CHROMOSOME DIAGNOSTICS IN CLINICAL MEDICINE

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By

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To Doris, Jim and Cathy,
whose patience and forbearence
made it possible, this work
is dedicated

FOREWORD

OUR Living Chemistry Series was conceived by Editor and Publisher to advance the newer knowledge of chemical medicine in the cause of clinical practice. The interdependence of chemistry and medicine is so great that physicians are turning to chemistry, and chemists to medicine in order to understand the underlying basis of life processes in health and disease. Once chemical truths, proofs and convictions become sound foundations for clinical phenomena, key hybrid investigators clarify the bewildering panorama of biochemical progress for application in everyday practice, stimulation of experimental research, and extension of postgraduate instruction. Each of our monographs thus unravels the chemical mechanisms and clinical management of many diseases that have remained relatively static in the minds of medical men for three thousand years. Our new Series is charged with the *nisus élan* of chemical wisdom, supreme in choice of international authors, optimal in standards of chemical scholarship, provocative in imagination for experimental research, comprehensive in discussions of scientific medicine, and authoritative in chemical perspective of human disorders.

Dr. Eggen of San Diego presents the principles and practice of clinical cytogenetics in simplified form for bedside application by pediatrician and physician. It encompasses the entire field from the normal mechanism of cell division through basic genetics to the clinical sequelae of chromosome abnormalities in man. Human chromosomes are amenable to direct studies for establishing the diagnosis of congenital malformations and sexual abnormalities. Fetal-cell chromosome studies bring to light malformed infants in the making while newborn-cell studies identify affected families to prevent congenital abnormalities in the future. Autosomal chromosome abnormalities may involve deviations in number or in

morphological appearance of the chromosomes or both. Nuclear sex is determined by examination of buccal smears, white blood cells or skin biopsy material. Sex chromatin at variance with the sex of the phenotype indicates an underlying sex chromosome abnormality but a concordant sex-chromatin result does not necessarily connote a normal sex chromosome constitution. Chromosomal aberrations viewed by current techniques represent gross genetic damage to the cell, for the smallest detectable deletion involves large numbers of genes while molecular cytogenics unravels submicroscopic molecular arrangements reflecting altered genic material in human mutations. All this and more is embodied in this practical manual on clinical chromosome analysis, complete with methods, indications, interpretations and limitations.

Maupertuis (1730) first advanced the theory of heredity based on the direct transmission of chemical particles from each parent. Brown (1831) of Brownian movement distinction, discovered the cell nucleus—the site of the chromosomes. In the nucleus the apparatus of cell government is at rest; in the chromosomes it is in movement. Hereditary characters are carried to the nucleus rather than the cytoplasm, and more specifically in the chromosomes of the nuclei. DNA in the cell is confined to the nucleus while most of RNA, a misnomer, by contrast in the cytoplasm. Chromosomes are among the largest molecules whose chemistry is pursued, the smallest living structures whose transformations are followed. Their maneuvers in mitation and fertilization were first observed about a century ago following the development of analine dyes and high power magnification. Weisman (1883) evolved the germ plasm theory in which chromosomes formed the basis of heredity and development. Roux (1883) considered them specific hereditary determiners in the cell nucleus presaging molecular genetics. Yet, Mendel (1866) had already demonstrated the principle of heredity in an eight-year experiment with sweet peas to prove the correctness of his graduate contention and thus vindicate his licentiate failure in agriculture science. But the data was not discovered until the turn of the century by de Vries and others in the obscure Brünn journal of the Abbey, rejected for publication in the national journal by the leading biologist who flunked him. Affirmante, non neganti, incumbit probatio. With

his transcendent capacity of taking trouble he proved his point and deduced Nature's laws in wretched seclusion.

Mendelian genetics is indispensable for interpretation of pedigrees of disease. But human genetics extends beyond mendelian bounds that inherited characteristics are transmitted from generation to generation in ratios of simple whole numbers. Biochemical genetics has progressed so far that it is now possible in some cases to pin-point the precise function of a gene. For example, the only detectable difference between normal and sickle hemoglobin is that in the latter valene has been substituted for glutamic acid in the peptide, a simple change that marks the difference between health and disease. It has its origin in either the abnormal DNA derived from the parent, which directs the formation of an abnormal RNA that serves as a template for the biosynthesis of abnormal protein, or from an error in the copying of the normal parental DNA which leads to the same sequence of abnormal reactions. The biochemical basis of genetically transmitted diseases is viewed in terms of the components that transmit genetic information and the phenotypes that determine molecular aberration. The author enables chromosome visualization by simple separation in hypotonic media to swell cell nuclei, by flattening the cell nuclei under slide pressure, by blocking cell division in mitosis with cytostatic agents to define the individual karyotype and by other ingenious methods. Cytogenic techniques applied to clinical problems create genetic syndromes by delineating individuals in particular positions of the homo sapiens spectrum in health and disease as the analytical answer to the uniqueness, unpredictability and unrepeatability of human beings. Clinical medicine is thus becoming a form of experimental and applied biology in the everyday service of our strange species.

"But beyond the bright searchlights of science,
Out of sight of the windows of sense,
Old riddles still bid us defiance,
Old questions of why and whence."

I. NEWTON KUGELMASS, M.D., PH.D., SC.D., *Editor*

PREFACE

IT IS a regrettable fact that human chromosome analysis is still generally regarded as an interesting laboratory curiosity rather than as a practical diagnostic medium. However regrettable this fact may be, it is not entirely astonishing.

The very rapidity with which these techniques have evolved militates to some degree against ready recognition of their value by clinicians. In less than a decade, human cytogenetics has become a discipline of most appreciable breadth.

To an even greater degree, a comparative inaccessibility of information must be held responsible for this lack of recognition. In the United States particularly, pertinent articles in this field are extremely infrequent in the most widely read medical journals where they appear only as sporadic case reports. A scan of the publications listed in the bibliography will reveal few of everyday familiarity. Even the few comprehensive review articles published have appeared in specialty journals.

There is, of course, a natural tendency on the part of specialists in any field to communicate with their fellows. Much of the pioneer investigation in cytogenetics has been performed by geneticists and cytologists, an appreciable number of whom are not clinicians (and not a few of whom are not in the medical sciences at all). Thus we have articles written by cytogeneticists about cytogenetics for the edification of other cytogeneticists *via* appropriate journals. This has proven a moderately successful method of keeping the field from the attention of the majority of practicing physicians.

My own experience has emphasized to me the difficulty in gleaning a comprehensive view of this subject by perusing the literature. The task is one of considerable magnitude if one is equipped with no sounder basic knowledge than a half-forgotten

course in elementary college genetics. For, as will soon become apparent to others who make such an attempt, geneticists writing for other geneticists made the tacit assumption that the reader already knows a good deal about genetics. This assumption is not always warranted.

It is now essential, in my opinion, that a concise source of reference material be available to physicians in all of the medical specialties. The techniques of cytogenetics are increasing in sophistication at an almost geometric pace. It is not unrealistic to predict that twenty years hence that man's chromosome pattern will be known with an exactitude now the exclusive province of the megachromosomal insects.

The purposes of this monograph are thus twofold:

1) To identify the clinical situations in which cytogenetic techniques are of proven diagnostic value and to show how best to apply them to maximum advantage.

2) to provide clinicians with a sufficiently detailed fund of basic genetic and cytologic knowledge that they may approach the literature in this field with enhanced assurance and comprehension.

In short, this is a monograph by a clinician for clinicians. I sincerely hope that it will fulfill its stated objectives.

ROBERT R. EGGEN, M.D.

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R. R. E.

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