Clinical Genetics

A Source Book for Physicians

LAIRD G. JACKSON / R. NEIL SCHIMKE

CLINICAL GENETICS

A SOURCE BOOK FOR PHYSICIANS

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Preface

The contemporary practicing physician, no matter what his area of expertise, usually becomes uneasy when the conversational topic turns to inherited disease. This feeling is understandable when considered in its perspective because only the most recent medical school graduates have had much experience in the application of genetic principles to man. Also, geneticists have tended to publish their interesting case material in the genetics journals, which are hardly a place where they will be encountered by the ordinary physician. Those of us interested in clinical genetics have broadened our literary horizons over the past few years. However, this has not substantially improved the picture for the non-geneticists, since the various papers are now scattered throughout a host of both general and special journals. Standard genetics texts are usually very basic in their orientation and frequently contain little information of clinical relevance. More specialized texts are available, but unless a physician has a nearly unlimited budget (and a similar amount of time), he cannot hope to encompass the field.

With all the above in mind, we felt it would be useful to compile most of the current information in clinical medical genetics into a single volume emphasizing its clinical application. We hope that this book can serve as a focal source for inquiry into a specific genetic disease in a designated organ system. Obviously, "new" conditions are appearing on the medical horizon with such discouraging regularity that no one text can hope to cover the field. Our contributors have performed a yeoman effort to make available a tremendous amount of information in a readable, clinically-oriented form that we hope will be useful to students, to physicians, and to nurses and paramedical personnel who come in contact with patients with heritable disease. It was occasionally necessary for us as editors to make some changes for the sake of both uniformity and brevity. It is likely that we occasionally overdid it. The content of the various chapters is sound; we can only apologize to our colleagues and our readers for our editorial shortcomings.

We are indebted to our secretaries, Alice Algie, Patricia Cionci, Jane Gottlieb, Joan Glazerman, and Barbara Lawson for collating, typing, assisting with the editing process (mainly by finding the pages we misplaced), and generally putting up with our bad penmanship and vile humor. Support for this work was provided in part by the Fogarty Foundation and the National Foundation—March of Dimes.

Laird G. Jackson, M.D.
R. Neil Schimke, M.D.

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Part 1

INTRODUCTION

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Fundamentals of Clinical Genetics

R. Neil Schimke
Laird G. Jackson

A BRIEF HISTORY OF GENETICS

Although sophisticated knowledge of the biologic and chemical bases of heredity is a fairly recent scientific acquisition, a thumbnail sketch of the salient historical developments is appropriate. Notions of genetics have been found among the stone carvings of the Chaldeans dating from 6,000 years ago, and the ancient Greeks advocated a stringent form of eugenics by recommending infanticide for the deformed. The Talmud contains proscriptions against circumcision for the brothers of males who were bleeders, thereby tacitly recognizing the X-linked inheritance of hemophilia. In the early eighteenth century, Pierre de Maupertuis studied certain single-gene disorders in man and developed a concept, albeit somewhat faulty, of the structural basis of heredity. Mendel, in the mid-nineteenth century, showed that the occurrence of simple physical characteristics in plants had a statistical predictability. At the turn of the present century, Johannsen coined the term gene and differentiated between an individual's genetic makeup, or genotype, and his external appearance, or phenotype.

Sutton and Boveri, in 1903, independently proposed the chromosomal theory of heredity. Garrod provided the basis for biochemical genetics through his study of alcaptonuria. His concept of heritable inborn errors of metabolism was confirmed and extended by Beadle and Tatum in the late 1930s and early 1940s, as they formulated the one gene:one enzyme concept* and, in essence, proved the correctness of Garrod's early twentieth-century conceptualization of an enzymatic error as being responsible for some of man's heritable diseases. Even prior to that time, a distinguished group of scientists including Morgan, Bridges and Sturtevant, working with the common fruit fly, *Drosophila,* established that genes were arranged in a linear sequence along chromosomes.

Avery, MacCleod and McCarty, in 1944, demonstrated that deoxyribonucleic acid (DNA) was the hereditary material, and a decade later the work of Wilkins, Franklin, Watson and Crick led to the proposal by Watson and Crick of the now

*Later it was shown that some proteins are composed of more than one polypeptide chain, e.g., hemoglobin, and are thus the product of more than one gene.

well-known double helical structure of DNA. In 1956, Tjio and Levan in Sweden and Ford and Hamerton in Great Britain reported that man had 46 rather than 48 chromosomes and three years later Lejeune demonstrated the chromosomal basis of the Down syndrome. In 1961, Nirenberg and Matthaei broke the genetic code, and elucidation of the translational mechanism followed shortly thereafter. At about the same time Jacob and Monod were reporting their now classic work on regulation and control of gene action.

These workers are but a few of those who have fostered interest in genetics over the centuries. Despite this background and the fact that every college-level biology text contains reference to genetics, the practical application of this discipline to the medical sciences did not occur before 1960. It is not surprising therefore that many clinicians know little about medical genetics. However, for many of them—not only pediatricians and obstetricians, but also those in the medicosurgical subspecialities—genetics is an important facet of clinical practice.

CHEMISTRY OF THE GENE

In this scientifically enlightened era, every schoolboy knows that deoxyribonucleic acid (DNA) is the genetic material. The DNA molecule is composed of two tightly coiled helical chains of nucleotides, or bases, the backbone of each chain being formed by sugar (deoxyribose)–phosphate groups. The two complementary chains of DNA are interconnected across the helical loops by hydrogen bonds between the bases, with adenine (A) being bonded to thymine (T), and guanine (G) to cytosine (C) (Fig. 1). During replication the two chains or strands come apart and each acts as a template for the synthesis of a complementary strand. The sequential attachment of new bases requires a specific enzyme, DNA-dependent DNA synthetase (replicase).

In this way each daughter cell contains a strand of DNA from the original cell plus a newly synthesized complementary molecule, a so-called semiconservative method of nucleic acid duplication. The genetic information is stored within the DNA in the form of a triplet code, i.e., each sequence of three bases codes for a single amino acid, and this triplet sequence is called a *codon*. A permutation of the four bases gives rise to 4^3 or 64 codons. Since there are only 20 amino acids, there appear to be excess codons. However, the code is degenerate, i.e., more than one triplet may code for a given amino acid; moreover certain codons act as starters or initiation points for translation of the genetic message, and others function as termination codons.

The genetic information in the DNA is then transcribed into a message of single-stranded ribonucleic acid (RNA) called *messenger RNA* (m-RNA). This process is achieved by a synthetic sequence similar to DNA duplication but requiring another specific enzyme, DNA-dependent RNA synthetase (transcriptase).† Each message is formed by a particular gene, or in some cases a number

†Some RNA viruses, the genetic information of which is stored in a double-stranded molecule of RNA, first transcribe this information to a molecule of DNA using an enzyme called reverse-transcriptase (RNA-dependent DNA synthetase). They are then able to use the cell's own enzyme to complete the process of information transfer as described herein.

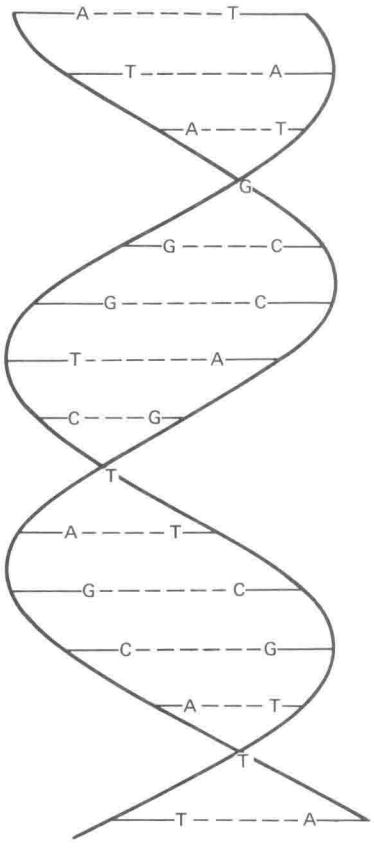

Figure 1. The DNA molecule. The two purines, adenine (A) and guanine (G), are joined to the pyrimidines, thymine (T) and cytosine (C) by hydrogen bonds to form the double helix. Chemical configuration of single strand of DNA molecule, showing sugar–phosphate "backbone" to which the four bases (A, C, G and T) are attached.

of genes, so that every base in the m-RNA is complementary to the corresponding base in DNA with the exception that adenine of DNA pairs rather with uracil (U) of RNA than with thymine (Fig. 2). The codons are usually expressed in m-RNA equivalents, i.e., UUU for phenylalanine rather than AAA (Table 1). The m-RNA then traverses the nuclear membrane and passes into the cytoplasm.

Here it becomes associated with another species of RNA, *ribosomal RNA* (r-RNA), aggregates of which are called *ribosomes.* Several ribosomes begin to attach to one end of the m-RNA and travel along it in a specific direction, "reading" the message as they go. This complex of m-RNA and ribosomes is the polysome, and the process—which results in protein synthesis—is *translation.* As the ribosome translates a codon, it calls for the proper amino acid to be inserted into the growing protein (polypeptide) chain, and the appropriate acid is brought into proper alignment by a third RNA, *transfer RNA* (t-RNA). The ribosome recognizes and pairs the m-RNA and t-RNA so that a peptide bond can be formed between the carboxy terminal of the growing polypeptide chain and the amino end of the amino acid brought into position by the t-RNA (Fig. 2).

The process continues until a chain-terminating codon is reached, at which juncture the completed polypeptide chain is released. This sequence continues

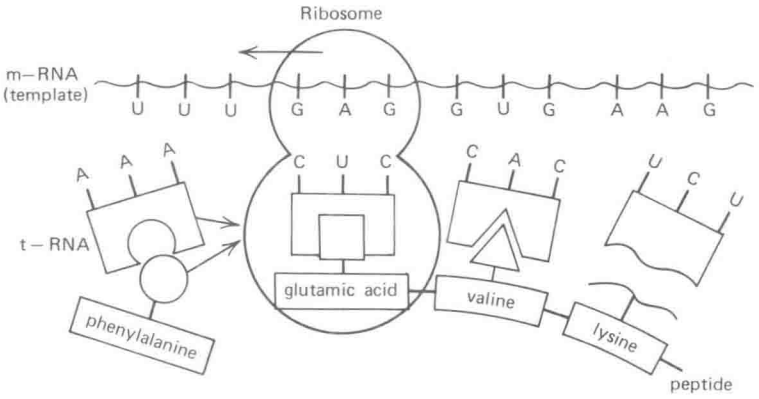

Figure 2. Protein synthesis. A strand of messenger RNA (m-RNA) is formed on DNA template in the nucleus. It then travels to the cytoplasm where it attaches to a ribosome. A t (transfer)-RNA–amino-acid complex the anticodon triplet of which matches the codon triplet being "read" (translated) on the m-RNA fits into place against the m-RNA. As m-RNA strand is being translated, t-RNA molecules are split from attached amino acids. The latter are joined by peptide bonds to form the protein molecule coded by the original DNA strand. T = thymine; U = uracil; C = cytosine; A = adenine; G = guanine.

until sufficient quantities of the polypeptide are produced. Control of this process ultimately may reside in the interaction of the specific gene with the polypeptide product (feedback inhibition), with nuclear protein or with other small molecules, the synthesis of which is under the control of still other genes. There are then *structural genes* that code for the structure of polypeptides, such as enzymes, hormones, hemoglobins and *regulatory genes,* or control genes, that control the extent of the translational process and hence the amount of structural genetic product.

The concept of regulatory, as distinct from structural, genes was first demonstrated by Jacob and Monod in *Escherichia coli.* They demonstrated the existence of a gene that directed or operated a set of structural genes to produce a series of proteins. These so-called operator genes were in turn regulated by molecules that could turn them on (*inducers*) or off (*repressors*). Although the original theory may have only limited, or perhaps no, direct applicability to a higher organism like man, it nonetheless supplies formal evidence for the existence of gene-control mechanisms. No regulatory devices like these have been rigorously demonstrated in higher animals, but they undoubtedly make up part of more complex genotypes.

Point Mutations

Abrupt heritable changes in the genetic makeup (genotype) of an organism are termed mutations, and they may be different types. The commonest is probably a point mutation in which a single base in the DNA is changed, perhaps by either