CHAPTER

1

An Introduction to Genetics

Chapter Concepts

Genetics is the science of heredity. The discipline has a rich history and involves investigations of molecules, cells, organisms, and populations, using many different experimental approaches. Not only does genetic information play a significant role during evolution, its expression influences the functioning of individuals at all levels. Genetics thus unifies the study of biology and has had a profound impact on human affairs.

Welcome to the study of genetics. You are about to explore a subject that many students before you have found to be the most interesting in the field of biology. This is not surprising, because an understanding of genetic processes is fundamental to the comprehension of life itself. Genetic information directs cellular function, determines an organism's external appearance, and serves as the link between generations in every species. Knowing how these roles are accomplished is important to understanding the living world. Knowledge of genetic concepts also helps us to understand other disciplines of biology. The topics studied in genetics overlap directly with molecular biology, cell biology, physiology, evolution, ecology, systematics, and behavior. The study of each of these disciplines is incomplete without knowledge of the genetic component underlying each of them. Genetics thus unifies biology and serves as its "core."

Fascination with this discipline stems further from the fact that, in genetics, many initially vague and abstract concepts have been so thoroughly investigated that subsequently they have become clearly and definitively understood. During these many investigations, genetics has established a rich history that exemplifies the nature of scientific inquiry and the analytical approach used to acquire information. Scientific analysis, moving from the unknown to the known, is one of the major forces that attracts students to biology.

The study of genetics is also extremely dynamic. Every year large numbers of significant findings are made. Over the past five decades, major research frontiers in genetics have been continually pushed forward, and new areas of investigation have resulted. In each case, the ensuing advances become part of an ever-expanding body of knowledge upon which further progress is based. It is exciting to be in the midst of these developments, whether you are studying or teaching genetics.

The Historical Context of Genetics

In the chapters that follow, we will discuss the nature of chromosomes, the way in which genetic information is transmitted from one generation to the next, and the way in which this information is stored, altered, expressed, and regulated. The most significant scientific findings, which serve as the foundation for our discussions, were obtained in the nineteenth century. As the twentieth century dawned, discoveries were made that began to clarify the understanding of the physical basis of living organisms and their relationship to one another. Several related ideas were gaining acceptance and were particularly significant: (1) Matter is composed of atoms; (2) cells are the fundamental units of living organisms; (3) nuclei somehow serve as the "life force" of cells; and (4) chromosomes housed within nuclei somehow play an important role in heredity. When these ideas were correlated with the newly rediscovered genetic findings of Gregor Mendel and integrated

with Darwin's theory of natural selection and the origin of species, a more complete picture of life at the level of the individual and of the population emerged. The era of modern-day biology was initiated on this foundation.

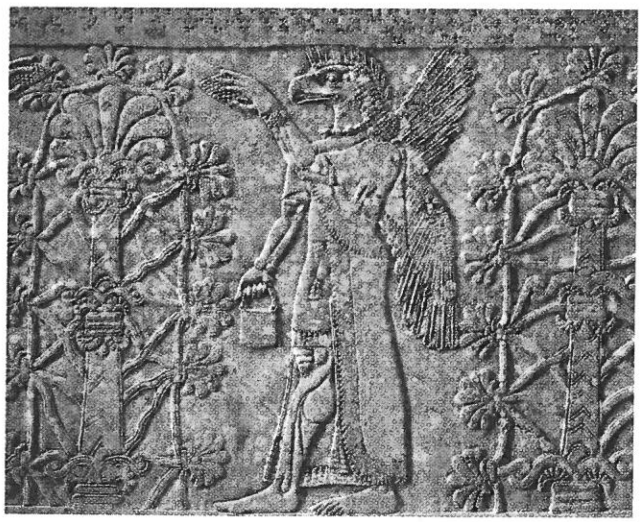
But what of the many important ideas and hypotheses that served as forerunners of nineteenth-century thought? In the following short section, we consider some of these, several of which can be traced back well over 1000 years!

Prehistoric Times: Domesticated Animals and Cultivated Plants

We may never know when people first recognized the existence of heredity. However, a variety of archeological evidence (e.g., primitive art, preserved bones and skulls, and dried seeds) have provided many insights. Such evidence documents the successful domestication of animals and cultivation of plants thousands of years ago. These efforts represent artificial selection of genetic variants within populations.

For example, between 8000 and 1000 B.C., horses, camels, oxen, and various breeds of dogs (derived from the wolf family) were domesticated to serve various roles. Cultivation of many plants, including maize, wheat, rice, and the date palm, is thought to have been initiated around 5000 B.C. Remains of maize dating to this period have been recovered in caves in the Tehuacan Valley of Mexico. Assyrian art depicts artificial pollination of the date palm, thought to have originated in Babylonia (Figure 1–1). Such cultivation very likely led to the types of date palms found in that region today, where over 400 varieties exist in just four oases in the Sahara Desert. They differ from one another in various traits such as fruit taste.

Prehistoric evidence of cultivated plants and domesticated animals documents our ancient ancestors' successful attempts to manipulate the genetic composition of useful species. There is little doubt that people soon learned that desirable and undesirable traits are passed to successive generations and more desirable varieties of animals and plants could be selected. Human awareness of heredity was thus apparent during prehistoric times.



■ Figure 1–1 Relief carving depicting artificial pollination of date palms during the reign of Assyrian King Assurnasirpal II (883–859 B.C.).

The Greek Influence: Hippocrates and Aristotle

Although few, if any, significant ideas were put forward to explain heredity during prehistoric times, philosophers directed much more attention to this subject during the Golden Age of Greek culture. They paid considerable attention to the subjects of reproduction and heredity, particularly as related to the origin of humans. This is particularly evident in the writings of the Hippocratic school of medicine (500–400 B.C.) and subsequently of the philosopher and naturalist Aristotle (384–322 B.C.).

Central to their explanation of the hereditary basis of reproduction of animals were hypotheses concerning (1) the source of the *physical substance* of the offspring and (2) the nature of the *generative force* that directs the physical substance as it materializes (develops) into an adult organism.

For example, the Hippocratic treatise *On the Seed* argues that male semen is formed in numerous parts of the body and is transported through blood vessels to the testicles. Active "humors" act as the bearers of hereditary traits and are drawn from various parts of the body to the semen. These humors could be healthy or diseased, the latter condition accounting for the appearance of newborns exhibiting congenital disorders or deformities. Furthermore, it was believed that these humors could be altered in individuals and, in their new form, could be passed on to offspring. In this way, newborns could "inherit" traits that their parents had "acquired" because of their environment.

Aristotle, who had studied under Plato for some 20 years, was more critical and more expansive than Hippocrates in his analysis of human origins and heredity. Aristotle proposed that male semen was formed from blood rather than from each organ and that its generative power resided in a "vital heat" that it contained. This vital heat had the capacity to produce offspring of the same "form" (i.e., basic structure and capacities) as the parent. Aristotle believed that it generated offspring by cooking and shaping the menstrual blood produced by the female, which was the "physical substance" giving rise to an offspring. The embryo developed from the initial "setting" of the menstrual blood by the semen into a mature offspring, not because it already contained the parts in miniature (as some Hippocratics had thought), but because of the shaping power of the vital heat. These ideas constituted only one part of Aristotelian philosophy of order in the living world.

Although the ideas of Hippocrates and Aristotle may sound primitive and naive today, we should recall that, prior to the 1800s, neither sperm nor eggs had yet been observed in mammals. Thus, the Greek philosophers' ideas were worthy ones in their time and for centuries to come. As we will see, their thinking was not so different from that of Charles Darwin in his formal proposal of the theory of pangenesis put forward during the nineteenth century.

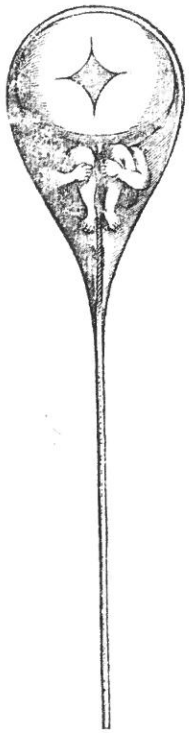
1600–1850: The Dawn of Modern Biology

During the ensuing 1900 years (300 B.C.–1600 A.D.), the theoretical understanding of genetics was not extended by significant, new ideas. However, interest in applied genetics remained strong. As early as Roman times, plant grafting and animal breeding were much emphasized. By the Middle Ages, naturalists, well aware of the impact of heredity on organisms they studied, were faced with reconciling their findings with current religious beliefs. The theories of Hippocrates and Aristotle still prevailed and, when applied to humans, they no doubt conflicted with the prevailing religious doctrines.

Between 1600 and 1850, major strides were made that provided much greater insights into the biological basis of life, setting the scene for the revolutionary work and principles presented by Charles Darwin and Gregor Mendel. In the 1600s the English anatomist William Harvey (1578–1657), better known for his experiments demonstrating that the blood is pumped by the heart through a circulatory system made up of the arteries and veins, also wrote a treatise on reproduction and development, patterned after Aristotle's work. In it he is credited with the earliest statement of the theory of **epigenesis**—that an organism is derived from substances present in the egg, which differentiate into adult structures during embryonic development. Patterned after Aristotle's ideas, epigenesis holds that new structures, such as body organs, are not present initially but instead are formed *de novo* in the embryo. Indeed, Harvey had studied Aristotle and was well aware of his ideas.

The theory of epigenesis conflicts directly with the **theory of preformation**, first put forward in the seventeenth century. Stating that sex cells contain a complete miniature adult called the **homunculus** (Figure 1–2), perfect in every form, preformation was popular well into the eighteenth century. However, work by the embryologist Casper Wolff (1733–1794) and others clearly disproved this theory, thus favoring epigenesis. Wolff was convinced that several structures, such as the alimentary canal, were not initially present in the earliest embryos he studied, but instead were formed later during development.

During this same period, other significant chemical and biological findings affected future scientific thinking. In 1808, John Dalton expounded his **atomic theory**, which stated that all matter is composed of small invisible units called atoms. Improved microscopes became available, and around 1830 Matthias Schleiden and



■ Figure 1–2 Depiction of the "homunculus," a sperm containing a miniature adult, perfect in proportion and fully formed.

Theodor Schwann proposed the **cell theory**: All organisms are composed of basic visible units called cells, which are derived from similar preexisting structures. By this time, the idea of **spontaneous generation**, the creation of living organisms from nonliving components, had clearly been disproved by the experiments of Francesco Redi (1621–1697), Lazzaro Spallanzani (1729–1799), and Louis Pasteur (1822–1895), among others. Thus, living organisms were considered to be derived from preexisting organisms and to consist of cells made up of atoms.

Another prevailing notion had a major influence on nineteenth century thinking: the **fixity of species**. According to this doctrine, animal and plant groups remain unchanged in form from the moment of their appearance on earth. Embraced particularly by those who also adhered to a belief in special creation, this doctrine was popularized by several people, including the Swedish physician and plant taxonomist Carolus Linnaeus (1707–1778), who is better known for devising the binomial system of classification.

The influence of this tenet is illustrated by considering the work of the German plant breeder Joseph Gottlieb Kolreuter (1733–1806), who worked with tobacco. He cross-bred two groups and derived a new hybrid form, which he then converted back to one of the parental types by repeated backcrosses. In other breeding experiments using carnations, he clearly observed segregation of traits, which was to become one of Mendel's

principles of genetics. These results seemed to contradict the idea of "fixed species" that do not change with time. Because of Kolreuter's belief in both special creation and the fixity of species, he was puzzled about these outcomes and failed to recognize the real significance of his findings.

Charles Darwin and Evolution

With the above information as background, we conclude our coverage of the historical context of genetics with a brief discussion of the work of Charles Darwin, who in 1859 published the book-length statement of his evolutionary theory, *The Origin of Species*. Darwin's many geological, geographical, and biological observations convinced him that existing species arose by descent with modification from other ancestral species. Greatly influenced by his now famous voyage on the H.M.S. *Beagle* (1831–1836), Darwin's thinking culminated in his formulation of the **theory of natural selection**, a theory that attempted to explain the causes of evolutionary change. Formulated and proposed at the same time, but independently, by Alfred Russel Wallace, natural selection is based on the observation that populations tend to consist of more offspring than the environment can support, leading to a struggle for survival among them. Those organisms with heritable traits that allow them to adapt to their environment are better able to survive and reproduce than those with less adaptive traits. Over a long period of time, slight but advantageous variations will accumulate. If a population bearing these inherited variations becomes reproductively isolated, a new species may result.

The primary gap in Darwin's theory was a lack of understanding of the genetic basis of variation and inheritance, a gap that left it open to reasonable criticism well into the twentieth century. Aware of this weakness in his theory of evolution, in 1868 Darwin published a second book, *Variations in Animals and Plants under Domestication*, in which he attempted to provide a more definitive explanation of how heritable variation arises gradually over time. Two of his major ideas, pangenesis and the inheritance of acquired characteristics, have their roots in the theories involving "humors," as put forward by Hippocrates and Aristotle.

In his provisional hypothesis of **pangenesis**, Darwin coined the term **gemmules** (rather than humors) to describe the physical units representing each body part that were gathered by the blood into the semen. Darwin felt that these gemmules determined the nature or form of each body part. He further believed that gemmules could respond in an adaptive way to an individual's external environment. Once altered, such changes would be passed on to offspring, allowing for the inheritance of acquired characteristics. Lamarck had previously formalized this idea in his 1809 treatise, *Philosophie Zoologique*. Lamarck's theory, which became known as the **doctrine of use and disuse**, proposed that organisms acquire or lose characteristics that then become heritable.

Even though Darwin never understood the basis for inherited variation, his ideas concerning evolution may be the most influential theory ever put forward in the history of biology. He was able to distill his extensive observations and synthesize his ideas into a cohesive hypothesis describing the origin of diversity of organisms populating the earth.

As Darwin's work ensued, the experiments of Gregor Johann Mendel (Figure 1–3) were performed between 1856 and 1863, forming the basis for his classic 1866 paper. In it, Mendel demonstrated a number of statistical patterns underlying inheritance and developed a theory involving hereditary factors in the germ cells to explain these patterns. His research was virtually ignored until it was partially duplicated and then cited by Carl Correns, Hugo de Vries, and Eric Von Tschermak around 1900 and subsequently championed by William Bateson.

By the early part of the twentieth century, chromosomes were discovered and support for the epigenetic interpretation of development had grown considerably.

■ Figure 1–3 Gregor Johann Mendel, who in 1866 put forward the major postulates of transmission genetics as a result of experiments with the garden pea.

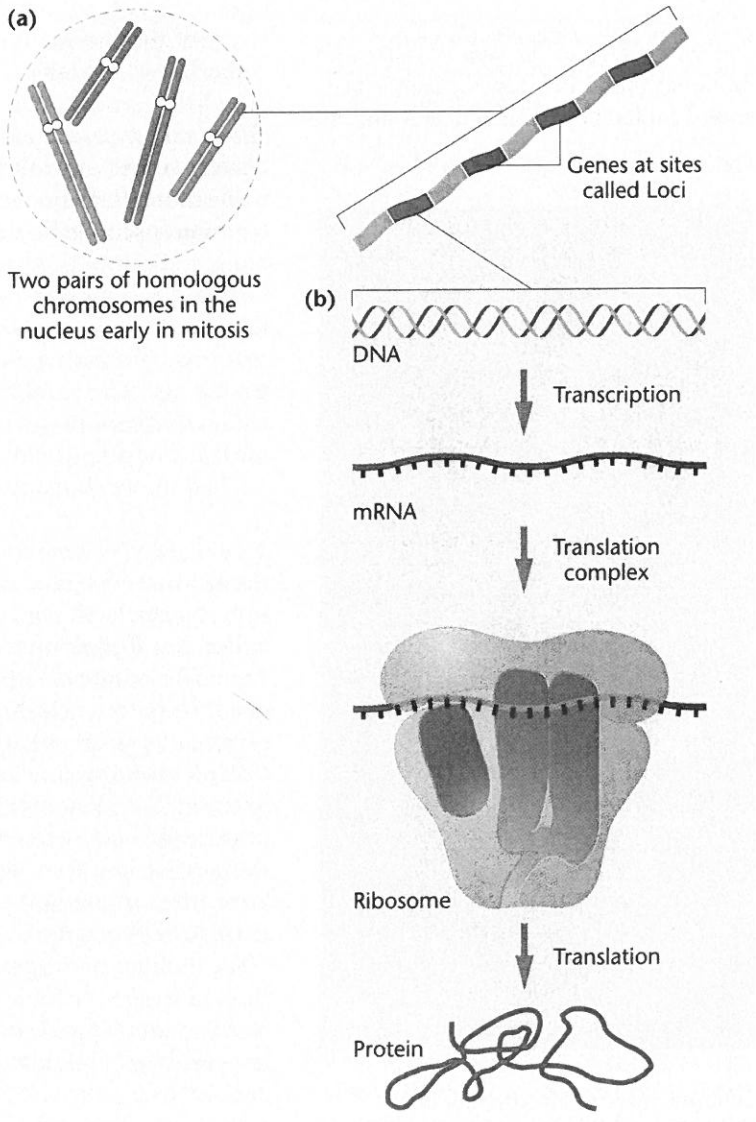
It gradually became clear that heredity and development were dependent on "information" contained in chromosomes, which were contributed by gametes to each individual. The "gap" in Darwin's theory had narrowed considerably.

In Chapter 3, we will return to a thorough analysis of Mendel's findings, which have served to this day as the foundation of genetics. His work was but one important part of the body of knowledge that would initiate the era of modern biological thought in the twentieth century.

Basic Concepts of Genetics

We now turn to a review of some of the simple but basic concepts in genetics, which you have undoubtedly already studied. By reviewing them at the outset, we can establish an initial vocabulary and proceed through the text with a common foundation of knowledge. We shall approach these basic concepts by asking and answering a series of questions. You may wish to write or think through an answer before reading the explanation of each question. A number of issues that are addressed below are summarized in Figure 1–4, so you may wish to refer to this figure as you read through this section. Throughout the text, the answers to these questions will be expanded as more detailed information is presented.

What does "genetics" mean? **Genetics** is the branch of biology concerned with heredity and variation. This discipline involves the study of cells, individuals, their offspring, and the populations within which organisms live. Geneticists investigate all forms of inherited variation as well as the molecular basis underlying such characteristics.



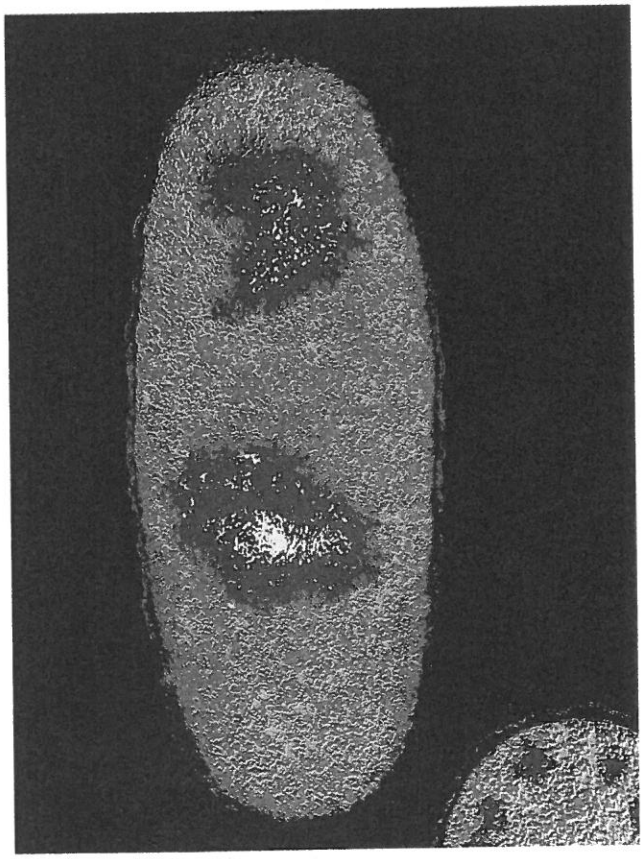
■ Figure 1–4 Depiction of (a) the storage of genetic information in homologous chromosomes, which contain genes made up of DNA; and (b) genetic expression involving transcription of DNA into mRNA, which can be translated on a ribosome into a protein.

What is the center of heredity in a cell? In eukaryotic organisms, the **nucleus** contains the genetic material. In prokaryotes, such as bacteria, the genetic material exists in an unenclosed but recognizable area of the cell called the **nucleoid region** (Figure 1–5). In viruses, which are not true cells, the genetic material is ensheathed in the protein coat, together constituting the viral head or capsid.

What is the genetic material? In eukaryotes and prokaryotes, **DNA** serves as the molecule storing genetic information. In viruses, either DNA or **RNA** serves this function.

What do DNA and RNA stand for? DNA and RNA are abbreviations for **deoxyribonucleic acid** and **ribonucleic acid**, respectively. These are the two types of nucleic acids found in organisms. Nucleic acids, along with carbohydrates, lipids, and proteins, compose the four major classes of organic biomolecules found in living things.

How is DNA organized to serve as the genetic material? DNA, although single-stranded in a few viruses, is usually a double-stranded molecule organized as a **double helix**. Contained within each DNA molecule are hereditary units called **genes**, which are part of larger elements, the **chromosomes**.



■ Figure 1–5 Enhanced electron micrograph of *Escherichia coli,* demonstrating the nucleoid regions (shown in blue). The bacterium has replicated its DNA and is about to begin cell division.

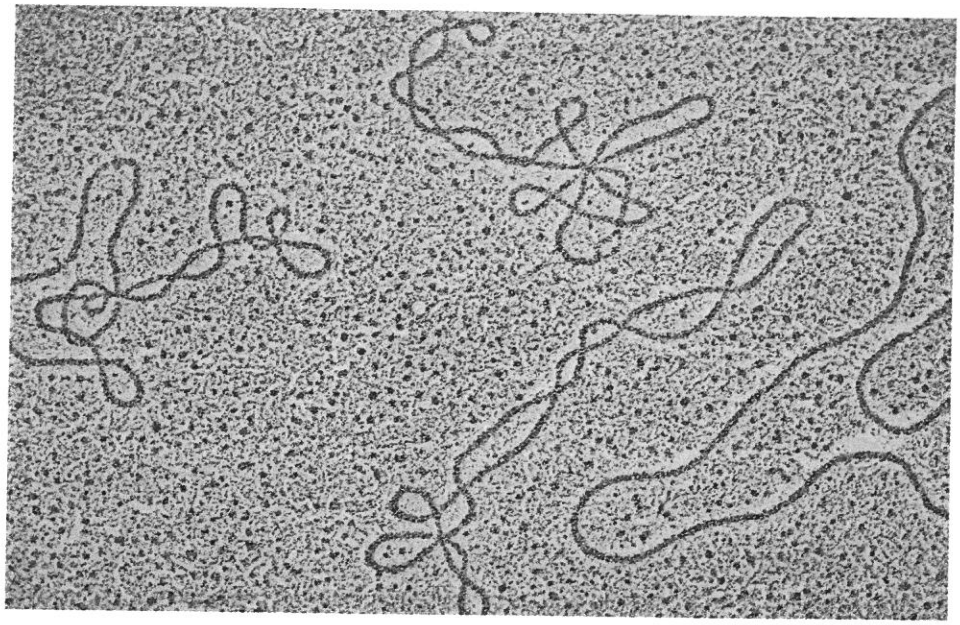
What is a gene? In simplest terms, the gene is the functional unit of heredity. In chemical terms, it is a linear array of nucleotides—the chemical building blocks of DNA and RNA. A more conceptual approach is to consider it as an **informational storage unit** capable of undergoing **replication**, **mutation**, and **expression**. As investigations have progressed, the gene has been found to be a very complex element.

What is a chromosome? In viruses and bacteria, which have only a single chromosome, a chromosome is most simply thought of as a long, usually circular DNA molecule organized into genes. Most eukaryotes have many chromosomes that are composed of linear DNA molecules intimately associated with proteins. In addition, eukaryotic chromosomes contain many nongenic regions. It is not yet clear what role, if any, is played by many of these regions. Our knowledge of the chromosome, like that of the gene, is continually expanding.

When and how can chromosomes be visualized? If the chromosomes are released from the viral head or the bacterial cell, they can be visualized under the electron microscope (Figure 1–6). In eukaryotes, chromosomes are most easily visualized under the light microscope when they are undergoing **mitosis** or **meiosis**. In these division processes, the material constituting chromosomes is tightly coiled and condensed, giving rise to the characteristic image of chromosomes. Following division, this material, called **chromatin**, uncoils during interphase, where it can be studied under the electron microscope.

How many chromosomes does an organism have? Although there are exceptions, members of most eukaryotic species have a specific number of chromosomes, called the **diploid number (2*n*)**, in each somatic cell. Upon close analysis, these chromosomes are found to occur in pairs, each member of which shares a nearly identical appearance when visible during cell division. Called **homologous chromosomes**, the members of each pair are identical in their length and in the location of the **centromere**, the point of spindle fiber attachment during division. They also contain the same sequence of gene sites, or **loci**, and pair with one another during gamete formation (the process of meiosis).

The number of different *types* of chromosomes in any diploid species is equal to half the diploid number and is called the **haploid (*n*)** number. Some organisms, such as yeasts, are haploid during most of their life cycle and contain only one "set" of chromosomes. Other organisms, especially many plant species, are sometimes characterized by more than two sets of chromosomes and are said to be **polyploid**.



■ Figure 1–6 DNA constituting the chromosome of a bacterial virus (a bacteriophage) viewed under the electron microscope.

What is accomplished during the processes of mitosis and meiosis? Mitosis is the process by which the genetic material of eukaryotic cells is duplicated and distributed during cell division. Meiosis is the process whereby cell division produces gametes in animals and spores in most plants. While mitosis occurs in somatic tissue and yields two progeny cells with an amount of genetic material identical to that of the progenitor cell, meiosis creates cells with precisely one-half of the genetic material. Each gamete receives one member of each homologous pair of chromosomes and is haploid. This reduction in chromosome number is essential if offspring arising from two gametes are to maintain a constant number of chromosomes characteristic of their parents and other members of the species.

What are the sources of genetic variation? Classically, there are two sources of genetic variation: **chromosomal mutations** and **gene mutations**. The former, also called chromosomal **aberrations**, include duplication, deletion, or rearrangement of chromosome segments. Gene mutations result from a change in the stored chemical information in DNA, collectively referred to as an organism's **genotype**. Such a change may include substitution, duplication, or deletion of nucleotides, which compose this chemical information. Alternative forms of the gene, which result from mutation, are called **alleles**. Genetic variation frequently, but not always, results in a change in some characteristic of an organism, referred to as its **phenotype**.

How does DNA store genetic information? There are four different forms of chemical building blocks called **nucleotides** in a segment of DNA constituting a gene. The sequence of nucleotides making up a gene encodes the chemical nature (the amino acid composition) of a protein, the end product of genetic expression. **Mutations** are produced when the nucleotide sequence (the genetic code) is altered, creating alternate forms of the genes, called **alleles**.

How is the genetic code organized? There are four different nucleotides in DNA, each varying in one of its components, the **nitrogenous base**. The genetic code is a triplet; therefore, each combination of three nucleotides constitutes a code word. Almost all possible codes specify one of 20 **amino acids**, the chemical building blocks of proteins.

How is the genetic code expressed? The coded information in DNA is first transferred during a process called **transcription** into a **messenger RNA (mRNA)** molecule. The mRNA subsequently associates with the cellular organelle, the **ribosome**, where it is **translated** into a protein molecule.

Are there exceptions where proteins are not the end product of a gene? Yes. For example, genes coding for **ribosomal RNA (rRNA)**, which is part of the ribosome, and for **transfer RNA (tRNA)**, which is involved in the translation process, are transcribed but not translated. Therefore, RNA is sometimes the end product of stored genetic information.

Why are proteins so important to living organisms that they serve as the end product of the vast majority of genes? Many proteins serve as highly specific biological catalysts, or enzymes. In this role, these proteins control cellular metabolism, determining which carbohydrates, lipids, nucleic acids, and other proteins are present in the cell. Many other proteins perform nonenzymatic roles. For example, hemoglobin, collagen, immunoglobulins, and some hormones are proteins that play diverse roles in living organisms.

Why are enzymes necessary in living organisms? As biological catalysts, enzymes lower the **activation energy** required for most biochemical reactions and speed the attainment of equilibrium. Otherwise, these reactions would proceed so slowly as to be ineffectual in organisms living under the physical conditions on earth. Some genes control the variety of enzymes present in any cell type, dictating its overall biochemical composition.

Investigative Approaches in Genetics

The scope of topics encompassed in the field of genetics is enormous. Studies have involved viruses, bacteria, and a wide variety of plants and animals and have spanned all levels of biological organization, from molecules to populations. It is helpful, before we embark on a detailed study of genetics, to categorize the types of investigations that have been used most often in this field. Although some overlap exists, most have used one of four basic approaches.

The most classical investigative approach is the study of **transmission genetics**, in which the patterns of inheritance of traits are examined. Experiments are designed so that the transmission of traits from parents to offspring can be analyzed through several generations. Patterns of inheritance are sought that will provide insights into genetic principles. The first significant experimentation of this kind to have a major impact on understanding heredity was performed by Gregor Mendel in the middle of the nineteenth century. Information derived from his work serves today as the foundation of transmission genetics. In human studies, where designed matings are neither possible nor desirable, **pedigree analysis** is often useful. In pedigree analysis, patterns of inheritance are traced through as many generations as possible, leading to inferences concerning the mode of inheritance of the trait under investigation.

The second approach involves **cytogenetics**—the study of chromosomes. The earliest such studies used light microscopy. The initial discovery of chromosome behavior during mitosis and meiosis, early in the twentieth century, was a critical event in the history of genetics. In addition to playing an important role in the rediscovery and acceptance of Mendelian principles, these observations served as the basis of the **chromosomal theory of inheritance**. This theory, which viewed the chromosome as the carrier of genes and the functional unit of transmission of genetic information, was the cornerstone for further studies in genetics throughout the first half of this century.

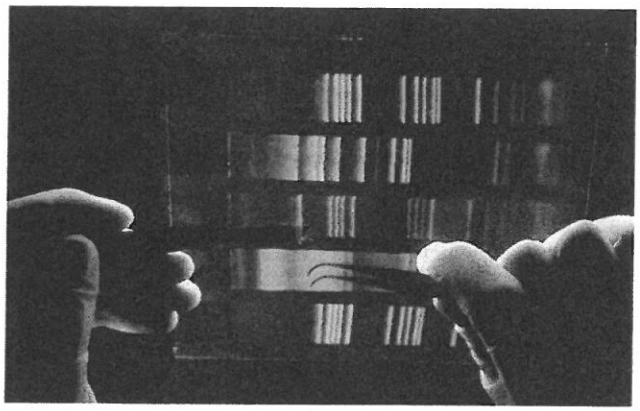
The light microscope continues to be useful in the investigation of chromosome structure and abnormalities and is instrumental in preparing **karyotypes**, which illustrate the chromosomes characteristic of any species arranged in a standard sequence.

With the advent of electron microscopy, the repertoire of investigative approaches in genetics has grown. In high-resolution microscopy, genetic molecules and their behavior during gene expression can be visualized directly.

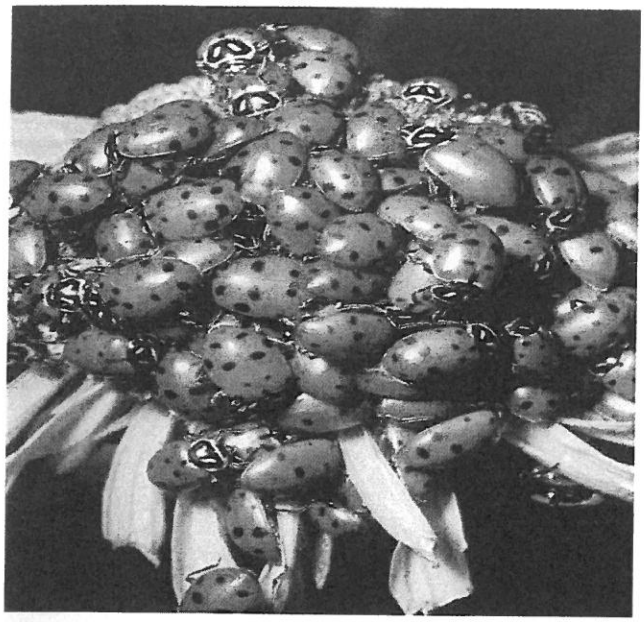
The third general approach involves **molecular genetic analysis**, which has had the greatest impact on the recent growth of genetic knowledge. Molecular studies, initiated in the early 1940s, have consistently expanded our knowledge of the role of genetics in life processes. Although experiments initially relied on bacteria and the viruses that infect them, extensive information is now available concerning the nature, expression, replication, and regulation of the genetic information in eukaryotes as well. The precise nucleotide sequence has been determined for many genes cloned in the laboratory. **Recombinant DNA** studies (Figure 1–7), in which genes from another organism are literally spliced into bacterial or viral DNA and cloned *en masse*, serve as the basis of a far-reaching research technology used in molecular genetic investigations. Building on this approach, the new field of **DNA biotechnology** now exists whereby genes are identified, sequenced, cloned, and manipulated. Furthermore, using the most recent technology, it is now possible to probe gene function in extreme detail. Such molecular and biochemical analysis has had profound implications in medicine, agriculture, and bioethics.

The final approach involves the study of **population genetics**. In these investigations, scientists attempt to define how and why certain genetic variation is maintained in populations, while other variation diminishes or is lost with time (Figure 1–8). Such information is critical to the understanding of evolutionary processes. Population genetics also allows us to predict gene frequencies in future generations.

Together these varied approaches used in investigative genetics have transformed a subject that was only poorly understood in 1900 into one of the most advanced scientific disciplines today. As a result, the impact of genetics on society has been immense. We shall discuss many examples of the applications of genetics in the following section and throughout the text.



■ Figure 1–7 Visualization of DNA fragments under ultraviolet light. The bands were produced using recombinant DNA technology.



■ Figure 1–8 Lady-bird beetles atop a daisy, illustrating genetic variation in populations.

Genetics and Society

In addition to acquiring information for the sake of extending knowledge in any discipline of science—an experimental approach called **basic research**—scientists conduct investigations to solve problems facing society or simply to improve the well-being of members of our society—an approach called **applied research**. Together, both types of genetic research have combined to: (1) enhance the quality of our existence on this planet; and (2) provide a more thorough understanding of life processes. As we shall see throughout this text, there is very little in our lives that genetics fails to touch.

Eugenics and Euphenics

There is always the danger that scientific findings will be used to formulate policies and/or actions that are unjust or even tragic. This section reviews such a case, which began near the end of the nineteenth century. At that time, Darwin's theory of natural selection provided a major influence on some people's thinking concerning the human condition. Our story recounts the initial attempt to apply genetic knowledge directly for the improvement of human existence. Championed in England by Francis Galton, the general approach is called **eugenics**, a term Galton coined in 1883.

Galton, a cousin of Charles Darwin, believed that many human characteristics were inherited and subject to artificial selection if human matings could be controlled. **Positive eugenics** encouraged parents displaying favorable characteristics to have large families. Superior intelligence, intellectual achievement, and artistic talent are examples. **Negative eugenics**, on the other hand, attempted to restrict reproduction of parents displaying unfavorable characteristics. Low intelligence, mental retardation, and criminal behavior are examples.

In the United States, the eugenics movement was a significant social force and led to state and federal laws that required sterilization of those considered "genetically inferior." Over half of the states passed such laws, commencing in 1907 with Indiana. Sterilization was mandated for "imbeciles, idiots, convicted rapists, and habitual criminals." By 1931, involuntary sterilization also applied to "sexual perverts, drug fiends, drunkards, and epileptics." Immigration to the United States from certain areas of Europe and from Asia was also restricted, to prevent the influx of what were regarded as genetically inferior people.

In addition to the violation of individual human rights, such policies were seriously flawed by an inadequate understanding of the genetic basis of various characteristics. Formulation of eugenic policies was premised on the mistaken notions that "superior" and "inferior" traits are totally under genetic control and that genes deemed unfavorable could be removed from a population by selecting against (sterilizing) individuals expressing those traits. The potential impact of the environment as well as genetic theory underlying population genetics were largely ignored as eugenic policies were developed.

In Nazi Germany in the 1930s, the concept of achieving a superior, racially pure group was an extension of the eugenics movement. Initially applied to those considered socially and physically defective, the underlying rationale of negative eugenics was soon applied to entire ethnic groups, including Jews and Gypsies. Fueled by various forms of racial prejudice, Adolf Hitler and the Nazi regime took eugenics to its extreme by instituting policies aimed at the extinction of these "impure" human populations. This deplorable disregard for human life was preceded by incremental policies involving forced sterilization and mercy killings. This movement, based on scientifically invalid premises, soon led to mass murder.

Even before the Nazi Party came to power in 1933, English and American geneticists began separating themselves from the eugenics movement. They were concerned about the validity of the premises underlying the movement and the evidence in support of these premises. Thus, many geneticists chose not to study human genetics for fear of being grouped with those who supported eugenics.

However, since the end of World War II, tremendous strides have been made in human genetics research. Today, a new term, **euphenics**, has replaced eugenics. Euphenics refers to medical and/or genetic intervention designed to reduce the impact of defective genotypes on individuals. The use of insulin by diabetics and the dietary control of newborn phenylketonurics are longstanding examples. Today, "genetic surgery" to replace defective genes rests clearly on the horizon. Furthermore, social policies now have a solid genetic foundation on which they may be based. Nevertheless, caution is still

required to ensure that our expanded knowledge of human genetics does not obscure the role played by the environment in determining an individual's phenotype.

Genetic Advances in Agriculture and Medicine

As a result of research in genetics, major benefits have accrued to society in the fields of agriculture and medicine. Although cultivation of plants and domestication of animals had begun long before, the rediscovery of Mendel's work in the early twentieth century spurred scientists to apply genetic principles to these human endeavors. The use of selective breeding and hybridization techniques has had the most significant impact in agriculture.

Plants have been improved in four major ways: (1) enhanced potential for more vigorous growth and increased yields, including the unique genetic phenomenon of **hybrid vigor (heterosis)**; (2) increased resistance to natural predators and pests, including insects and disease-causing microorganisms; (3) production of hybrids exhibiting a combination of superior traits derived from two different strains or even two different species (Figure 1-9); and (4) selection of genetic variants with desirable qualities such as increased protein value, increased content of limiting amino acids, which are essential in the human diet, or smaller plant size, reducing vulnerability to adverse weather conditions.

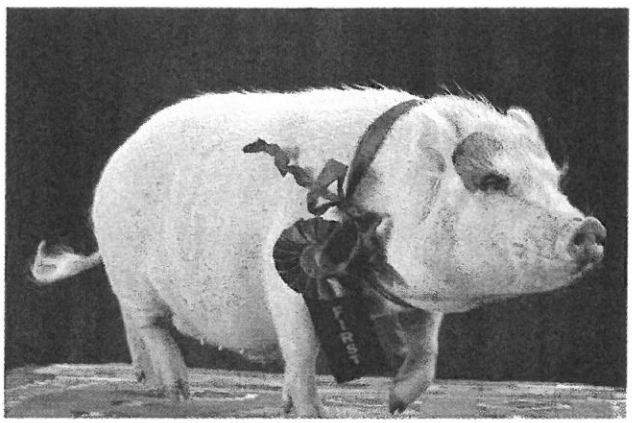
Over the past five decades, these improvements have resulted in a tremendous increase in yield and nutrient value in such crops as barley, beans, corn, oats, rice, rye, and wheat. It is estimated that in the United States the use of improved genetic strains has led to a threefold increase in crop yield per acre. In Mexico, where corn is the staple crop, a significant increase in protein content and yield has occurred. A substantial effort has also been made to improve the growth of Mexican wheat. Led by Norman Borlaug, a team of researchers developed varieties of wheat that incorporated favorable genes from other strains found in various parts of the world, revolutionizing wheat production in Mexico and other underdeveloped countries. Because of this effort, which led to the well-publicized "Green Revolution," Borlaug received the Nobel Peace Prize in 1970. There is little question that this application of genetics has contributed to the well-being of our own species by improving the quality of nutrition worldwide.

Applied research in genetics has also resulted in the development of superior breeds of livestock (Figure 1–10). Selective breeding has produced chickens that grow faster, produce more high-quality meat per chicken, and lay greater numbers of larger eggs. In larger animals, including pigs and cows, the use of artificial insemination has been particularly important. Sperm samples derived from a single male with superior genetic traits may now be used to fertilize thousands of females located in all parts of the world.

Equivalent strides have been made in medicine as a result of advances in genetics, particularly since 1950. Numerous disorders in humans have been discovered

■ Figure 1–9 *Triticale*, a hybrid grain derived from wheat and rye, produced as a result of applied genetic research.

to result from either a single mutation or a specific chromosomal abnormality. For example, the genetic basis of disorders such as sickle-cell anemia, erythroblastosis fetalis, cystic fibrosis, hemophilia, muscular dystrophy, Tay–Sachs disease, Down syndrome, and many metabolic disorders is now well documented and often understood at the molecular level. The importance of acquiring knowledge of inherited disorders is underscored by the estimate that more than 10 million children or adults in the United States suffer from some form of genetic affliction and that every child-bearing



■ Figure 1–10 The effects of breeding and selection, as illustrated by the production of this Vietnamese pot-bellied pig.

GENETICS, TECHNOLOGY, AND SOCIETY

The Fruits of Plant Biotechnology: Edible Vaccines

Almost lost amid the furor over the cloned sheep Dolly was the original purpose of the undertaking: to genetically engineer an animal that would produce a valuable pharmaceutical product, eventually leading to a herd of genetically identical drug-producing animals. The goal, in other words, was to be able to turn sheep, cattle, and other animals into living drug factories.

Meanwhile, almost unnoticed by the general public, the genetic engineering of plants to serve a simlar role is much closer to reality. When foreign genes are inserted into the plant genome, transgenic plants are created that produce the foreign gene product. One of the most intriguing and potentially life-saving objectives is the genetic engineering of plants to produce vaccines against human diseases. Immunization would then involve eating foods altered to contain a protein that acts as an antigen and stimulates the production of antibodies to protect against bacterial or viral infection.

Plants have many advantages as vaccine-producers. Since plants can be grown in large numbers, plant-produced vaccines should be less expensive than conventional vaccines. Further, extensive purification and refrigerated transport and storage of vaccines will not be required. This is important in parts of the world where the supply of electricity is unreliable. Finally, since people would simply eat the vaccine-containing food, there would be no need for syringes and needles, or medical staff to give injections.

Leading the effort to develop edible vaccines in plants is Charles J. Arntzen, formerly at Texas A&M University and now president of the Boyce Thompson Institute for Plant Research at Cornell University. Arntzen's research team is focusing on intestinal diseases, especially cholera. Cholera may at first seem an odd target, since it is a disease that has not been a major public health problem in this country for over a century. But cholera remains a leading cause of death of infants and children throughout the Third World, where basic sanitation is lacking and water supplies are often contaminated. For example, in July of 1994, 70,000 cases of cholera were reported among the Rwandans crowded into refugee camps in Goma, Zaire, leading to 12,000 fatalities. A cholera epidemic struck East Africa in the fall of 1997 killing nearly 3000. And after an absence of over 100 years, cholera has reappeared in Latin America in 1991, spreading from Peru to Mexico and claiming more than 10,000 lives.

The causative agent of cholera is *Vibrio cholerae,* a curved, rod-shaped bacterium found mostly in rivers and oceans. Most strains of *V. cholerae* are harmless; only one strain, called O1, is pathogenic. Infection occurs when a person drinks water or eats food contaminated with this strain. Once in the digestive system, the bacteria colonize the small intestine and begin producing proteins called enterotoxins. The cholera enterotoxin binds to the surface of the mucosal cells lining the intestine, triggering the massive secretion of water and dissolved salts from these cells. This results in violent diarrhea, which, if untreated, is followed by severe dehydration, muscle cramps, lethargy, and often death.

The cholera enterotoxin consists of two polypeptides, called the A and B subunits, which individually have no effect. For the toxin to be active, one A subunit must be linked to five B subunits. Since it is the B subunit of this complex that binds to intestinal cells, Arntzen's group decided to use this polypeptide as their antigen, reasoning that antibodies against it would potentially prevent toxin binding and render the bacteria harmless.

Their test of this idea involved the B subunit of an *E. coli* enterotoxin, which is similar in structure and immunological properties to the cholera protein. The DNA coding sequence of the B-subunit gene was obtained, to which they attached a promoter that would prompt transcription in all tissues of the plant. They then introduced this hybrid gene into potato plants by means of *Agrobacterium*-mediated transformation. They chose the potato not only because methods for transformation and regeneration of this plant are fairly routine, but also so they could assay the effectiveness of the antigen in the edible part of the plant, the tuber. Analysis showed that the engineered plants expressed their new gene and produced the enterotoxin.

After feeding mice a few grams of these genetically engineered tubers that had produced the B subunit, they found that the mice began to produce specific antibodies against it and to secrete them into the small intestinal. And, most critically, mice later fed purified enterotoxin were protected from its effects. They did not develop the symptoms of cholera. Clinical trials are now planned to test the efficacy of the potato-produced vaccine in humans.

In the meantime, the Arntzen group is also working towards producing edible vaccines in bananas, which have several advantages over potatoes. For one thing, bananas can be grown almost anywhere throughout the tropical or sub-tropical developing countries of the world, exactly where they are needed the most. And unlike potatoes, bananas are usually eaten raw, avoiding the potential inactivation of the antigenic proteins by cooking. Finally, bananas are well liked by infants and children, making this approach to immunization a more feasible one.

Procedures are now being perfected for the transformation of banana cells with genes encoding the cholera enterotoxin and the regeneration of transgenic plants. It will be some time before the engineered bananas are ready to test, however, since it takes three years to grow a banana crop. If all goes as planned, it may someday be possible to immunize all Third World children against cholera and other intestinal diseases, saving untold thousands of young lives.

References

Arntzen, C.J. 1997. Edible vaccines. *Public Health Rep.* 112: 190–197.

Haq, T.A., Mason, H.S., Clements, J.D., and Arntzen, C.J. 1995. Oral immunization with a recombinant bacterial antigen produced in transgenic plants. *Science* 268: 714–716.

Sanchez, J.L., and Taylor, D.N. 1997. Cholera. *Lancet* 349: 1825–1830.

couple stands an approximately 3 percent risk of having a child with some form of genetic anomaly.

Additionally, it has gradually become clear during the current decade that most, if not all, forms of **cancer** have a genetic basis. Although cancer is not usually an inherited disorder, it is now very clear that *cancer is a genetic disorder at the somatic cell level.* That is, most cancers are derived from somatic cells that have undergone some type of genetic change; malignant tumors are then derived from the genetically altered cell. In some cases, such changes are inherited, conferring a genetic predisposition to cancer.

Recognition of the molecular basis of human genetic disorders and cancer has provided the impetus for the development of methods for detection and treatment. **Genetic counseling** provides couples with objective information on which they can base rational decisions about child-bearing. In the case of cancer, recent genetic discoveries have already led to more effective early detection and more efficient approaches to treatment.

Applied research in genetics has also provided other medical benefits. Advances in **immunogenetics** have made possible compatible blood transfusions as well as organ transplants. In conjunction with immunosuppressive drugs, transplant operations involving human organs, including the heart, liver, pancreas, and kidney, are increasing annually and in many cases are now considered routine surgery.

The most recent advances in human genetics have been dependent on the application of **DNA biotechnology**. First developed in the 1970s, **recombinant DNA techniques** paved the way for manipulating and cloning a variety of genes, including those that encode many medically important molecules, such as insulin, blood clotting factors, growth hormone, and interferon. Human genes were isolated and spliced into vectors and transferred to host cells that serve as "production centers" for the synthesis of these proteins.

Recombinant DNA techniques have now been extended considerably. DNA of any organism of interest is routinely manipulated in the laboratory. Human genes responsible for inherited disorders such as **cystic fibrosis** and **Huntington disease** have been identified, isolated, cloned, and studied. It is hoped that such research will pave the way for **gene therapy**, whereby genetic disorders are treated by inserting normal copies of genes into the cells of afflicted individuals.

Perhaps the most far-reaching utilization of DNA biotechnology involves the **Human Genome Project**, in which the entire genetic complement (the **genome**) of several species, including our own, is being sequenced. The genomic sequencing of several bacterial species as well as that of yeast is now completed. The sequencing of the entire 3.2 billion nucleotides constituting the human genome is scheduled for completion in the year 2003.

In later chapters, the applications of DNA biotechnology to agriculture and medicine are discussed in greater detail. Although other scientific disciplines are also expanding in knowledge, none has paralleled the growth of information that is occurring in genetics. By the end of this course, we are confident you will agree that the present truly represents the "Age of Genetics."

Chapter Summary

1. The history of genetics, which emerged as a fundamental discipline of biology early in the twentieth century, dates back to prehistoric times.
2. Numerous concepts and a basic vocabulary essential to the study of genetics have been presented.
3. Four investigative approaches are most often used in the study of genetics, including transmission genetic studies, cytogenetic analyses, molecular experimentation, and inquiries into the genetic structure of populations.
4. Genetic research can be either basic or applied. Basic genetic research extends our knowledge of the discipline; the objective of applied genetics research is to solve specific problems affecting the quality of our lives and society in general.
5. Eugenics, the application of knowledge of genetics for the improvement of human existence, has a long and controversial history. Euphenics, genetic intervention designed to ameliorate the impact of genotypes on individuals, represents the modern eugenic approach.
6. Genetic research has had a highly positive impact on many facets of agriculture.
7. DNA biotechnology has greatly expanded our research capability. It also has had a profound impact in elucidating the basis of inherited diseases, has made possible the mass production of medically important gene products, and will serve as the foundation on which gene therapy is developed.

Key Terms

activation energy, 10
allele, 9
amino acid, 9
applied research, 11
basic research, 11
cell theory, 5