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Genetics

Third Edition

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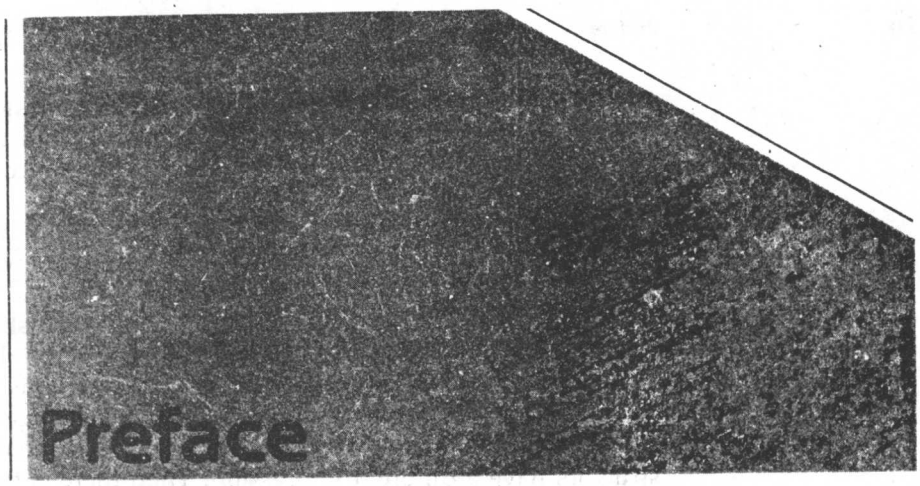
SAUNDERS COLLEGE PUBLISHING
Philadelphia New York Chicago
San Francisco Montreal Toronto
London Sydney Tokyo Mexico City
Rio de Janeiro Madrid
HOLT-SAUNDERS JAPAN



Preface

Do DNA sequences belong in a genetics textbook? This was the most important question I faced as I undertook writing a third edition of this text in the midst of the cloning/sequencing "revolution." The DNA sequences prevailed, as a glance through the text will indicate. My reasoning can be summarized as follows.

Genetics seems to have been embroiled in an identity crisis since 1953, when genes began to be actively analyzed as molecular units as well as heritable units of function. Scientists who studied the molecular properties of genes came to call themselves molecular biologists, whereas those who continued to study genes as heritable units of function called themselves geneticists. Pedagogical distinctions soon followed: molecular biology textbooks were devoid of mapping functions and epistasis, whereas genetics textbooks rarely mentioned histone phosphorylation or C_0t plots. A dichotomy also developed in teaching styles: whereas undergraduate courses in molecular biology were full of the "latest news," with relatively little attention paid to the development of the field, courses in genetics were usually taught in an historical fashion, with much emphasis placed on the intellectual approaches taken during and since Mendel's original experiments.

I have written this edition with the conviction that these distinctions are already obsolete in practice and should be made obsolete in the classroom. Molecular biologists, now able to clone genes at will and sequence them in weeks, have come knocking on the doors of geneticists to obtain strains with interesting genetic properties. Geneticists, meanwhile, have come to realize that gene fine structure will never again be productively tackled by the heroic genetic approaches of Benzer, Sherman, or Judd, and they are increasingly receptive to the knocks on the door from their molecular colleagues. Population geneticists are using restriction enzymes to detect polymorphisms; evolutionists are discovering that the genomes of modern organisms contain a rich fossil record of their genetic ancestry;

molecular biologists attend conferences on hybrid dysgenesis in *Drosophila* and the dissociator-activator system in maize. With the old distinctions rapidly blurring in the laboratory, why should they continue to be perpetrated on undergraduates?

I usually hear three answers to this question. One is the notion that the molecular material is "too hard," that students won't understand it. This is certainly true for non-science majors, for whom this text is definitely not written, but biology majors take required chemistry courses that provide ample background for understanding the principles of molecular genetics when they are carefully presented. Indeed, it is my experience that most students are able to understand the implications of a DNA sequence far more readily than a coefficient of coincidence, but perhaps other instructors have a different impression. Then there is the intellectual argument. Once students grasp the construction of a brilliant genetic proof, are they not better trained in science? I strongly agree that they are, and the text includes detailed presentations of many "strictly genetic" experiments. But if these experiments are presented in a molecular vacuum, then the training is incomplete: the student emerges steeped in genetic logic but has not been allowed to combine that logic with a knowledge of how genes are constructed and how they recombine, mutate, and express themselves.

Finally, it is argued that students will learn "that stuff" in another course. I agree that such subjects as DNA replication, renaturation kinetics, and sequencing are rightly considered in considerable depth in biochemistry and molecular biology courses. They are presented quite superficially in this text. It hardly follows, however, that genes should not be the focal subject of a genetics course.

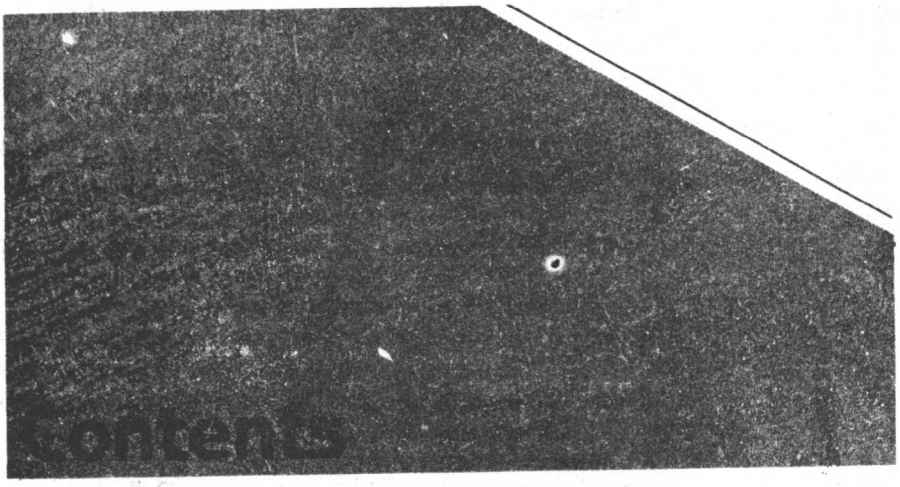
In a field moving as rapidly as genetics, it proves impossible to simply "update" a previous edition. Therefore, this is once again an almost entirely new book. Major changes from the second edition include the following:

1. New chapters have been added on somatic cell genetics, transposable elements, and immunogenetics, three of the most rapidly advancing fields in the past five years.
2. Such topics as mutation, recombination, chromosome structure, and gene structure are each presented in two chapters, the first giving a general overview and the second a more detailed molecular view (*see* Table of Contents). This should allow instructors more flexibility in determining the "molecular depth" of their assignments.
3. Population and quantitative genetics have been expanded considerably.
4. By popular request, Mendel's experiments are included *per se*.

I have been fortunate to obtain excellent critiques on the previous and current editions. Particular thanks go to Drs. Julian Adams (University of Michigan), Fred Allendorf (University of Montana), Alan Atherly (Iowa

State), C. William Birky (Ohio State), Barbara Brownstein (Temple University), Darrel Falk (Syracuse University), Peter Kuempel (University of Colorado), Gustavo Maroni (University of North Carolina), H. James Price (Texas A & M University), W. Stuart Riggsby (University of Tennessee), Raymond Rodriquez (University of California, Davis), Carol Sibley (University of Washington), Richard Siegal (U.C.L.A.), Edward Simon (Purdue University), Millard Susman (University of Wisconsin), Eric Weinberg (University of Pennsylvania), and Herbert Wiesmeyer (Vanderbilt University) for their overall reviews and to Drs. Douglas Berg (Washington University), Richard Borowsky (New York University), Nam-Hai Chua (Rockefeller University), Jeffrey Davidson (Eleanor Roosevelt Institute, Denver), W. J. Dickinson (University of Utah), John Drake (National Institute of Environmental Health Sciences), Sarah Elgin (Washington University), Nancy Martin (University of Texas, Dallas), Janice Pero and Vicki Sato (Harvard University), and Christopher Woodcock (University of Massachusetts, Amherst) for their individual chapter reviews. Michael Brown, Biology Editor at Saunders, provided important help at many stages in the production process.

This edition was written almost entirely in the serenity of Chilmark, Massachusetts, in the loving presence of my four children—Jason, Mathea, Jessica, and Thomas—and my husband, John Heuser. The book is the product of the peace of mind, and hence the clarity of thought, that they all bring to me.



The 20 chapters displayed in black present the "core material" of present-day genetics; the 8 chapters displayed in gray offer detailed presentations of topics in molecular genetics.

1 DNA (and RNA) as the Genetic Material in Chromosomes

Introduction

Today, when the terms **gene** or **genetics** are mentioned, most biologists immediately think of **DNA.** DNA, or **deoxyribonucleic acid,** is well known as the chemical bearer of genetic information; **RNA (ribonucleic acid)** serves this function in certain viruses.

In the history of genetics as a science, DNA became the center of attention only relatively recently. Focus first centered on **heredity,** on the patterns of inheritance of a given trait (blue eyes, red flower color, short tail) from parent to offspring. It was postulated that these inherited traits were somehow dictated by genes and that genes were linearly arranged along the chromosomes of higher animals and plants. "Maps" of gene order on chromosomes were constructed, and many of the details of gene transmission from generation to generation were worked out well before much was known about what a gene is and how it acts.

As the science of genetics developed, increased attention was given to how genes function, and more experimental use was made of microorganisms, notably bacteria and bacterial viruses. During this period it was proposed, with good evidence, that **the function of most genes is to specify the formation of proteins.** When it was eventually established that most genes are borne within molecules of DNA, primary attention was given to the chemical nature of the gene itself.

In beginning our text with DNA and RNA and in developing a molecular picture of genes and gene function at the same time as we establish patterns of heredity, we are, in one sense, violating the sequence set by scientific history. In another sense, of course, we are more closely following evolutionary history, since genes almost certainly developed their fundamental properties well before the hereditary patterns exhibited by modern organisms were established.

The Requirements to be Met by Genetic Material

Certain requirements must be met by any molecules if they are to qualify as the substances that transmit genetic information. These requirements extend directly from what is known about the continuity of species and the process of evolutionary change.

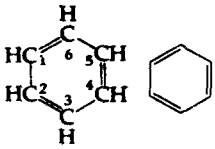
1. **Genetic material must contain biologically useful information that is maintained in a stable form.**
2. **Genetic information must be reproduced and transmitted faithfully** from cell to cell or from generation to generation.
3. **Genetic material must be able to express itself** so that other biological molecules, and ultimately cells and organisms, will be produced and maintained. Implicit in this requirement is that some mechanism be available for decoding, or translating, the information contained in the genetic material into its "productive" form. A narrow, but important, distinction is thus made between a molecule that can generate only its own kind and a molecule that can also generate new kinds of molecules. A salt crystal can "seed" a salt solution so that new salt crystals are formed, but this is the extent of its influence over its surroundings.
4. **Genetic material must be capable of variation.** This requirement is somewhat contradictory to the first requirement, which demanded stability of the genetic material. There is, in fact, no *a priori* reason why genetic material should have built-in provisions for change; one could certainly design a hypothetical genetic system in which information would be rigidly conserved from one generation to another. The dominant theme in the history of life is, however, organic evolution, and

this demands that genetic material be capable of change, if only infrequently.

Two sources of change have been recognized in present-day genetic systems: **mutations** and **recombination.** A mutation changes the nature of the information transmitted from parent to offspring and thus represents a relatively drastic way of bringing about variation. If the change is deleterious (and it usually is), the offspring may be greatly handicapped and may die soon after conception, or else it may introduce a deleterious gene into the population. Recombination is a more moderate way of producing variation. It occurs during the course of some sort of sexual process, and it involves the precise shuffling of parental genetic information such that new combinations of genes are produced. These are then inherited by the offspring.

With these four requirements in mind, we can study the physical and chemical properties of DNA and RNA, putting the molecular facts into a genetic context. Table 1-1 reviews some key definitions from organic chemistry that are relevant to the next few sections of this chapter.

TABLE 1-1 Definitions from Organic Chemistry

	Benzene ring, with = indicating double bonds where two carbon atoms share four electrons between them. The common abbreviated version of a benzene ring is shown at right.
$-CH_3$	Methyl group
$-OH$	Hydroxyl group
$=O$	Keto group
$-C(=O)H$	Aldehyde group
$-C(=O)-OH$	Carboxyl group, characteristically acidic ($-COO^-$)
$-NH_2$	Amino group, characteristically basic ($-NH_3^+$)
Covalent bond	A strong bond formed when two atoms share a pair of electrons between them.
Hydrogen bond	A weak attractive force between an electronegative (electron-seeking) atom (usually N or O) and a hydrogen atom covalently linked to a second electronegative atom (usually O—H or N—H).
Hydrolysis	Breaking a large molecule into two or more smaller molecules by adding water.

The Structure of DNA and RNA

1.1 The Polynucleotide

DNA and RNA are composed of two different classes of nitrogen-containing bases, the **purines** and the **pyrimidines.** The two most commonly occurring purines in DNA are **adenine** and **guanine,** and the common pyrimidines are **cytosine** and **thymine.** Their structures are shown in Figure 1-1. Thymine is not found in most species of RNA; instead, one finds the pyrimidine **uracil,** which is also shown in Figure 1-1. Modified forms of these bases (5-methyl cytosine, for example) are occasionally found as well, particularly in certain specialized forms of RNA described in Chapter 10.

The purines and the pyrimidines can be seen in Figure 1-1 to contain several conjugated double bonds. Molecules containing such bonds are potentially able to exist in a number of different chemical forms, for their hydrogen atoms have a certain freedom. A hydrogen atom can, for example, move away from an amino group (—NH_2), leaving an imino group (—NH) and a net negative charge that is absorbed by the conjugated ring system of the molecule. Such chemical fluctuations are called **tautomeric shifts,** and the different molecular structures that result are called **tautomers.** It turns out that under physiological conditions, the purines and pyrimidines exist almost invariably in the forms that have been drawn in Figure 1-1; the other tautomeric forms of these bases rarely occur. In other

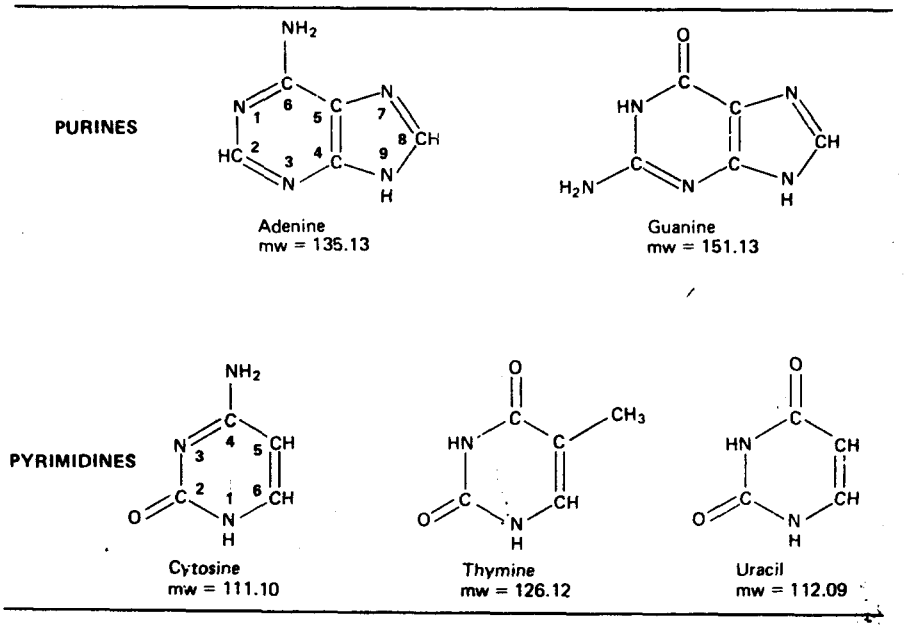


FIGURE 1-1 Purine and pyrimidine bases. Molecular weights (mw) are given in dalton units (see Table 1-2).