Genetics in Medicine

THOMPSON & THOMPSON

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Third Edition

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W. B. SAUNDERS COMPANY
Philadelphia London Toronto

W. B. Saunders Company: West Washington Square
Philadelphia, PA 19105

1 St. Anne's Road
Eastbourne, East Sussex NB21 3UN, England

1 Goldthorne Avenue
Toronto, Ontario M8Z 5T9, Canada

Library of Congress Cataloging in Publication Data

Thompson, James S

Genetics in medicine.

Bibliography: p. 361.

Includes index.

1. Medical genetics. I. Thompson, Margaret W., joint author. II. Title. [DNLM: 1. Genetics, Human. QH431 T473g]

RB155.T5 1979 616'.042 78-64726

ISBN 0-7216-8857-8

Listed here are the latest translated editions of this book together with the language of the translation and the publisher.

Italian (*2nd Edition*)—UTET (Unione Tipografica Editrice Torinese) Turin, Italy

Spanish (*2nd Edition*)—Salvat Editores, S. A., Barcelona, Spain

Portuguese (*2nd Edition*)—Livraria Atheneu, Rio de Janeiro, Brazil

French (*2nd Edition*)—Doin Editeurs, Paris, France

Genetics in Medicine ISBN 0-7216-8857-8

Last digit is the print number: 9 8 7 6 5 4 3

PREFACE

When the first edition of this book appeared in 1966, the place of genetics in medicine was not at all assured. In the intervening years, virtually all medical schools, at least in North America, have included genetics in the undergraduate medical curriculum and steps are underway in both the United States and Canada to establish genetics as a clinical specialty.

These changes indicate widespread recognition by the medical profession and by other health scientists of the crucial role of genetics in the scientific basis of medicine and its increasing significance in clinical practice. Advances in such fields as human cytogenetics, and the mapping of the human genome and the manipulation of human cells in tissue culture are yielding much information that can be promptly applied to patient management. Simultaneously there has been much progress in the delineation of genetic syndromes and in prenatal diagnosis of genetic disorders, and clinical geneticists are achieving increasing recognition of their particular skills. This book has been written primarily to introduce medical students to the principles and language of human genetics and to indicate some of its fruitful clinical applications.

A major problem in teaching genetics to medical students is that in any one class there is a wide range in background knowledge of the scientific basis of the field, though there is rarely much information about its medical application. We have assumed that the student using this book will have little or no knowledge of genetics and its vocabulary, though we realize that some students will not require such an elementary approach. However, we believe that the latter will find much to assist them in understanding the genetic basis of disease.

Many advances in both the basic science and clinical applications of genetics are beyond the scope of an introductory text such as this, but we have attempted to provide a background that will make the literature in medical genetics accessible to readers who require more specialized information. Because the field is in such a rapid phase of growth, we have had to be highly selective in choosing material to elucidate principles without swamping the reader in minutiae or expanding the text far beyond the limits of the time available for its use. We regret that this has forced us to omit discussion of many notable contributions to genetics.

We have had help from numerous sources in the preparation of this edition. We are grateful to the many colleagues in Toronto and elsewhere who have assisted us with information and illustrations, and to students who have helped us to recognize which parts of the previous editions were erroneous or unclear. In particular we wish to thank medical artist Margo Siminovitch

for many of the new illustrations used in this edition; Dr. Ron Worton and his assistant Chin Chin Ho, who prepared a number of cytogenetic illustrations especially for our use; and other members of the staff of The Hospital for Sick Children, especially Eva Struthers of the Department of Visual Education, medical librarian Irene Jeryn, and secretaries Pauline Kowal and Baba Torres. We have relied heavily on their helpfulness, knowledge and special skills. The preparation of this edition began while one of us (MWT) was on sabbatical leave at the Galton Laboratory, University College, London, and our debt to the Galton staff for intellectual stimulation and practical assistance is gratefully acknowledged. Finally, we wish to thank the W. B. Saunders Company and editor Roberta Kangilaski for their continuing support.

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INTRODUCTION

The place of genetics in medicine was not always as obvious as it is today. Though the significance of genetics both for the conceptual basis of medicine and for clinical practice is now generally appreciated, not many years ago the subject was thought to be concerned only with the inheritance of trivial, superficial and rare characteristics, and the fundamental role of the gene in basic life processes was not understood.

The discovery of the principles of heredity by the Austrian monk Gregor Mendel in 1865 received no recognition at all from medical scientists and virtually none from other biologists. Instead, his work lay unnoticed in the scientific literature for 35 years. Charles Darwin, whose great work *The Origin of Species* (published in 1859) emphasized the hereditary nature of variability among members of a species as an important factor in evolution, had no idea how inheritance worked. At that time inheritance was regarded as blending of the traits of the two parents, and Lamarck's idea of the inheritance of acquired characteristics was still accepted. Mendel's work could have clarified Darwin's concept of the mechanism of inheritance of variability, but Darwin seems never to have been aware of its significance or even of its existence. Darwin's cousin, Francis Galton, one of the great figures of early medical genetics, also remained ignorant of Mendel's work despite its relevance to his own studies of "nature and nurture." Mendel himself, perhaps discouraged by the results of later, less favorably designed experiments, eventually took the course followed by many successful scientists — he abandoned research and became an administrator.

Mendel's laws, which form the cornerstone of the science of genetics, were derived from his experiments with garden peas, in which he crossed pure lines differing in one or more clear-cut characteristics and followed the progeny of the crosses for at least two generations. The three laws he derived from the results of his experiments may be stated as follows:

1. **Unit inheritance.** Prior to Mendel's time, the characteristics of the parents were believed to blend in the offspring. Mendel clearly stated that blending did not occur, and the characteristics of the parents, though they might not be expressed in the first-generation offspring, could reappear quite unchanged in a later generation. Modern teaching in genetics places little stress upon this law, but in Mendel's time it was an entirely new concept.

2. **Segregation.** The two members of a *single* pair of genes are never found in the same gamete but instead always segregate and pass to different

gametes. In exceptional circumstances, when the members of a chromosome pair fail to segregate normally, this rule is broken, but the typical consequence of such a failure is severe abnormality.

3. **Independent assortment.** Members of *different* gene pairs assort to the gametes independently of one another. In other words, there is random recombination of the paternal and maternal chromosomes in the gametes.

With the dawn of the new century, the rest of the scientific community was ready to catch up with Mendel. By a curious coincidence, three workers (de Vries in Holland, Correns in Germany and Tschermak in Austria) independently and simultaneously rediscovered Mendel's laws. The development of genetics as a science dates not from Mendel's own paper but from the papers that reported the rediscovery of his laws.

The universal nature of Mendelian inheritance was soon recognized, and as early as 1902 Garrod, who ranks with Galton as a founder of medical genetics, could report in alcaptonuria the first example of mendelian inheritance in man. In his paper Garrod generously admitted his debt to the biologist Bateson, who had seen the genetic significance of consanguineous marriage in the parents of recessively affected persons. This is the first clear evidence of the interaction in research between medical and nonmedical geneticists, which has continued to the present day.

A growing understanding of the universal nature of the biochemical structure and functioning of living organisms has brought about an awareness of the crucial role of genes in living organisms. The work of Garrod foreshadowed this knowledge, though in the early years of genetics its fundamental significance was not apparent. The concept was formulated clearly by Beadle and Tatum in 1941 as the "one gene–one enzyme" hypothesis.

The growth in genetic knowledge and in its applications during recent years has had fruitful consequences for clinical medicine. It is estimated that today one-third of the children in pediatric hospitals are there because of genetic disorders. This is a great change from the early years of this century, and even from the preantibiotic era. Before the days of immunization, improved nutrition and antibiotics, many children were in the hospital because of infectious diseases or nutritional disorders such as rickets. Today some of those with infections have genetic defects that impair their resistance, and at least in developed countries, most cases of rickets arise not from faulty nutrition but from deleterious genes. Life-saving advances in clinical techniques (transfusion, tube feeding, maintenance of body fluids by intravenous drip) for the management of medical emergencies also play a part in increasing the prevalence of genetic defects. Improvements in surgical procedures have also contributed to the profound alteration that has been effected during the twentieth century.

Though medical genetics grew up in close association with pediatrics, it is also relevant to many other branches of medicine. One of the most recent applications of medical genetics has been in obstetrics, in which prenatal diagnosis of certain genetic defects has become an important aspect of adequate prenatal care. In adult medicine, it is increasingly obvious that many common conditions, such as coronary heart disease, hypertension, and diabetes mellitus, have important genetic components and that preventive medicine could be much more efficient if it could be directed toward special high-risk groups rather than toward the general population.

CLASSIFICATION OF GENETIC DISORDERS

In medical practice, the chief significance of genetics is its role in the etiology of a large number of disorders. Virtually any trait is the result of the combined action of genetic and environmental factors, but it is convenient to distinguish between those disorders in which defects in the **genetic information** are of prime importance, those in which **environmental hazards** (including hazards of the intrauterine environment) are chiefly to blame and those in which a **combination** of genetic constitution and environment is responsible.

Broadly speaking, genetic disorders are of three main types:

1. Single-gene disorders
2. Chromosome disorders
3. Multifactorial disorders

The initial step in analysis of the genetics of a given disorder is to determine to which of these three categories it belongs.

Single-gene defects are caused by mutant genes. The mutation may be present on only one chromosome of a pair (matched with a normal gene on the partner chromosome) or on both chromosomes of a pair. In either case, the cause of the defect is a single major error in the genetic information. Single-gene disorders usually exhibit obvious and characteristic pedigree patterns. Most such disorders are rare, the upper limit of frequency being about 1 in 2000.

In **chromosome disorders,** the defect is not due to a single mistake in the genetic blueprint but to developmental confusion arising from an excess or deficiency of whole chromosomes or chromosome segments, which upsets the normal balance of the genome. For example, the presence of a specific extra chromosome, chromosome 21, produces a characteristic disorder, Down syndrome, even though all the genes on the extra chromosome may be quite normal. Usually chromosome disorders do not run in families, though there are exceptions. On the whole these disorders are very common, affecting about seven individuals per thousand births and accounting for about half of all spontaneous first-trimester abortions.

Multifactorial inheritance is seen in a number of common disorders, especially developmental disorders resulting in congenital malformations. Here again there is no one major error in the genetic information but rather a combination of small variations that together can produce a serious defect. Multifactorial disorders tend to cluster in families but do not show the clear-cut pedigree patterns of single-gene traits.

Each of these three types of inheritance is discussed in some detail later in this book.

Not all disorders that affect more than one member of a family are genetic. On the contrary, occasionally a clearly definable environmental cause (for example, an infection or teratogen) may affect more than one member of a family at a time. Since it is not always obvious whether a particular problem is genetically determined, Neel and Schull (1954) have provided a useful list of indications of a genetic etiology:

1. The occurrence of the disease *in definite proportions* among persons related by descent, when environmental causes can be ruled out.

2. The failure of the disease to appear in unrelated lines (e.g., in spouses or in-laws).

3. A characteristic onset age and course, in the absence of known precipitating factors.

4. Greater concordance in monozygotic than in dizygotic twins.

The foregoing list was prepared some years before the role of chromosomal disorders was known. Now it is possible to add the following criterion:

5. The presence in the propositus of a characteristic phenotype (usually including mental retardation) and a demonstrable chromosomal abnormality, with or without a family history of the same or related disorders.

THE FAMILY HISTORY

Taking an adequate family history is an essential part of the assessment of a patient with a genetic disorder; it is also helpful in eliminating the possibility that a condition has a genetic basis (Fraser, 1963). Because few of us know our pedigress in any detail, family history details are often difficult and time-consuming to obtain and verify.

A genetic history should always deal with data *pertinent to the patient's condition.* (Many hospital histories record the family history only with respect to a few defects such as diabetes, asthma and "mental retardation," regardless of their relevance to the patient's problem.) Negative information, i.e., the absence of a disorder in any relative, may be as important as a positive finding. To record "family history negative" after one or two brief questions to the patient or his nearest available relative may give a completely erroneous impression. It is necessary to ask specifically about age, sex and health (present and past) of parents, sibs and other near relatives and to ask about each person separately. Miscarriages and stillbirths should be listed. If any relative of the patient has or has had a similar condition, every effort should be made to confirm the diagnosis. The age at death of deceased relatives and the causes of their deaths (if known) should be recorded. If the cause was established by autopsy, this fact should also be noted. Usually the pedigree need not extend over many generations; the more remote the relative, the less accurate the information. It is especially important to check whether there is any consanguinity in the pedigree, especially in the parents of the propositus, and to determine whether both parents are from the same geographic area or ethnic isolate.

The exact relationship of the relatives to the propositus and to one another should be established, and for this purpose it is useful to construct a pedigree chart (see Chapter 4), which will show at a glance the relationship of affected relatives to the propositus and to one another.

MAN AS AN OBJECT OF GENETIC RESEARCH

A mouse can complete a generation within two months, a fruit fly within two weeks and a microorganism within 20 minutes; but man has a generation

time of at least 20 years. In lower forms it is possible to make test matings to acquire desired information or to test hypotheses, but in man Nature makes the experiment and the investigator can only record the outcome. A mouse can produce scores of offspring in its lifetime, a fruit fly hundreds and a microorganism millions; human families average about three children each. Faced with these formidable obstacles we must ask ourselves what compensations man has to offset his disadvantages as a suitable animal for genetic research.

Probably most medical geneticists would subscribe to Pope's dictum that "the proper study of mankind is man." Man's fascination with himself has facilitated research into his genetics. Since we consider man so important (in Pope's phrase, "the glory, jest, and riddle of the world"), we have expended more effort upon him than upon some of the more suitable research organisms. Man seems more variable genetically than many other species, or at least his variants are better explored and documented, and since many of them are deleterious they tend to come to medical attention. Though individual families are small and becoming smaller, the total population is very large and becoming even larger; and though we cannot ethically perform experimental matings, we often find that somewhere in the population Nature has performed the experiments for us, or that new tricks such as those of somatic cell genetics will allow us to approach problems in human genetics from a different angle. Exploration of the genetics of human variation has already been so successful that some variants, notably the hemoglobinopathies and the blood groups, have even provided models upon which part of the conceptual structure of genetics has been erected. Some of the many areas in which genetics and medicine mutually illuminate and enrich one another are described in the following chapters.

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2

THE CHROMOSOMAL BASIS OF HEREDITY

When a cell divides, the nuclear material (chromatin) loses the relatively homogeneous appearance characteristic of nondividing cells, and condenses to form a number of rod-shaped organelles which are called **chromosomes** (*chromos;* color; *soma,* body) because they stain deeply with certain biological stains. Units of genetic information (**genes**) are encoded in the deoxyribonucleic acid (**DNA**) of the chromosomes.

Each species has a characteristic chromosome constitution (**karyotype**), not only with respect to chromosome number and morphology but also with respect to the genes on each chromosome and their locations (the **gene map**). The genes are arranged along the chromosomes in linear order, each gene having a precise position or **locus**. Genes which have their loci on the same chromosome are said to be **linked** or, more precisely, **syntenic** (in synteny). Alternative forms of a gene which can occupy the same locus are called **alleles.** Any one chromosome bears only a single allele at a given locus, though in the population as a whole there may be multiple alleles, any one of which can occupy that locus.

The **genotype** of an individual is his genetic constitution, usually with reference to a single locus. The **phenotype** is the expression of the genotype as a morphological, biochemical or physiological trait. The term **genome** refers to the full DNA content of the chromosome set.

Little was known about human cytogenetics until 1956 when Tjio and Levan developed effective techniques for chromosome study and found the normal human chromosome number to be 46, not 48 as had been previously believed. Since that time much has been learned about the human chromosomes, their molecular composition and their numerous and varied abnormalities. An appreciable proportion of the human genes have already been assigned a place on the chromosome map. Chromosome abnormalities are clinically important because they are major causes of birth defects, mental

retardation and spontaneous abortion. The development of methods for determining the karyotype during fetal life has given rise to the important new field of prenatal diagnosis.

THE HUMAN CHROMOSOMES

The 46 chromosomes of normal human somatic cells constitute 23 homologous pairs. The members of a homologous pair match with respect to the genetic information each carries; i.e., they have the same gene loci in the same sequence, though at any one locus they may have either the same or different alleles. One member of each chromosome pair is inherited from the father, the other from the mother, and one of each pair is transmitted to each child. Twenty-two pairs are alike in males and females and hence are called **autosomes.** The two **sex chromosomes,** the remaining pair, differ in males and females and are of major importance in sex determination. Normally the members of a pair of autosomes are microscopically indistinguishable, and the same is true of the female sex chromosomes, the X chromosomes. In the male the members of the pair of sex chromosomes are different from one another; one is an X, identical to the X's of the female, and the other, which is known as the Y chromosome, is smaller than the X and appears not to be homologous to it except with respect to a few genes (see Chapter 7).

There are two kinds of cell division — mitosis and meiosis. **Mitosis** is ordinary cell division by which the body grows and replaces dead or injured cells. It results in two daughter cells that are precisely identical to the parent cell in chromosome complement and genetic information. **Meiosis** occurs only once in a life cycle and results in the production of reproductive cells (gametes), each of which has a complement of 23 chromosomes. Somatic cells are said to have the **diploid** or $2n$ chromosome number (*diploos*, double), whereas gametes have the **haploid** or n chromosome number (*haploos*, single). Though a few specialized cell types are polyploid and abnormal chromosome numbers can arise both in somatic cells and in gametes by accidents of cell division, the general rule is that somatic cells are diploid and gametes are haploid.

Because human females are XX, all ova carry a single X chromosome; in contrast, males are XY and produce two kinds of sperm, X-bearing and Y-bearing. Hence, we speak of the human female as the **homogametic** sex and the male as the **heterogametic** sex. This arrangement is characteristic of many living forms but not of all; in birds the female is the heterogametic sex.

MITOSIS

In mitotic division, the cytoplasm of the cell simply cleaves into two approximately equal halves, but the nucleus undergoes a complicated sequence of activities. Four stages of mitosis can be distinguished — prophase, metaphase, anaphase and telophase. These stages are shown diagrammatically in Figure 2-1. In this figure, each homologous chromosome pair has one member outlined and one in solid black to signify that one homologue is derived from the father, the other from the mother.