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the metabolic basis of inherited disease

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FOURTH EDITION

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PREFACE

More than 20 years have passed since *The Metabolic Basis of Inherited Disease* was conceived, and 17 years since the first edition appeared. Rapid extension of information now dictates another edition: new disorders have been described, and the complexity of others has come into focus. For still others new levels of understanding have been achieved.

One of the axioms of genetic disease is that what at first appears to be a single disorder proves on closer scrutiny to be a heterogeneous group of conditions with similar clinical manifestations. The rate of demonstration of new metabolic errors or new syndromes seems now to be diminishing, whereas the rate of recognition of new variants of well established syndromes is accelerating. These variants are being identified at two levels. The first concerns clinically similar and metabolically related disorders involving deficiencies of different enzymes. These are attributable to mutations in different genes and are known as genocopies. The second involves different alterations in the same enzyme due to different mutations at a single locus. These variants are known as allelic series.

In 1952 only one type of enzyme deficiency glycogen storage disease was known. This was von Gierke's disease, in which there is a virtually complete absence of activity of glucose 6-phosphatase. Today, we recognize at least ten forms of glycogen storage disease, only some of which are differentiable on clinical grounds. The group of nonspherocytic hemolytic anemias provides another example of expanding recognition of genocopies. In the first edition only glucose 6-phosphate dehydrogenase deficiency was recognized. Today, we discern more than a dozen different types of hemolytic disease, each attributable to specific enzyme abnormalities of the red cell.

The second level of heterogeneity is based upon the recognition of a multiplicity of mutations occurring at a single genetic locus. This situation allows for multiple allelic homozygous states, often with profound differences in phenotypic expression, and also for interesting compound heterozygous conditions presenting mixed features of two discrete syndromes. Common examples of allelic series are the more than 100 different mutations involving the β chain of hemoglobin and the comparable number of variants of glucose 6-phosphate dehydrogenase. Much of the progress reported in this new edition relates to recognition of new allelic variants of known conditions involving enzyme deficiency states. For example, perhaps as many as ten variants of hypoxanthine-guanine phosphoribosyltransferase deficiency can now be postulated.

Inherited disease occurs when the structure of a variant protein is so altered genetically that fitness of the individual is impaired. One of the tasks of the clinician is to distinguish between new diseases and new variants of known disorders showing subtle differences from the prototypical condition. The problem for the biochemical geneticist is to isolate and characterize variant proteins responsible for these disorders and to demonstrate how the changed structure alters biological function. Remarkable progress in this direction has recently been derived from a coupling of new capabilities in cell and tissue culture with ascending power of tools for microchemical analysis. Not only has the pace of discovery been quickened, but observations are now permitted that would have been impossible only a few years ago. Indeed, one of the pleasures of editing successive editions of this book has been the vantage point it affords for observing the growth in illumination of medicine provided by scientific advances in these last two decades.

With few exceptions, each chapter from the previous edition has been extensively revised or entirely rewritten. The staggering growth of the literature has required omission of many older bibliographic citations, leaving these stepping stones to be found in the corresponding chapters of the third or earlier editions. An explosive advance in knowledge of disorders arising from chromosomal aberrations has necessitated a whole new approach in that chapter. Changing concepts of the nature of diabetes mellitus and its genetics have required an entirely new presentation of this subject. The classification of the inherited diseases of lipid metabolism continues to evolve, and that section has been restructured. Similarly, technical and conceptual advances in protein chemistry have required yet another different approach to the presentation of the hemoglobinopathies and thalassemia.

Increasing appreciation of the phenomena of multiple allelism and genocopy has required much subdividing and reordering of familiar disorders long thought to be relatively simple or unimodal. In addition a number of new disorders have entered the domain of this book; eight entirely new chapters have been added. We now include chapters on that extraordinarily interesting disorder xeroderma pigmentosum, disorders of glutathione biosynthesis, on the pseudohermaphroditism group, on the group of inherited disorders of folate metabolism, on β-mercaptolactatecysteine disulfiduria, on storage of cholesterol and β-sitosterol, on the collagen disorders, and on Farber's lipogranulomatosis.

Fourteen chapters from previous editions have been written by new contributors in order to approach each set of diseases from a fresh or different point of view, and to gain the perspective of workers currently most active in each field. We remain indebted to earlier authors for their splendid contributions upon which their successors have built. One chapter, that on periodic paralysis, has been omitted from this edition because time has not clarified either its genetic component or its biochemical nature.

We are saddened to record the death of John Jepson. His chapter on Hartnup's disease in this volume is a token and symbol of his contributions to medical science. We also wish to acknowledge with sadness the deaths of colleagues who wrote for previous editions: Drs. Charles Burnett, Mary Efron, Harry Heller, Harvey Marver, Milton Shy, and Harry Waisman.

The value of this book to students and medical scientists derives from the authority and dedication of its contributors. They have been graciously responsive to suggestions directed toward a uniformity in style and presentation. We are grateful to them.

We are privileged to have had the devoted help of our several secretaries. Especially we wish to thank Ms. Susan Anderson, Susan Johnson, Christine Connaire, Patsey Sutphin, and Sandra Mangum, all of whom have immeasurably lightened the burden of our work.

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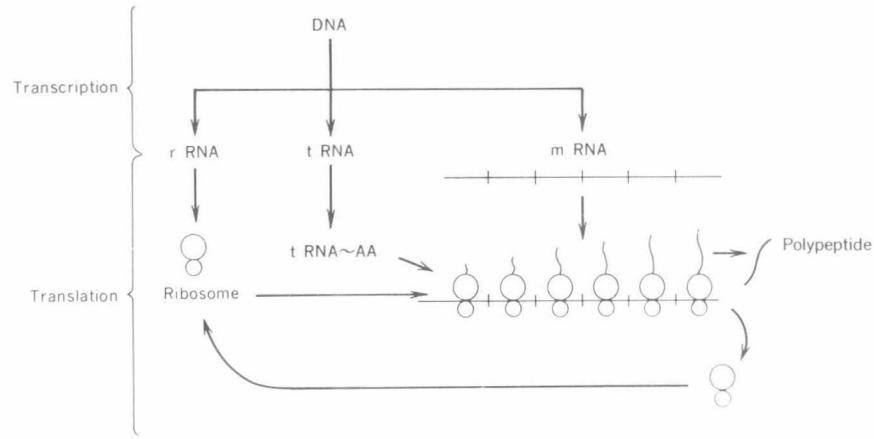
INTRODUCTION

Schema of the genetic control of protein synthesis. (*Courtesy, Dr. Irving M. London.*)



chapter one

INHERITED VARIATION AND METABOLIC ABNORMALITY

THE EDITORS

This volume is concerned with inherited variations of human beings that can be described in biochemical terms. Most of the variations included are diseases, in that they produce symptoms, or structural abnormalities, which impair the fitness of the individual. The etiologic agent of these disorders is the mutant gene. Attention is focused chiefly upon the mechanism by which the mutant gene produces clinical manifestations, and upon methods for interrupting that mechanism or compensating for it.

Some of the heritable diseases presented in this book are common; many are rare. The latter are important out of proportion to their numerical incidence, for they teach us much about the nature of normal metabolic events and their genetic controls. The details of many metabolic sequences and systems, of ganglioside catabolism or the clotting of blood, for example, first became visible through experiments of nature in which a specific biochemical reaction was faulty because of an inborn metabolic error. Studies of hereditary disorders continue to offer tantalizing clues to the understanding of metabolic regulation, growth, differentiation, cellular and humoral defenses, neoplastic transformation, and other fundamental biologic mechanisms.

GENETIC AND BIOCHEMICAL INDIVIDUALITY

The correct chromosome number of human beings was established as 46 by Tjio and Levan in 1956 [*1*]. The inheritance of humans is determined by the information carried on these 23 pairs of chromosomes, which are estimated to contain about 50,000 different gene pairs, or loci [*2*]. The structure of each gene is subject to variation. Variant genes of a given locus are called *alleles*. The cause of genetic heterogeneity, i.e., of differences between members of homologous gene pairs, is *mutation* of gene structure. Variations of chromosome content are introduced by *recombination*, a process in which genetic material is exchanged between homologous chromosomes during the pairing that takes place in meiosis, and by *translocation*, a process in which chromosomal breakage and reunion result in the insertion of whole segments of chromosomes in new positions within the same or another chromosome (intra- or interchromosomal translocation). Additional variation of the genetic constitution, or genotype, results from the *random distribution* ("independent assortment") of one member of each paired chromosome into daughter cells during reductive division of the germ cells. The interplay of all these forces provides each human being, except monovular twins, with a unique inheritance.

Certain genes specify the sequence of amino acids in proteins, others control the rates or times of protein synthesis. The immediate consequence of gene mutation is a change in quality or quantity of a specific protein. Examination of the structure and properties of many proteins has disclosed extensive qualitative and quantitative variation among healthy individuals. Many variations are trivial, lead to no recognizable biologic advantage or disadvantage, and are probably neutral from the evolutionary point of view. Others lead to some slight advantage in fitness or reproductive capacity in the heterozygous state, and produce a positive selection pressure in the population. The best-known example is the relative resistance to *plasmodium falciparum* malaria of the person heterozygous for the sickle-cell hemoglobin trait. These obser-

vations provide a basis for an understanding of the structural and biochemical individuality of human beings. Structural individuality is everywhere visible. Biochemical individuality is exhibited in variations of protein composition, of constituents of tissues and body fluids, of quantitative needs for specific nutrients, pharmacologic responses to specific drugs, and numerous other ways.

In certain instances a mutation proves to be harmful to its bearer because the change in quality or quantity of protein results in a structural or functional change which reduces the fitness or reproductive capacity of the individual. Some mutations are deleterious in single dose, e.g., that causing intermittent acute porphyria. Others require a double dose, i.e., either the homozygous state (characterized by two *identical* mutant alleles at one locus) or the "compound heterozygous" state (characterized by two *different* mutant alleles at one locus), in order to produce deleterious effects. Harris [3] estimates that normal individuals may be heterozygous at as many as 16 percent of loci. It has also been estimated that the average healthy individual is a heterozygous carrier of at least three to five harmful mutations, of the type responsible in the homozygous state for the disorders described in this book. The majority of mutations responsible for genetic disorders are probably not fundamentally different in kind or mechanism from those that account for the subtle or even gross variation considered to fall within the range of normal for the species. Possible exceptions are those involving gross chromosomal damage, including certain translocations or deletions.

McKusick [4] has published a catalogue of Mendelian characteristics of human beings in which he lists 2336 genetically determined variations reported until 1975. Most of these are diseases, usually rare and often involving many organ systems. In most of these disorders it is not yet possible to identify the product of the mutant gene, whose presence is suggested by the Mendelian distribution of the phenotype. In only about 20 percent has a relation between a given gene and a particular metabolic function been recognized; in only about 10 percent is information sufficient to indicate that either the quality or the availability of a specific protein has been altered [5]. This volume treats chiefly this last subgroup of genetically determined disorders of humans. In a limited number of these the precise structural modification of a protein is known, and from this information the specific modification of DNA structure can be deduced.

Few if any diseases are either wholly genetic or wholly environmental in their etiology. Even such disorders as phenylketonuria and galactosemia are not exclusively genetic, for control of diet can induce important modifications in phenotype. The controversy of an earlier day over genetics and environment, nature and nurture, no longer rages; it is now widely appreciated that both factors are important and are coordinated.

HISTORICAL CONSIDERATIONS

Concept of inborn errors of metabolism (Garrod)

Shortly before the turn of the present century Sir Archibald Garrod began his studies on alcaptonuria which were to culminate in his classic Croonian Lectures in 1908 [6] and in his monograph, *Inborn Errors of Metabolism*, which appeared in 1909 and again in 1923 [7].

Garrod had observed that patients with alcaptonuria [8] excreted large, rather constant quantities of homogentisic acid throughout their lifetimes, whereas other persons excreted none at all. He observed that this condition had a familial distribution and that while frequently one or more sibs were involved, parents and more distant relatives were normal. There was a high incidence of consanguine marriages in the parents of his patients, as well as in the parents of similar patients studied elsewhere. On conferring with Bateson, one of the earliest of the great school of British geneticists, Garrod learned that the situation could readily be explained as a recessive condition in terms of the recently rediscovered laws of Mendel [9, 10].

From his observations on alcaptonuria, albinism, cystinuria, and pentosuria, Garrod developed the concept that certain diseases of lifelong duration arise because an enzyme governing a single metabolic step is reduced in activity or missing altogether. Garrod viewed the accumulation of homogentisic acid in alcaptonuria as evidence that this substance is a normal metabolite in the dissimulation of tyrosine, and he correctly attributed its accumulation to a failure of oxidation of homogentisic acid. A half-century later Garrod's hypothesis was proved by the demonstration of unmeasurable activity of homogentisic acid oxidase in the liver of a patient with alcaptonuria [11].

Similarly, the failure of pigment formation in the skin in albinism, the excretion of large amounts of cystine in the urine in cystinuria, and the appearance of pentose in the urine in essential pentosuria were viewed by Garrod as the results of blocks in normal metabolic pathways. He attributed the first instance to failure of melanin formation and the other two to excretion of metabolites accumulating proximal to a metabolic block.

One gene—one enzyme concept

The term *gene* was first applied to the hereditary determinant of a unit characteristic by Johannsen in 1911 [12]. The relationship between gene and enzyme attained clear definition in the one gene-one enzyme principle, first succinctly stated by Beadle in 1945 [13]. This formulation, now a biologic precept, emerged gradually from studies of eye color in the fruit fly, *Drosophila*, by Beadle and Tatum [14, 15] and Ephrussi [16]. It received extensive support from the classic studies of Beadle and Tatum on induced mutants of *Neurospora crassa*, in which the acquisitions of requirements for specific metabolites in the culture medium were traced to losses of single chemical transformations, each dependent on a different enzyme [15, 17].

The one gene-one enzyme concept which developed from these experiments has been well expressed by Tatum [18] as follows:

1 All biochemical processes in all organisms are under genic control.
2 These biochemical processes are resolvable into series of individual stepwise reactions.
3 Each biochemical reaction is under the ultimate control of a different single gene.
4 Mutation of a single gene results only in an alteration in the ability of the cell to carry out a single primary chemical reaction.

The one gene–one enzyme hypothesis has since been made more precise [19], and extended to cover proteins that are not enzymes, as well as complex proteins composed of noniden-