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INTRODUCTION

STUDY OBJECTIVES

1. To examine a brief overview of the modern history of genetics 3
2. To gain an overview of the topics included in this book—the syllabus of genetics 4
3. To analyze the scientific method 5
4. To look at why certain organisms and techniques have been used preferentially in genetics research 7

STUDY OUTLINE

Chameleon, *Cameleo pardalis*.

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Genetics is the study of inheritance in all of its manifestations, from the distribution of human traits in a family pedigree to the biochemistry of the genetic material in our chromosomes—deoxyribonucleic acid, or DNA. It is our purpose in this book to introduce and describe the processes and patterns of inheritance. In this chapter, we present a broad outline of the topics to be covered as well as a summary of some of the more important historical advancements leading to our current understanding of genetics.

A BRIEF OVERVIEW OF THE MODERN HISTORY OF GENETICS

For a generation of students born at a time when incredible technological advances are commonplace, it is valuable to see how far we have come in understanding the mechanisms of genetic processes by taking a very brief, encapsulated look at the modern history of genetics. Although we could discuss prehistoric concepts of animal and plant breeding and ideas going back to the ancient Greeks, we will restrict our brief look to events beginning with the discovery of cells and microscopes. For our purposes, we divide this recent history into four periods: before 1860, 1860–1900, 1900–1944, and 1944 to the present.

Before 1860

Before 1860, the most notable discoveries paving the way for our current understanding of genetics were the development of light microscopy, the elucidation of the cell theory, and the publication in 1859 of Charles Darwin's *The Origin of Species.* In 1665, Robert Hooke coined the term *cell* in his studies of cork. Hooke saw, in fact, empty cells observed at a magnification of about thirty power. Between 1674 and 1683, Anton van Leeuwenhoek discovered living organisms (protozoa and bacteria) in rainwater. Leeuwenhoek was a master lens maker and produced magnifications of several hundred power from single lenses (fig. 1.1). More than a hundred years passed before compound microscopes could equal Leeuwenhoek's magnifications. In 1833, Robert Brown (the discoverer of Brownian motion) discovered the nuclei of cells, and between 1835 and 1839, Hugo von Mohl described mitosis in nuclei. This era ended in 1858, when Rudolf Virchow summed up the concept of the cell theory with his Latin aphorism *omnis cellula e cellula:* all cells come from preexisting cells. Thus, by 1858, biologists had an understanding of the continuity of cells and knew of the cell's nucleus.

1860–1900

The period from 1860 to 1900 encompasses the publication of Gregor Mendel's work with pea plants in 1866 to the rediscovery of his work in 1900. It includes the discoveries of chromosomes and their behavior—insights that shed new light on Mendel's research.

From 1879 to 1885, with the aid of new staining techniques, W. Flemming described the chromosomes—first noticed by C. von Nägeli in 1842—including the way they split during division, and the separation of sister chromatids and their movement to opposite poles of the dividing cell during mitosis. In 1888, W. Waldeyer first used the term *chromosome.* In 1875, O. Hertwig described the fusion of sperm and egg to form the zygote. In the 1880s, Theodor Boveri, as well as K. Rabl and E. van Breden, hypothesized that chromosomes are individual structures with continuity from one generation to the next despite their "disappearance" between cell divisions. In 1885, August Weismann stated that inheritance is based exclusively in the nucleus. In 1887, he predicted the occurrence of a reductional division, which we now call meiosis. By 1890, O. Hertwig and T. Boveri had described the process of meiosis in detail.

1900–1944

From 1900 to 1944, modern genetics flourished with the development of the chromosomal theory, which showed

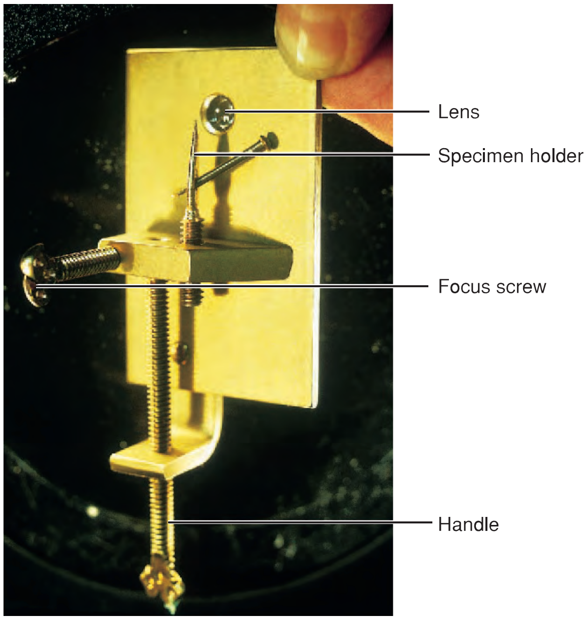

Figure 1.1 One of Anton van Leeuwenhoek's microscopes, ca. 1680. This single-lensed microscope magnifies up to 200x. (© Kathy Talaro/Visuals Unlimited, Inc.)

that chromosomes are linear arrays of genes. In addition, the foundations of modern evolutionary and molecular genetics were derived.

In 1900, three biologists working independently—Hugo de Vries, Carl Correns, and Erich von Tschermak—rediscovered Mendel's landmark work on the rules of inheritance, published in 1866, thus beginning our era of modern genetics. In 1903, Walter Sutton hypothesized that the behavior of chromosomes during meiosis explained Mendel's rules of inheritance, thus leading to the discovery that genes are located on chromosomes. In 1913, Alfred Sturtevant created the first genetic map, using the fruit fly. He showed that genes existed in a linear order on chromosomes. In 1927, L. Stadler and H. J. Muller showed that genes can be mutated artificially by X rays.

Between 1930 and 1932, R. A. Fisher, S. Wright, and J. B. S. Haldane developed the algebraic foundations for our understanding of the process of evolution. In 1943, S. Luria and M. Delbrück demonstrated that bacteria have normal genetic systems and thus could serve as models for studying genetic processes.

1944–Present

The period from 1944 to the present is the era of molecular genetics, beginning with the demonstration that DNA is the genetic material and culminating with our current explosion of knowledge due to recombinant DNA technology.

In 1944, O. Avery and colleagues showed conclusively that deoxyribonucleic acid—DNA—was the genetic material. James Watson and Francis Crick worked out the structure of DNA in 1953. Between 1968 and 1973, W. Arber, H. Smith, and D. Nathans, along with their colleagues, discovered and described restriction endonucleases, the enzymes that opened up our ability to manipulate DNA through recombinant DNA technology. In 1972, Paul Berg was the first to create a recombinant DNA molecule.

Since 1972, geneticists have cloned numerous genes. Scientists now have the capability to create transgenic organisms, organisms with functioning foreign genes. For example, we now have farm animals that produce pharmaceuticals in their milk that are harvested easily and inexpensively for human use. In 1997, the first mammal was cloned, a sheep named Dolly. The sequence of the entire human genome was determined in 2000; we will spend the next century mining its information in the newly created field of genomics, the study of the complete genetic complement of an organism. Although no inherited disease has yet been cured by genetic intervention, we are on the verge of success in numerous diseases, including cancer.

The material here is much too brief to convey any of the detail or excitement surrounding the discoveries of modern genetics. Throughout this book, we will expand on the discoveries made since Darwin first published his book on evolutionary theory in 1859 and since Mendel was rediscovered in 1900.

THE THREE GENERAL AREAS OF GENETICS

Historically, geneticists have worked in three different areas, each with its own particular problems, terminology, tools, and organisms. These areas are classical genetics, molecular genetics, and evolutionary genetics. In *classical genetics,* we are concerned with the chromosomal theory of inheritance; that is, the concept that genes are

Table 1.1 **The Three Major Areas of Genetics—Classical, Molecular, and Evolutionary—and the Topics They Cover**

Classical Genetics	Molecular Genetics	Evolutionary Genetics
Mendel's principles	Structure of DNA	Quantitative genetics
Meiosis and mitosis	Chemistry of DNA	Hardy-Weinberg equilibrium
Sex determination	Transcription	Assumptions of equilibrium
Sex linkage	Translation	Evolution
Chromosomal mapping	DNA cloning and genomics	Speciation
Cytogenetics (chromosomal changes)	Control of gene expression	
	DNA mutation and repair	
	Extrachromosomal inheritance	

located in a linear fashion on chromosomes and that the relative positions of genes can be determined by their frequency in offspring. *Molecular genetics* is the study of the genetic material: its structure, replication, and expression, as well as the information revolution emanating from the discoveries of recombinant DNA techniques (genetic engineering, including the Human Genome Project). *Evolutionary genetics* is the study of the mechanisms of evolutionary change, or changes in gene frequencies in populations. Darwin's concept of evolution by natural selection finds a firm genetic footing in this area of the study of inheritance (table 1.1).

Today these areas are less clearly defined because of advances made in molecular genetics. Information coming from the study of molecular genetics allows us to understand better the structure and functioning of chromosomes on the one hand and the mechanism of natural selection on the other. In this book we hope to bring together this information from a historical perspective. From Mendel's work in discovering the rules of inheritance (chapter 2) to genetic engineering (chapter 13) to molecular evolution (chapter 21), we hope to present a balanced view of the various topics that make up genetics.

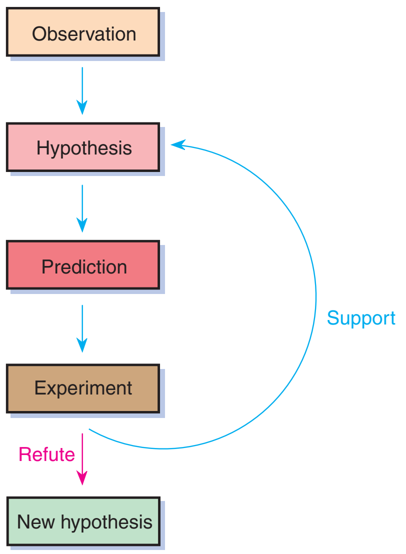

Figure 1.2 A schematic of the scientific method. An observation leads the researcher to propose a hypothesis, and then to make predictions from the hypothesis and to test these predictions by experiment. The results of the experiment either support or refute the hypothesis. If the experiment refutes the hypothesis, a new hypothesis must be developed. If the experiment supports the hypothesis, the researcher or others design further experiments to try to disprove it.

HOW DO WE KNOW?

Genetics is an empirical science, which means that our information comes from observations of the natural world. The *scientific method* is a tool for understanding these observations (fig. 1.2). At its heart is the experiment, which tests a guess, called a hypothesis, about how something works. In a good experiment, only two types of outcomes are possible: outcomes that support the hypothesis and outcomes that refute it. Scientists say these outcomes provide *strong inference.*

For example, you might have the idea that organisms can inherit acquired characteristics, an idea put forth by Jean-Baptiste Lamarck (1744–1829), a French biologist. Lamarck used the example of short-necked giraffes evolving into the long-necked giraffes we know of today. He suggested that giraffes that reached higher into trees to get at edible leaves developed longer necks. They passed on these longer necks to their offspring (in small increments in each generation), leading to today's long-necked giraffes. An alternative view, *evolution by natural selection,* was put forward in 1859 by Charles Darwin. According to the Darwinian view, giraffes normally varied in neck length, and these variations were inherited. Giraffes with slightly longer necks would be at an advantage in reaching edible leaves in trees. Therefore, over time, the longer-necked giraffes would survive and reproduce better than the shorter-necked ones. Thus, longer necks would come to predominate. Any genetic *mutations* (changes) that introduced greater neck length would be favored.

To test Lamarck's hypothesis, you might begin by designing an experiment. You could do the experiment on giraffes to test Lamarck's hypothesis directly; however, giraffes are difficult to acquire, maintain, and breed. Remember, though, that you are testing a general hypothesis about the inheritance of acquired characteristics rather than a specific hypothesis about giraffes. Thus, if you are clever enough, you can test the hypothesis with almost any organism. You would certainly choose one that is easy to maintain and manipulate experimentally. Later, you can verify the generality of any particular conclusions with tests on other organisms.

You might decide to use lab mice, which are relatively inexpensive to obtain and keep and have a relatively short generation time of about six weeks, compared with the giraffe's gestation period of over a year. Instead of looking at neck length, you might simply cut off the tip of the tail of each mouse (in a painless manner), using shortened tails as the acquired characteristic. You could then

BOX 1.1

Ethics and Genetics

The Lysenko Affair

As the pictures of geneticists throughout this book indicate, science is a very human activity; people living within societies explore scientific ideas and combine their knowledge. The society in which a scientist lives can affect not only how that scientist perceives the world, but also what that scientist can do in his or her scholarly activities. For example, the United States and other countries decided that mapping the entire human genome would be valuable (see chapter 13). Thus, granting agencies have directed money in this direction. Since much of scientific research is expensive, scientists often can only study areas for which funding is available. Thus, many scientists are working on the Human Genome Project. That is a positive example of society directing research. Examples also exist in which a societal decision has had negative consequences for both the scientific establishment and the society itself. An example is the Lysenko affair in the former Soviet Union during Stalin's and Krushchev's reigns.

Trofim Denisovich Lysenko was a biologist in the former Soviet Union researching the effects of temperature on plant development. At the same time, the preeminent Soviet geneticist was Nikolai Vavilov. Vavilov was interested in improving Soviet crop yields by growing and mating many varieties and selecting the best to be the breeding stock of the next generation. This is the standard way of improving a plant crop or livestock breed (see chapter 18, "Quantitative Inheritance"). The method conforms to genetic principles and therefore is successful. However, it is a slow process that only gradually improves yields.

Lysenko suggested that crop yields could be improved quickly by the inheritance of acquired characteristics (see chapter 21, "Evolution and Speciation"). Although doomed to fail because they denied the true and correct mechanisms of inheritance, Lysenko's ideas were greeted with much enthusiasm by the political elite. The enthusiasm was due not only to the fact that Lysenko promised immediate improvements in crop yields, but also to the fact that Lysenkoism was politically favored. That is, Lysenkoism fit in very well with communism; it promised that nature could be manipulated easily and immediately. If people could manipulate nature so easily, then communism could easily convert people to its doctrines.

Not only did Stalin favor Lysenkoism, but Lysenko himself was favored politically over Vavilov because Lysenko came from peasant stock, whereas Vavilov was from a wealthy family. (Remember that communism

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mate these short-tailed mice to see if their offspring have shorter tails. If they do not, you could conclude that a shortened tail, an acquired characteristic, is not inherited. If, however, the next generation of mice have tails shorter than those of their parents, you could conclude that acquired characteristics can be inherited.

One point to note is that every good experiment has a *control,* a part of the experiment that ensures that some unknown variable, often specific to a particular time and place, is not causing the observed changes. For example, in your experiment, the particular food the mice ate may have had an effect on their growth, resulting in offspring with shorter tails. To control for this, you could handle a second group of mice in the exact same way that the experimental mice are handled, except you would not cut off their tails. Any reduction in the lengths of the tails of the offspring of the control mice would indicate an artifact of the experiment rather than the inheritance of acquired characteristics.

The point of doing this experiment (with the control group), as trivial as it might seem, is to determine the answer to a question using data based on what happens in nature. If you design your experiment correctly and carry it out without error, you can be confident about your results. If your results are negative, as ours would be here, then you would reject your hypothesis. Testing hypotheses and rejecting those that are refuted is the essence of the scientific method.

In fact, most of us live our lives according to the scientific method without really thinking about it. For example, we know better than to step out into traffic without looking because we are aware, from experience (observation, experimentation), of the validity of the laws of physics. Although from time to time anti-intellectual movements spread through society, few people actually give up relying on their empirical knowledge of the world to survive (box 1.1).

Nothing in this book is inconsistent with the scientific method. Every fact has been gained by experiment or observation in the real world. If you do not accept something said herein, you can go back to the *original literature,* the published descriptions of original experiwas a revolution of the working class over the wealthy aristocracy.) Supported by Stalin, and then Krushchev, Lysenko gained inordinate power in his country. All visible genetic research in the former Soviet Union was forced to conform to Lysenko's Lamarckian views. People who disagreed with him were forced out of power; Vavilov was arrested in 1940 and died in prison in 1943. It was not until Nikita Krushchev lost power in 1964 that Lysenkoism fell out of favor. Within months, Lysenko's failed pseudoscience was repudiated and Soviet genetics got back on track.

For thirty years, Soviet geneticists were forced into fruitless endeavors, forced out of genetics altogether, or punished for their heterodox views. Superb scientists died in prison while crop improvement programs failed, all because the Soviet dictators favored Lysenkoism. The message of this affair is clear: Politicians can support research that agrees with their political agenda and punish scientists doing research that disagrees with this agenda, but politicians cannot change the truth of the laws of nature. Science, to be effective, must be done in a climate of open inquiry and free expression of ideas. The scientific method cannot be subverted by political bullies.

Trofim Denisovich Lysenko (1898–1976) shows branched wheat to collective farmers in the former Soviet Union. (© SOVFOTO.)

ments in scientific journals (as cited at the end of the book) and read about the work yourself. If you still don't believe a conclusion, you can repeat the work in question either to verify or challenge it. This is in keeping with the nature of the scientific method.

As mentioned, the results of experimental studies are usually published in scientific journals. Examples of journals that many geneticists read include *Genetics, Proceedings of the National Academy of Sciences, Science, Nature, Evolution, Cell, American Journal of Human Genetics, Journal of Molecular Biology,* and hundreds more. The reported research usually undergoes a process called *peer review* in which other scientists review an article before it is published to ensure its accuracy and its relevance. Scientific articles usually include a detailed justification for the work, an outline of the methods that allows other scientists to repeat the work, the results, a discussion of the significance of the results, and citations of prior work relevant to the present study.

At the end of this book, we cite journal articles describing research that has contributed to each chapter. (In chapter 2, we reprint part of Gregor Mendel's work, and in chapter 9, we reprint a research article by J. Watson and F. Crick in its entirety.) We also cite secondary sources, that is, journals and books that publish syntheses of the literature rather than original contributions. These include *Scientific American, Annual Review of Biochemistry, Annual Review of Genetics, American Scientist,* and others. You are encouraged to look at all of these sources in your efforts both to improve your grasp of genetics and to understand how science progresses.

WHY FRUIT FLIES AND COLON BACTERIA?

As you read this book, you will see that certain organisms are used repeatedly in genetic experiments. If the goal of science is to uncover generalities about the living world, why do geneticists persist in using the same few organisms

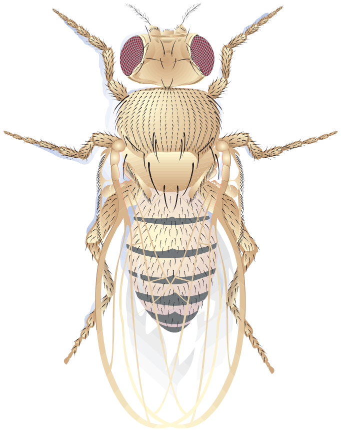

Figure 1.3 Adult female fruit fly, *Drosophila melanogaster.* Mutations of eye color, bristle type and number, and wing characteristics are easily visible when they occur.

Figure 1.4 Scanning electron micrograph of *Escherichia coli* bacteria. These rod-shaped bacilli are magnified 18,000x.
(© K. G. Murti/Visuals Unlimited, Inc.)

in their work? The answer is probably obvious: the organisms used for any particular type of study have certain attributes that make them desirable *model organisms* for that research.

In the early stages of genetic research, at the turn of the century, no one had yet developed techniques to do genetic work with microorganisms or mammalian cells. At that time, the organism of preference was the fruit fly, *Drosophila melanogaster,* which developmental biologists had used (fig. 1.3). It has a relatively short generation time of about two weeks, survives and breeds well in the lab, has very large chromosomes in some of its cells, and has many aspects of its *phenotype* (appearance) genetically controlled. For example, it is easy to see the external results of mutations of genes that control eye color, bristle number and type, and wing characteristics such as shape or vein pattern in the fruit fly.

At the middle of this century, when geneticists developed techniques for genetic work on bacteria, the common colon bacterium, *Escherichia coli,* became a favorite organism of genetic researchers (fig. 1.4). Because it had a generation time of only twenty minutes and only a small amount of genetic material, many research groups used it in their experiments. Still later, bacterial viruses, called *bacteriophages,* became very popular in genetics labs. The viruses are constructed of only a few types of protein molecules and a very small amount of genetic material. Some can replicate a hundredfold in an hour. Our point is not to list the major organisms geneticists use, but to suggest why they use some so commonly. Comparative studies are usually done to determine which generalities discovered in the elite genetic organisms are really scientifically universal.

TECHNIQUES OF STUDY

Each area of genetics has its own particular techniques of study. Often the development of a new technique, or an improvement in a technique, has opened up major new avenues of research. As our technology has improved over the years, geneticists and other scientists have been able to explore at lower and lower levels of biological organization. Gregor Mendel, the father of genetics, did simple breeding studies of plants in a garden at his monastery in Austria in the middle of the nineteenth century. Today, with modern biochemical and biophysical techniques, it has become routine to determine the sequence of *nucleotides* (molecular subunits of DNA and RNA) that make up any particular gene. In fact, one of the most ambitious projects ever carried out in genetics is the mapping of the human genome, all 3.3 billion nucleotides that make up our genes. Only recently was the technology available to complete a project of this magnitude.

CLASSICAL, MOLECULAR, AND EVOLUTIONARY GENETICS

In the next three sections, we briefly outline the general subject areas covered in the book: classical, molecular, and evolutionary genetics.

Classical Genetics

Gregor Mendel discovered the basic rules of transmission genetics in 1866 by doing carefully controlled breeding experiments with the garden pea plant, *Pisum sativum.* He found that traits, such as pod color, were controlled by genetic elements that we now call *genes* (fig. 1.5). Alternative forms of a gene are called *alleles.* Mendel also discovered that adult organisms have two copies of each gene (*diploid* state); gametes receive just one of these copies (*haploid* state). In other words, one of the two parental copies segregates into any given gamete. Upon fertilization, the zygote gets one copy from each gamete, reconstituting the diploid number (fig. 1.6). When Mendel looked at the inheritance of several

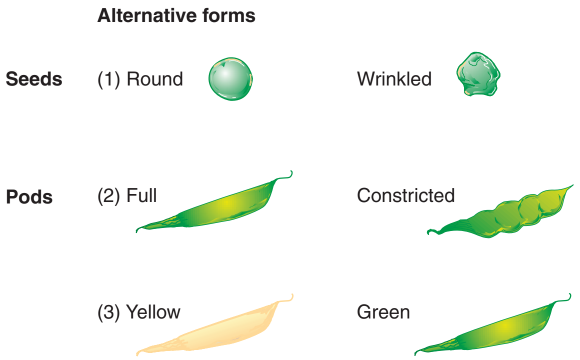

Figure 1.5 Mendel worked with garden pea plants. He observed seven traits of the plant—each with two discrete forms—that affected attributes of the seed, the pod, and the stem. For example, all plants had either round or wrinkled seeds, full or constricted pods, or yellow or green pods.

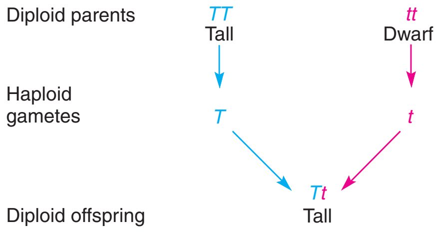

Figure 1.6 Mendel crossed tall and dwarf pea plants, demonstrating the rule of segregation. A diploid individual with two copies of the gene for tallness (*T*) per cell forms gametes that all have the *T* allele. Similarly, an individual that has two copies of the gene for shortness (*t*) forms gametes that all have the *t* allele. Cross-fertilization produces zygotes that have both the *T* and *t* alleles. When both forms are present (*Tt*), the plant is tall, indicating that the *T* allele is *dominant* to the *recessive t* allele.

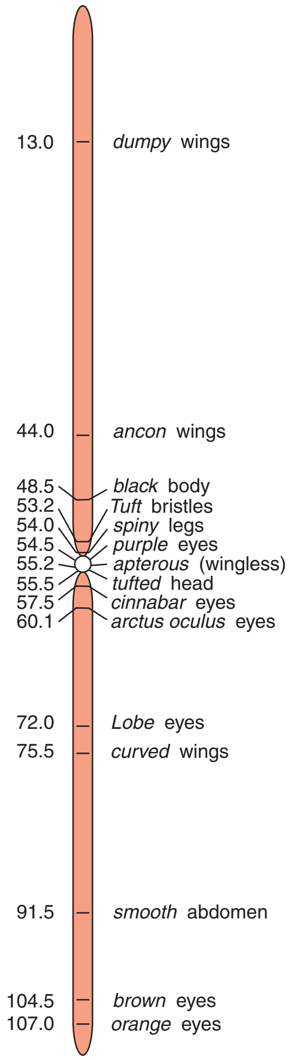

Figure 1.7 Genes are located in linear order on chromosomes, as seen in this diagram of chromosome 2 of *Drosophila melanogaster,* the common fruit fly. The centromere is a constriction in the chromosome. The numbers are map units.

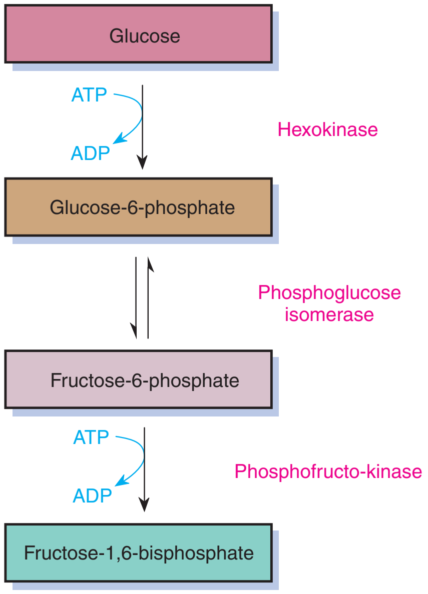

Figure 1.8 Biochemical pathways are the sequential changes that occur in compounds as cellular reactions modify them. In this case, we show the first few steps in the glycolytic pathway that converts glucose to energy. The pathway begins when glucose + ATP is converted to glucose-6-phosphate + ADP with the aid of the enzyme hexokinase. The enzymes are the products of genes.

traits at the same time, he found that they were inherited independently of each other. His work has been distilled into two rules, referred to as *segregation* and *independent assortment.* Scientists did not accept Mendel's work until they developed an understanding of the segregation of chromosomes during the latter half of the nineteenth century. At that time, in the year 1900, the science of genetics was born.

During much of the early part of this century, geneticists discovered many genes by looking for changed organisms, called *mutants.* Crosses were made to determine the genetic control of mutant traits. From this research evolved chromosomal mapping, the ability to locate the relative positions of genes on chromosomes by crossing certain organisms. The proportion of recombinant offspring, those with new combinations of parental alleles, gives a measure of the physical separation between genes on the same chromosomes in distances called *map units.* From this work arose the chromosomal theory of inheritance: Genes are located at fixed positions on chromosomes in a linear order (fig. 1.7, p. 9). This "beads on a string" model of gene arrangement was not modified to any great extent until the middle of this century, after Watson and Crick worked out the structure of DNA.

In general, genes function by controlling the synthesis of proteins called *enzymes* that act as biological catalysts in biochemical pathways (fig. 1.8). G. Beadle and E. Tatum suggested that one gene controls the formation of one enzyme. Although we now know that many proteins are made up of subunits—the products of several genes—and that some genes code for proteins that are not enzymes and other genes do not code for proteins, the *one-gene-one-enzyme* rule of thumb serves as a general guideline to gene action.

Molecular Genetics

With the exception of some viruses, the genetic material of all cellular organisms is double-stranded DNA, a double helical molecule shaped like a twisted ladder. The backbones of the helices are repeating units of sugars (deoxyribose) and phosphate groups. The rungs of the

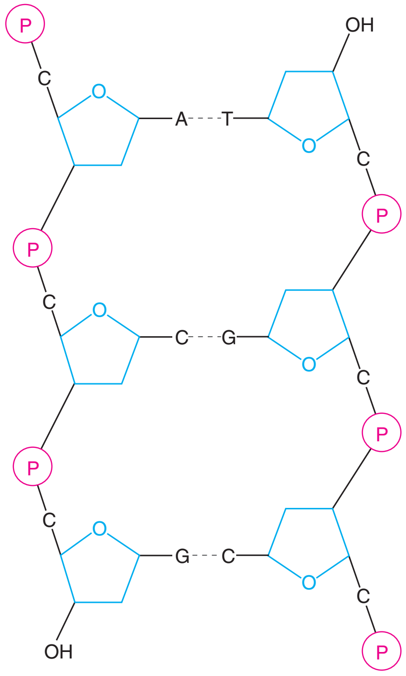

Figure 1.9 A look at a DNA double helix, showing the sugar-phosphate units that form the molecule's "backbone" and the base pairs that make up the "rungs." We abbreviate a phosphate group as a "P" within a circle; the pentagonal ring containing an oxygen atom is the sugar deoxyribose. Bases are either adenine, thymine, cytosine, or guanine (A, T, C, G).

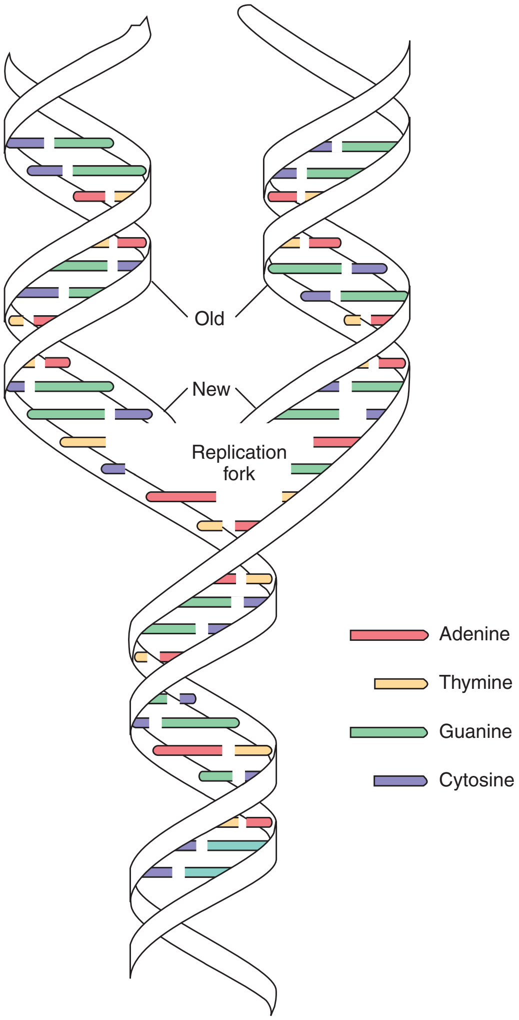

Figure 1.10 The DNA double helix unwinds during replication, and each half then acts as a template for a new double helix. Because of the rules of complementarity, each new double helix is identical to the original, and the two new double helices are identical to each other. Thus, an AT base pair in the original DNA double helix replicates into two AT base pairs, one in each of the daughter double helices.

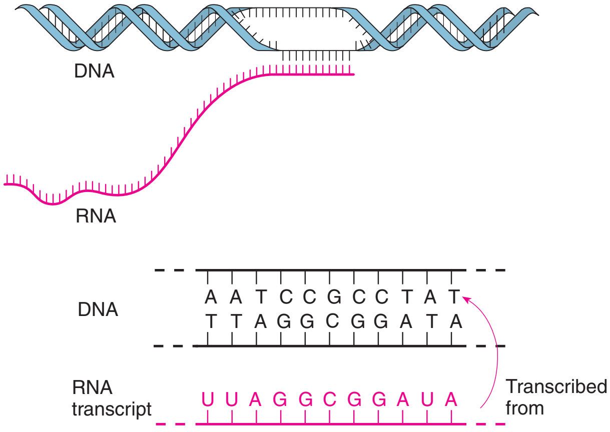

Figure 1.11 Transcription is the process that synthesizes RNA from a DNA template. Synthesis proceeds with the aid of the enzyme RNA polymerase. The DNA double helix partially unwinds during this process, allowing the base sequence of one strand to serve as a template for RNA synthesis. Synthesis follows the rules of DNA-RNA complementarity: A, T, G, and C of DNA pair with U, A, C, and G, respectively, in RNA. The resulting RNA base sequence is identical to the sequence that would form if the DNA were replicating instead, with the exception that RNA replaces thymine (T) with uracil (U).

ladder are base pairs, with one base extending from each backbone (fig. 1.9). Only four bases normally occur in DNA: adenine, thymine, guanine, and cytosine, abbreviated A, T, G, and C, respectively. There is no restriction on the order of bases on one strand. However, a relationship called *complementarity* exists between bases forming a rung. If one base of the pair is adenine, the other must be thymine; if one base is guanine, the other must be cytosine. James Watson and Francis Crick deduced this structure in 1953, ushering in the era of molecular genetics.

The complementary nature of the base pairs of DNA made the mode of replication obvious to Watson and Crick: The double helix would "unzip," and each strand would act as a template for a new strand, resulting in two double helices exactly like the first (fig. 1.10). Mutation, a change in one of the bases, could result from either an error in base pairing during replication or some damage to the DNA that was not repaired by the time of the next replication cycle.

Information is encoded in DNA in the sequence of bases on one strand of the double helix. During gene expression, that information is *transcribed* into RNA, the other form of nucleic acid, which actually takes part in protein synthesis. RNA differs from DNA in several respects: it has the sugar ribose in place of deoxyribose; it has the base uracil (U) in place of thymine (T); and it usually occurs in a single-stranded form. RNA is transcribed from DNA by the enzyme *RNA polymerase,* using DNA-RNA rules of complementarity: A, T, G, and C in DNA pair with U, A, C, and G, respectively, in RNA (fig. 1.11). The DNA information that is transcribed into RNA codes for the amino acid sequence of proteins. Three nucleotide bases form a *codon* that specifies one of the twenty

Table 1.2 The Genetic Code Dictionary of RNA

Codon	Amino Acid	Codon	Amino Acid	Codon	Amino Acid	Codon	Amino Acid
UUU	Phe	UCU	Ser	UAU	Tyr	UGU	Cys
UUC	Phe	UCC	Ser	UAC	Tyr	UGC	Cys
UUA	Leu	UCA	Ser	UAA	STOP	UGA	STOP
UUG	Leu	UCG	Ser	UAG	STOP	UGG	Trp
CUU	Leu	CCU	Pro	CAU	His	CGU	Arg
CUC	Leu	CCC	Pro	CAC	His	CGC	Arg
CUA	Leu	CCA	Pro	CAA	Gln	CGA	Arg
CUG	Leu	CCG	Pro	CAG	Gln	CGG	Arg
AUU	Ile	ACU	Thr	AAU	Asn	AGU	Ser
AUC	Ile	ACC	Thr	AAC	Asn	AGC	Ser
AUA	Ile	ACA	Thr	AAA	Lys	AGA	Arg
AUG	Met (START)	ACG	Thr	AAG	Lys	AGG	Arg
GUU	Val	GCU	Ala	GAU	Asp	GGU	Gly
GUC	Val	GCC	Ala	GAC	Asp	GGC	Gly
GUA	Val	GCA	Ala	GAA	Glu	GGA	Gly
GUG	Val	GCG	Ala	GAG	Glu	GGG	Gly

Note: A codon, specifying one amino acid, is three bases long (read in RNA bases in which U replaced the T of DNA). There are sixty-four different codons, specifying twenty naturally occurring amino acids (abbreviated by three letters: e.g., Phe is phenylalanine—see fig. 11.1 for the names and structures of the amino acids). Also present is *stop* (UAA, UAG, UGA) and *start* (AUG) information.

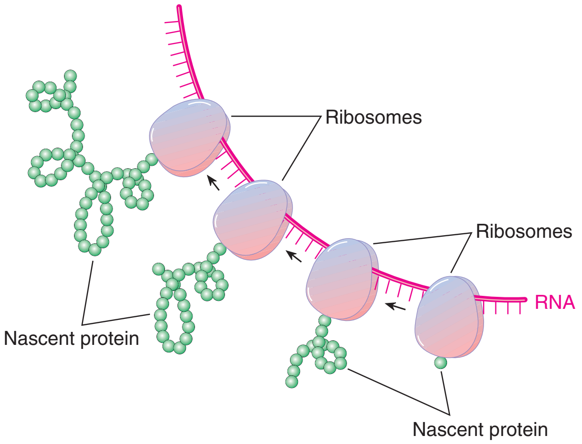

Figure 1.12 In prokaryotes, RNA translation begins shortly after RNA synthesis. A ribosome attaches to the RNA and begins reading the RNA codons. As the ribosome moves along the RNA, amino acids attach to the growing protein. When the process is finished, the completed protein is released from the ribosome, and the ribosome detaches from the RNA. As the first ribosome moves along, a second ribosome can attach at the beginning of the RNA, and so on, so that an RNA strand may have many ribosomes attached at one time.

naturally occurring amino acids used in protein synthesis. The sequence of bases making up the codons are referred to as the genetic code (table 1.2).

The process of *translation,* the decoding of nucleotide sequences into amino acid sequences, takes place at the ribosome, a structure found in all cells that is made up of RNA and proteins (fig. 1.12). As the RNA moves along the ribosome one codon at a time, one amino acid attaches to the growing protein for each codon.

The major control mechanisms of gene expression usually act at the transcriptional level. For transcription to take place, the RNA polymerase enzyme must be able to pass along the DNA; if this movement is prevented, transcription stops. Various proteins can bind to the DNA, thus preventing the RNA polymerase from continuing, providing a mechanism to control transcription. One particular mechanism, known as the *operon model,* provides the basis for a wide range of control mechanisms in prokaryotes and viruses. Eukaryotes generally contain no operons; although we know quite a bit about some control systems for eukaryotic gene expression, the general rules are not as simple.

In recent years, there has been an explosion of information resulting from *recombinant DNA techniques.* This revolution began with the discovery of *restriction endonucleases,* enzymes that cut DNA at specific sequences. Many of these enzymes leave single-stranded ends on the cut DNA. If a restriction enzyme acts on both a *plasmid,* a small, circular extrachromosomal unit found in some bacteria, and another piece of DNA (called foreign DNA), the two will be left with identical single-stranded free ends. If the cut plasmid and cut foreign DNA are mixed together, the free ends can re-form double helices, and the plasmid can take in a single piece of foreign DNA (fig. 1.13). Final repair processes create a completely closed circle of DNA. The hybrid plasmid is then reinserted into the bacterium. When the bacterium grows, it replicates the plasmid DNA, producing many copies of the foreign DNA. From that point, the foreign DNA can be isolated and sequenced, allowing researchers to determine the exact order of bases making up the foreign DNA. (In 2000, scientists announced the complete sequencing of the human genome.) That sequence can tell us much about how a gene works. In addition, the foreign genes can function within the bacterium, resulting in bacteria expressing the foreign genes and producing their protein products. Thus we have, for example, *E. coli* bacteria that produce human growth hormone.

This technology has tremendous implications in medicine, agriculture, and industry. It has provided the opportunity to locate and study disease-causing genes, such as the genes for cystic fibrosis and muscular dystrophy, as well as suggesting potential treatments. Crop plants and farm animals are being modified for better productivity by improving growth and disease resistance. Industries that apply the concepts of genetic engineering are flourishing.

One area of great interest to geneticists is cancer research. We have discovered that a single gene that has lost its normal control mechanisms (an *oncogene*) can cause changes that lead to cancer. These oncogenes exist normally in noncancerous cells, where they are called proto-oncogenes, and are also carried by viruses, where they are called viral oncogenes. Cancer-causing viruses are especially interesting because most of them are of the RNA type. AIDS is caused by one of these RNA viruses, which attacks one of the cells in the immune system. Cancer can also occur when genes that normally prevent cancer, genes called anti-oncogenes, lose function. Discovering the mechanism by which our immune system can produce millions of different protective proteins (*antibodies*) has been another success of modern molecular genetics.

Evolutionary Genetics

From a genetic standpoint, evolution is the change in allelic frequencies in a population over time. Charles Darwin described evolution as the result of natural selection. In the 1920s and 1930s, geneticists, primarily Sewall Wright, R. A. Fisher, and J. B. S. Haldane, provided algebraic models to describe evolutionary processes. The marriage of Darwinian theory and population genetics has been termed *neo-Darwinism.*

In 1908, G. H. Hardy and W. Weinberg discovered that a simple genetic equilibrium occurs in a population if the population is large, has random mating, and has negligible effects of mutation, migration, and natural selection. This equilibrium gives population geneticists a baseline for comparing populations to see if any evolutionary

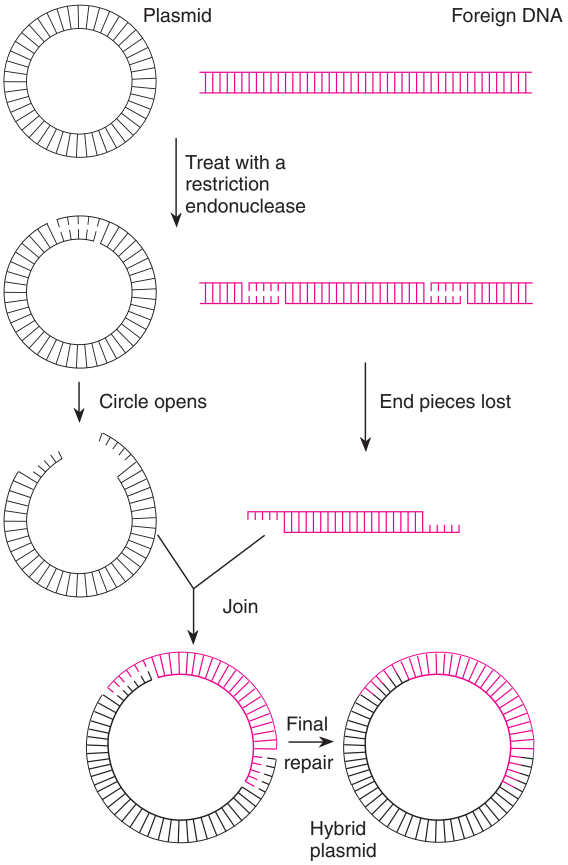

Figure 1.13 Hybrid DNA molecules can be constructed from a plasmid and a piece of foreign DNA. The ends are made compatible by cutting both DNAs with the same restriction endonuclease, leaving complementary ends. These ends will re-form double helices to form intact hybrid plasmids when the two types of DNA mix. A repair enzyme, DNA ligase, finishes patching the hybrid DNA within the plasmid. The hybrid plasmid is then reinjected into a bacterium, to be grown into billions of copies that will later be available for isolation and sequencing, or the hybrid plasmid can express the foreign DNA from within the host bacterium.

processes are occurring. We can formulate a statement to describe the equilibrium condition: If the assumptions are met, the population will not experience changes in allelic frequencies, and these allelic frequencies will accurately predict the frequencies of *genotypes* (allelic combinations in individuals, e.g., *AA, Aa,* or *aa*) in the population.

Recently, several areas of evolutionary genetics have become controversial. Electrophoresis (a method for separating proteins and other molecules) and subsequent DNA sequencing have revealed that much more *polymorphism* (variation) exists within natural populations than older mathematical models could account for. One of the more interesting explanations for this variability is that it is neutral. That is, natural selection, the guiding force of evolution, does not act differentially on many, if not most, of the genetic differences found so commonly in nature. At first, this theory was quite controversial, attracting few followers. Now it seems to be the view the majority accept to explain the abundance of molecular variation found in natural populations.

Another controversial theory concerns the rate of evolutionary change. It is suggested that most evolutionary change is not gradual, as the fossil record seems to indicate, but occurs in short, rapid bursts, followed by long periods of very little change. This theory is called *punctuated equilibrium.*

A final area of evolutionary biology that has generated much controversy is the theory of *sociobiology.* Sociobiologists suggest that social behavior is under genetic control and is acted upon by natural selection, as is any morphological or physiological trait. This idea is controversial mainly as it applies to human beings; it calls altruism into question and suggests that to some extent we are genetically programmed to act in certain ways. People have criticized the theory because they feel it justifies racism and sexism.

SUMMARY

The purpose of this chapter has been to provide a brief history of genetics and a brief overview of the following twenty chapters. We hope it serves to introduce the material and to provide a basis for early synthesis of some of the material that, of necessity, is presented in the discrete units called chapters. This chapter also differs from all the others because it lacks some of the end materials that should be of value to you as you proceed: solved problems, and exercises and problems. These features are presented chapter by chapter throughout the remainder of the book. At the end of the book, we provide answers to exercises and problems and a glossary of all **boldface** words throughout the book.

Suggested Readings for chapter 1 are on page B-1.