pregnancy and is the result of gross chromosomal abnormalities and/or malformation. Numerous studies have documented an

increased frequency of chromosomal and genetic abnormalities in losses from the second and third trimesters.

Thus, premature delivery may reflect late fetal wastage rather than maternal disease. Postmaturity rarely occurs today

because of improved fetal monitoring techniques. In years

before the widespread use of ultrasound, anencephaly

typically presented in pregnancies that continued well beyond