GENE ACTION

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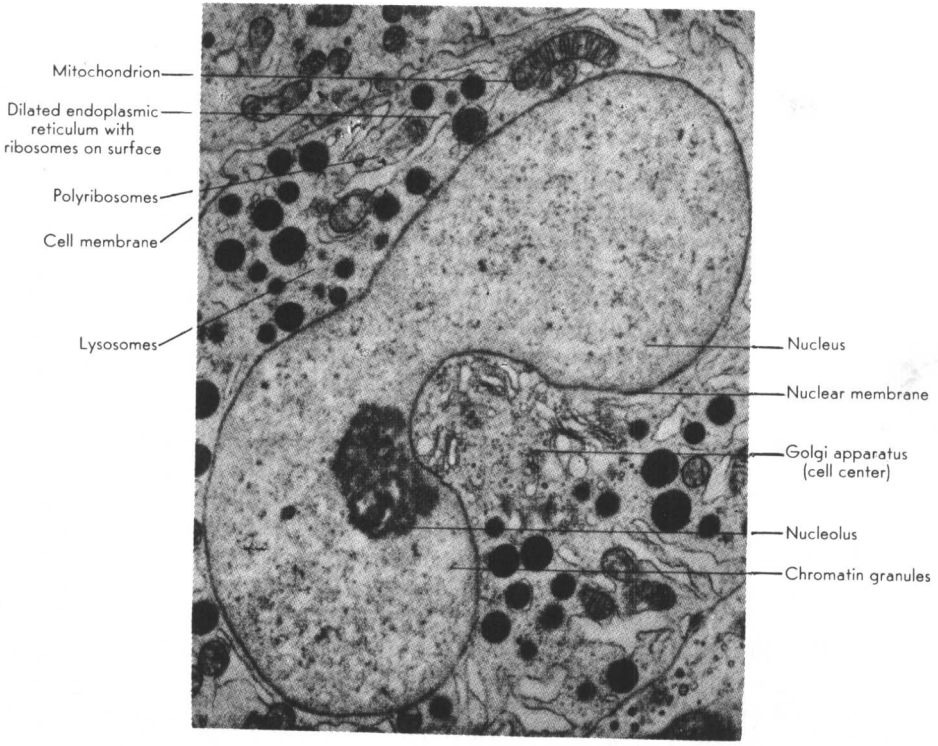

Frontispiece. Electron micrograph of bone marrow cell of the rat, stained with lead. Photograph courtesy of Dr. Leon P. Weiss, Department of Anatomy, The Johns Hopkins University School of Medicine. Magnification on page ii: 42,500×. Reproduced above in reduced size with identifying labels.

Foundations of Modern *Genetics*

Genetic research is alive with excitement and revolutionary advances. Important to the development of science and to the evolution of social structure, genetic thought is widening its impact on many areas: immunology, protein chemistry, cellular physiology, developmental biology, medicine, agriculture, and industry.

So many partnerships and such rapidly expanding methodology demand a fresh approach to genetic training —an approach attempted in this series.

The basic principles of genetics are few and simple. We present them with enough description of accessory scientific areas to allow comprehension not only of the principles themselves but also of the types of experiments from which the concepts have evolved. Such an approach compels the reader to ask: What is the *evidence* for this concept? What are its *limitations?* What are its *applications?*

The Prentice-Hall Foundations of Modern Genetics Series presents the evidence upon which *current* genetic thought is based. It is neither a history nor a survey of all genetic knowledge. The short volumes make possible a stimulating, selective treatment of the various aspects of genetics at the intermediate level, and sectional divisions allow free choice of emphasis in differently oriented college genetics courses.

The references cited in each volume and the current research literature are the immediate sequels to this series, but the true sequel remains in the hands of the alert reader. He will find here the seed of more than one enigma, the solution of which he, himself, may help bring into man's comprehension sometime in the future.

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Contents

Base Pairing and Gene Action

Genetics currently occupies the position of keystone in the broad-based structure of the biological sciences. Cytological, developmental, physiological, biochemical, medical, ecological, and evolutionary problems increasingly are drawing from and contributing to contemporary genetic thought. This interdisciplinary stimulus, arising from the physical as well as the biological sciences, has resulted in rapid advance in the area of molecular genetics. In this book, we are concerned with the chemical nature of the genetic material and the manner in which it functions. Our approach to the problem of how genes act will be simple and direct: gene action will be equated with protein formation and function, and it will be assumed that from this all other consequences arise.

In *The Mechanics of Inheritance,* a companion volume in this series, Franklin W. Stahl presents the evidence that permits us to state confidently that the genetic material of many organisms is composed of large-polymer deoxyribonucleic acid (DNA) molecules. These molecules generally contain the four bases, adenine, thymine, guanine, and cytosine. The bases represent the four letters in the genetic code and are abbreviated A, T, G, and C. Ordinarily, twenty different amino acids must be placed in proper sequence in polypeptide chains to have normal, fully functional protein molecules. How the four letters code for the twenty amino acids is discussed in Chapter 9.

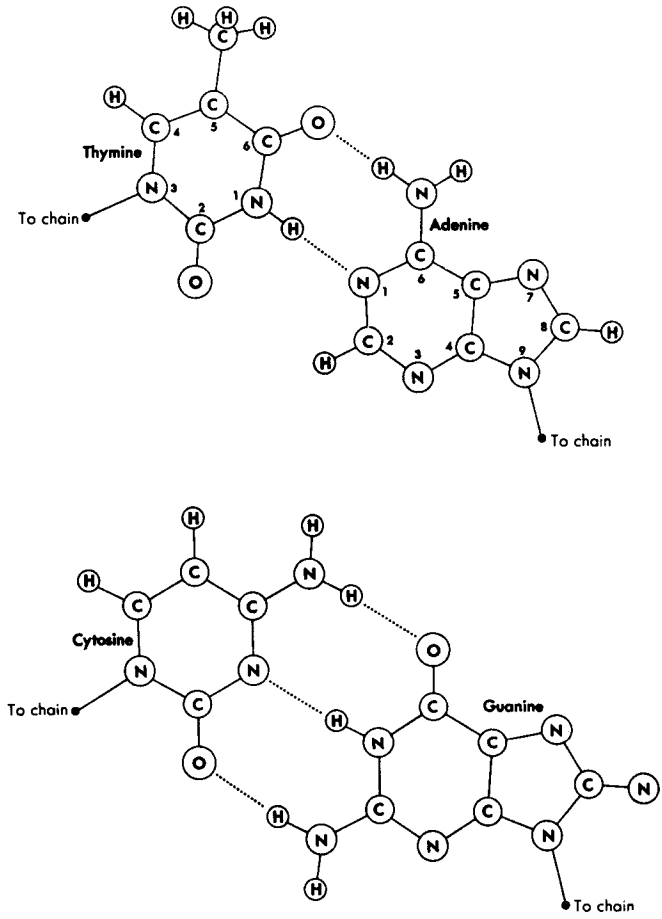
The immediately succeeding chapters deal with a more

general problem: what is the protein-synthesizing machinery and how does it read and translate the nucleic acid code into an accurate positioning of amino acids in the polypeptide chain of the protein? As background for appreciation of this topic, we discuss, in Chapter **2**, protein structure and the methods by which it is elucidated.

Watson–Crick base pairing

Recall the rules of specific base pairing (Watson–Crick pairing) in double-stranded DNA: adenine pairs with thymine and guanine pairs with cytosine (Fig. 1.1). Stahl's *The Mechanics of Inheritance* presents the evidence for the existence of these hydrogen-bonded base pairs in DNA and stresses their importance in DNA replication.

Fig. 1.1. The Watson–Crick base pairs in DNA: adenine-thymine and guanine-cytosine.



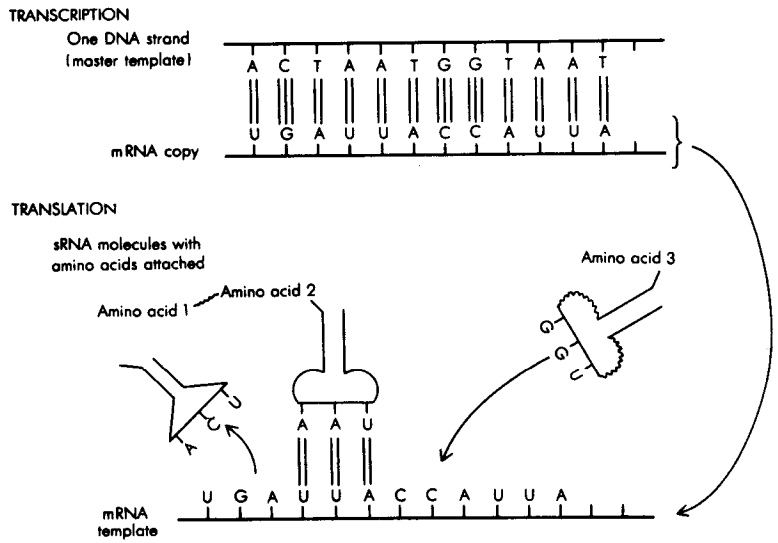


Fig. 1.2. Some principal steps in protein biosynthesis and the important roles base pairing (between adenine-uracil and guanine-cytosine) plays in the process.

Just as guanine pairs with cytosine in the two strands of the DNA double helix, so can a guanine in a DNA strand pair with a cytosine in a ribonucleic acid (RNA) strand (and vice versa). Similarly, the adenine of DNA can pair with the uracil in RNA, the thymine in DNA with the adenine in RNA. The basic hydrogen-bonding rules that apply to these DNA-RNA hybrid molecules are those that apply to the two strands of DNA itself. Two RNA strands also can form a duplex structure by similar rules.

These base-pairing rules provide a mechanism that is extremely important in the determination of the amino acid sequence of a polypeptide chain (Fig. 1.2). In protein biosynthesis, DNA (most likely only one strand of the duplex) serves as a template for a messenger RNA (mRNA) complement made in accordance with the pairing rules. The result is a DNA-RNA hybrid stage with a specific, inherited sequence of bases. The mRNA can then serve as a template upon which adaptor RNA (sRNA) molecules are oriented, in a sequence that also is determined by the Watson–Crick pairing rules. As a result of this step, the individual amino acids can be ordered in a specific sequence (or primary structure), for each sRNA molecule carries a specific amino acid. Finally, the amino acids are linked by peptide bonds to form a polypeptide chain. The amino acid sequence of this chain, then, has been dictated by the original DNA code, transcribed through messenger RNA, and translated by adaptor RNA through the mechanism provided by the base-pairing rules.

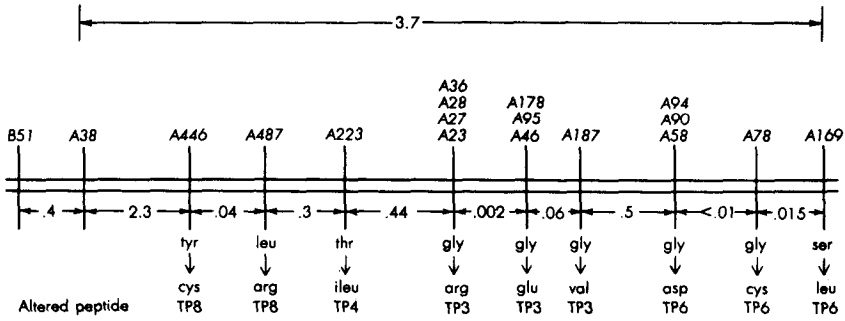


Fig. 1.3. The colinearity of mutationally altered sites in the A gene and amino acid substitutions in the A proteins of various mutants. Based on data from C. Yanofsky, B. C. Carlton, J. R. Guest, D. R. Helinski, and U. Henning, *Proc. Nat. Acad. Sci. U.S., 51* (1964), 266-72.

Implicit in this discussion is the concept of colinearity of gene structure and protein structure, which says that the linear sequence of nucleotides in the gene, and subsequently in the mRNA, specifies the linear sequence of amino acids in the protein. Until recently, this concept was unsupported by direct genetic and biochemical evidence. However, through the elegant studies of C. Yanofsky and his coworkers, strong evidence is now available for the *colinearity* of amino acids in the bacterial enzyme, tryptophan synthetase, and the gene that controls its structure. This has been accomplished, as shown in Fig. 1.3, by demonstrating that recombination distances between positions in the gene parallel the distances between affected amino acid residues in the protein. You might think about the importance and the significance of this observation as you read the chapters that follow.

In the next two chapters, we shall consider some of the basic chemistry of protein structure as well as certain aspects of protein biosynthesis you will need in later discussions.

References, including extensive introductions to microbial and biochemical genetics

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NOTE: Other volumes in this series are cited in each chapter to which they pertain. We recommend that you consult them for important background information and for discussions related to many topics in this book.

The legends to many of our figures contain references to the source of the material explicitly detailed therein. These sources generally are good starting points where you may find more information concerning the topic under discussion.

Protein Structure

From both a structural and a functional standpoint, proteins are a most important chemical constituent of cells. Enzymes, the proteins with catalytic activities, are largely responsible for the phenotype or properties of a cell in a particular environment. The genotype of a cell, its total genetic material, determines the *potential* types and relative amounts of protein the cell can produce. Thus, the environment influences the *expression* of the genetic potentialities of the cell, while the genotype sets limits on these potentialities.

In considering the types of proteins produced by a cell, we must take into account not only the particular catalytic activities of the proteins, but also other important features and properties of their structure that profoundly affect their role in cellular physiology. Proteins are immensely versatile macromolecules. Built into their structure is information that instructs them in "what to do" (catalytic activity), "where to go" in the cell (intracellular organization), and "when and how to perform" (control of function through interaction with other proteins, small activators, or inhibitors).

A single mutation in the genetic material may lead to a multitude of diverse effects on the phenotype of an organism. When these phenotypic changes have been traced back through the complex web of metabolism, they have been found to result from a simple but critical change in the structure of a single protein. Thus, the ultimate