GENETIC MEDICINE

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Preface

This book is addressed primarily to medical students engaged in the usual 24-hour course in human genetics in the required preclinical curriculum. However, the book should prove useful to a broader audience of those needing an introduction to, or a brief review of, human genetics. That audience would include college students and paramedical students in human genetics courses, medical students in clinical years, and physicians.

I use the book as a companion to a 32-hour course, "Genetic Medicine," that I teach at the University of Miami School of Medicine. The course is unusual, in fact probably unique, among medical genetics courses in American medical schools, in that it is the first course of the 4-year curriculum. "Genetic Medicine" then serves not only as a course in genetics but as an introduction to all of medicine. In my view the interaction of genetics and environment, nature and nurture, is the foundation for all health and disease, and I present the material in the context of that philosophy, acknowledging genetic aspects of tuberculosis and malaria, and refusing to view genetics as a medical subspeciality that deals with rare diseases alone. Some medical students might wish never to encounter the rare genetic diseases, but no medical student can hope to avoid the ever-present genetic factors in all health and illness.

This book reflects parts of the course and supplements the informational content of lectures, but the book is not the course, and cannot be. The course is rich in activities designed to create and enhance a lifelong interest in genetic medicine, and in that content the course complements and enhances the book. I provide these descriptions of the course and book to explain what may appear to be an eclectic textbook of genetic medicine. Medical students, for reasons of previous academic experience and pressures of time, seek informational sources that are at once concise and all encompassing. One lesson that we begin in "Genetic Medicine" is that diverse sources must provide the knowledge unique to every scholar just as diverse genes provide the uniqueness of every person.

The study of genetics has many possible approaches, beginnings, and thought sequences. The historical approach to genetics is fascinating and enriching, but does not lend itself to the transfer of condensed information. For this book I chose to start with

DNA. Having done so, I was immediately confronted with what I call "the definition problem": undefined words must be introduced and defined with other undefined words. Thus in an early sentence about DNA I might write about *genes* and *chromosomes*, neither of which is defined at that point. The definition problem recurs throughout the text. In confronting this problem it was comforting to me to realize that children acquire primary language without dictionaries, in constant exposure to multiple undefined but related words. The organization of this book represents, in part, an attempt to minimize the definition problem. The general sequence of ideas in this book has been tested over my two decades of teaching genetics to medical students. Their academic backgrounds are diverse, but none have been so unexposed to genetics in primary, secondary, college, and lay press education not to have some notion of genetic definitions. I shall assume the same background knowledge for my readers, and I have provided a glossary to help.

With respect to content and organization of the book:

1. Several thousand human genetic disorders are known so far. This book describes some of them either because they are relatively common or because they are particularly interesting to the author, or because they illustrate basic principles. Physicians and medical students may feel overwhelmed by the large number of genetic disorders, each with a complicated and unique pathophysiology, the variety seeming to defy mastery. However, basic principles bind diverse genetic disorders into a comprehensible package. This book will emphasize those principles.
2. Molecular genetics is divided into Chapter 2, on gene structure, and Chapter 12, on gene expression. I believe that gene structure is the best starting point for understanding genetics. However, an understanding of molecular mechanisms for gene expression is not essential background for Chapters 3–11. On the other hand, the acquisition of genetic concepts presented in those chapters allows the presentation of gene expression with a clinical dimension, and I have used that approach in Chapter 12.
3. Aspects of genetic counseling pertain to every genetic disorder. Therefore, brief comments about genetic counseling are scattered throughout the book as needed. A discussion focusing on genetic counseling is in Chapter 14, "Genetics in Practice."
4. Prenatal diagnosis involves the practical application of imaging, surgical, and laboratory skills to certain genetic problems that are mentioned for other reasons throughout the book. Specific attention is given to prenatal diagnosis in the last chapter.

5. Population genetics is not separated into a chapter of its own. Instead, some principles of population genetics are introduced as they relate to clinical genetics. Thus, the concepts of gene frequencies and of the Hardy-Weinberg law are introduced after autosomal recessive inheritance, and the concepts of mutation rate and selective disadvantage are introduced after autosomal dominant inheritance.
6. Some sections are set in smaller type either because they include mathmatical detail not required for subsequent sections, because they contain information of restricted interest, or because they may be read after subsequent sections have been covered.

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From Richard L. Kirschner, Class of 1989, University of Miami School of Medicine:

> Alas, our frailty is the cause, not we!
> For, such as we are made of, such we be.
> Viola, in Shakespeare, *Twelfth Night*

In essence the science of human genetics is that delicate quest for insight into the secret fashion by which Nature deals the cards of human variability—her strategies, capriciousness, and fallibility—the great purpose of which is in acquiring the knowledge of how to anticipate her whims, of how best to improve our hand, and, in the face of hopeless odds, of when it is time to fold.

From James Mosely, Class of 1989, University of Miami School of Medicine:

Genetics is the study which tugs at the veil of Fate, permitting man to view, ever after, the mystery of his creation, from the trembling order of his atoms to the "angels"—sublime or fallen—of his mind; yet it remains the mystery of how a ceaseless generation of uniqueness enshrines the enduring essence of humankind.

Contents

Chapter 1 The Growing Role of Genetics in Medicine

As the incidence of infectious disease decreases, while survival rates for those with genetic conditions increase, we can expect that genetic disease will form a growing share of all medical problems.

Rose Weitz, *Social Biology*

The impact of genetics on modern clinical medicine is accelerating. The many individually rare genetic disorders add up to an aggregate of chronic health problems that frequently confront physicians. The burden of genetic disorders is formidable. In 1976 an estimated 12 million Americans had genetic disorders, and life years lost to such disorders were 6.5 times greater than those lost to heart disease. An estimated 30% of pediatric and 10% of adult hospital admissions are for disorders that are wholly or partially genetic. The human molecular genetics revolution, sparked by the advent of gene manipulation techniques based on restriction endonucleases, is now changing the nature of medical practice. The changes are profound. More will follow and they will engender and even catalyze others.

Medical schools are struggling to meet the increasing demand for curriculum on human genetics. However, a 1981 survey revealed that only 72% of American medical schools provide a required course in genetics. Those courses averaged only 24 hours in length. Clearly, changes are needed and, without doubt, are forthcoming.

Genetics in Adult Medicine

For physicians who had premedical genetics courses, the word elicits visions of fruit flies and mice. Others think of genetics in terms of infants and children with debilitating genetic disorders,

such as Down syndrome or cystic fibrosis. Because of medical advances children with genetic disorders that were previously incompatible with normal adult life are now not only surviving but are marrying and reproducing. Examples of such disorders are hemophilia and phenylketonuria. Adult patients with cystic fibrosis are no longer rare. These changes in survival and reproductive patterns, coupled with the fact that many genetic disorders first appear clinically in adulthood, pose new problems for physicians primarily engaged in the care of adults. All of these factors have contributed to the growing importance of genetics in adult medicine.

Demand for Genetic Information

The demand for genetic information is increasing for many reasons: (1) Research is elucidating genetic factors in common diseases, such as hypertension and cancer; (2) research is describing the biochemical mechanisms for diseases previously known to be genetic; ie, certain forms of gout and atherosclerosis; (3) research is offering remedies if not genotypic cures for many genetic disorders, and a whole new science of genetic engineering has grown up from the demonstration in 1972 that genes of one organism can be covalently bonded to the genes of another organism; (4) a social revolution with respect to sex, marriage, reproduction, and the roles of the sexes has greatly increased options in family planning and has engaged public attention to genetic aspects of these issues; (5) the burgeoning technologies of prenatal diagnosis and in vitro fertilization have raised a whole new set of choices with attendant ethical and legal problems for prospective parents; finally (6), the lay press is publishing a profusion of information concerning these matters.

Goal of Genetic Medicine

With increasing costs of medical care and with too much of the health-care dollar spent for the last 10% of life, public attention is focusing on preventive medicine. Genetics is a paradigm for preventive medicine, because the goal of genetic medicine is prevention of disease.

Within genetic medicine prevention has several meanings. Perhaps too much attention has accrued to the first of these; ie, prevention of the birth of affected or genetically damaged individuals. Nevertheless, prenatal diagnosis is a major area of genetic activity in the clinic and in the research laboratory. One should not automatically connect prenatal diagnosis with elective abortion. For those not choosing to abort a fetus with serious genetic defects, knowing the diagnosis before birth aids in proper obstetrical management to minimize existing damage and to prevent its extension. For example, knowledge that an infant will be born with myelomeningocele allows for planning of delivery by cesarean section to prevent trauma to the exposed and vulnerable

spinal cord. Infants so managed have a much better prognosis for use of the lower limbs and for bowel and bladder control. Furthermore, knowing about a serious genetic defect before birth allows for the emotional preparation of the parents and family. Being surprised in the delivery room is probably the worst way for parents to learn that their infant has Down syndrome. If abortion is the choice after prenatal diagnosis of a severe genetic defect, that decision can be viewed in a positive light as an attempt by a parental couple to have a healthy child.

The intense interest in prenatal diagnosis may overshadow other important areas of prevention in genetic medicine. One of these areas is the prevention of the development of disease in a genetically latent, affected person who would, in time, develop the disease without prophylactic intervention. An example is hemochromatosis, in which the homozygous person, estimated to be about 1 out of every 400 in the white population, eventually develops cirrhosis, diabetes mellitus, and heart failure because of organ damage from excessive iron stores. The abnormal iron storage is preventable and even reversible by the simple expedient of periodic blood removal, which totally prevents the disease. We should note that a prevalence of 1 in 400 is a high number by genetic standards.

Another form of prevention in genetic medicine is to delay the onset of a clinical illness in a person genetically destined to be ill. An example of this is familial hypercholesterolemia. Here the prevalence of heterozygotes in all races is about 1 in 500. The disorder accounts for only a small percentage of all those persons with hypercholesterolemia, but offspring and siblings of affected persons are at 50% risk, and the disorder is detectable and treatable even in childhood. Untreated males usually suffer coronary artery occlusion by age 50. The cost of that or of coronary artery bypass surgery certainly justifies early testing of relatives at risk.

Another variety of prevention in genetic medicine is the amelioration of expression of a genetic disorder that can be neither prevented nor delayed in appearance. For example, the disastrous hemarthroses that complicate hemophilia can be decreased in number and in severity by treatment with factor VIII concentrate.

Because of the preventive nature of genetic medicine, the activity of the specialty is directed not only toward affected individuals seeking medical care, but also to the detection of new cases. This case-finding activity has parallels in the specialty of infectious disease, which is the model for environmental causes of illness.

Case Finding

Case finding can be usefully divided into (1) identification of persons at risk and (2) testing of those persons. For some disorders, early treatment is so dramatic and effective that perinatal screen-

ing of all infants is required by law. Examples are phenylketonuria and galactosemia. However, for a larger number of disorders the identification of persons predisposed, at risk, or affected but not yet ill, relies on genetic clues to be cost effective, because not all members of the population can be screened for all genetic disorders. One genetic clue is race or ethnic background, which alone might suffice as a reason for testing. For example, experts agree that blacks should be offered sickle cell screening and that Ashkenazic Jews should be offered Tay-Sachs screening.

Another genetic clue is the relatedness of a person to an affected person. This relationship is established by the construction of the pedigree, the one activity which most distinguishes geneticists as members of a practicing specialty. Yet another indicator for genetic case finding is advanced maternal age, which increases the risk for chromosomal nondisjunctional events in gametogenesis and can be a setting for Down syndrome.

After case finding, appropriate testing is done. The testing may be prenatal for those disorders detectable in utero or may be postnatal for a host of the same and other disorders. Prenatal testing may be noninvasive, as in the ultrasonographic examination of the fetus, or may be invasive, as in amniocentesis or in chorionic villus biopsy. The invasive tests provide fluid and/or cells for chromosome analysis, enzymatic assays, other biochemical assays (such as α-fetoprotein determination), and DNA linkage analysis by restriction fragment length polymorphisms.

These tests and others, such as serum iron or cholesterol levels, provide a vast diagnostic armamentarium in postnatal genetic diagnosis. Subsequently, appropriate management encompasses the entire array of medical and surgical therapeutics, to say nothing of genetic counseling, which ranks with pedigree taking in specificity for geneticists. These topics will be discussed further in Chapter 14. In the meantime, think of genetics as a model for preventive medicine.

Available Services

The primary physician will occasionally be unable to answer genetic questions arising in his practice. His medical and legal responsibility is then to obtain, or at least advise, expert consultation. It is more difficult to locate American physicians who provide genetic counseling than to locate other medical specialists, because clinical geneticists are not usually listed by specialty in local telephone directories. A new American Board of Medical Genetics began accreditation in 1982; thus the accessibility of American medical geneticists should increase with such accreditation and with recognition of the accrediting body. In Canada, the Canadian College of Medical Geneticists accredits holders of the PhD, MD, or DDS degrees who possess the necessary qualifications in medical genetics. A list of about 500 centers where

genetic consultation is available is given in the *International Directory of Genetic Services* (1986), and in *Comprehensive Clinical Genetic Service Centers, a National Directory* (1985).

Indications for Genetic Counseling

The primary physician should consider the need for genetic counseling when a patient or a patient's close relative has one or more of the following:

1. An anatomical defect present at birth
2. Abnormal development of sexual organs, secondary sexual characteristics, sexual function, or fertility
3. Repeated abortions or miscarriages
4. Abnormal mental development
5. Abnormal physical growth or stature
6. A chromosomal abnormality
7. A metabolic or endocrine disorder
8. Any disorder known to be concentrated in a family
9. Consanguinity

The counseling may need to include some of the patient's family members, who may be at risk or whose progeny may be at risk. Impending marriage, possible parenthood, or pregnancy sharpen concern. Particular indications in pregnancy are advanced age, and exposure to drugs, radiation, and infection.

Probably 90% of persons with these indications do not receive genetic counseling. Perhaps this book will help primary physicians to meet the obvious need.