1 Introduction to Genetics

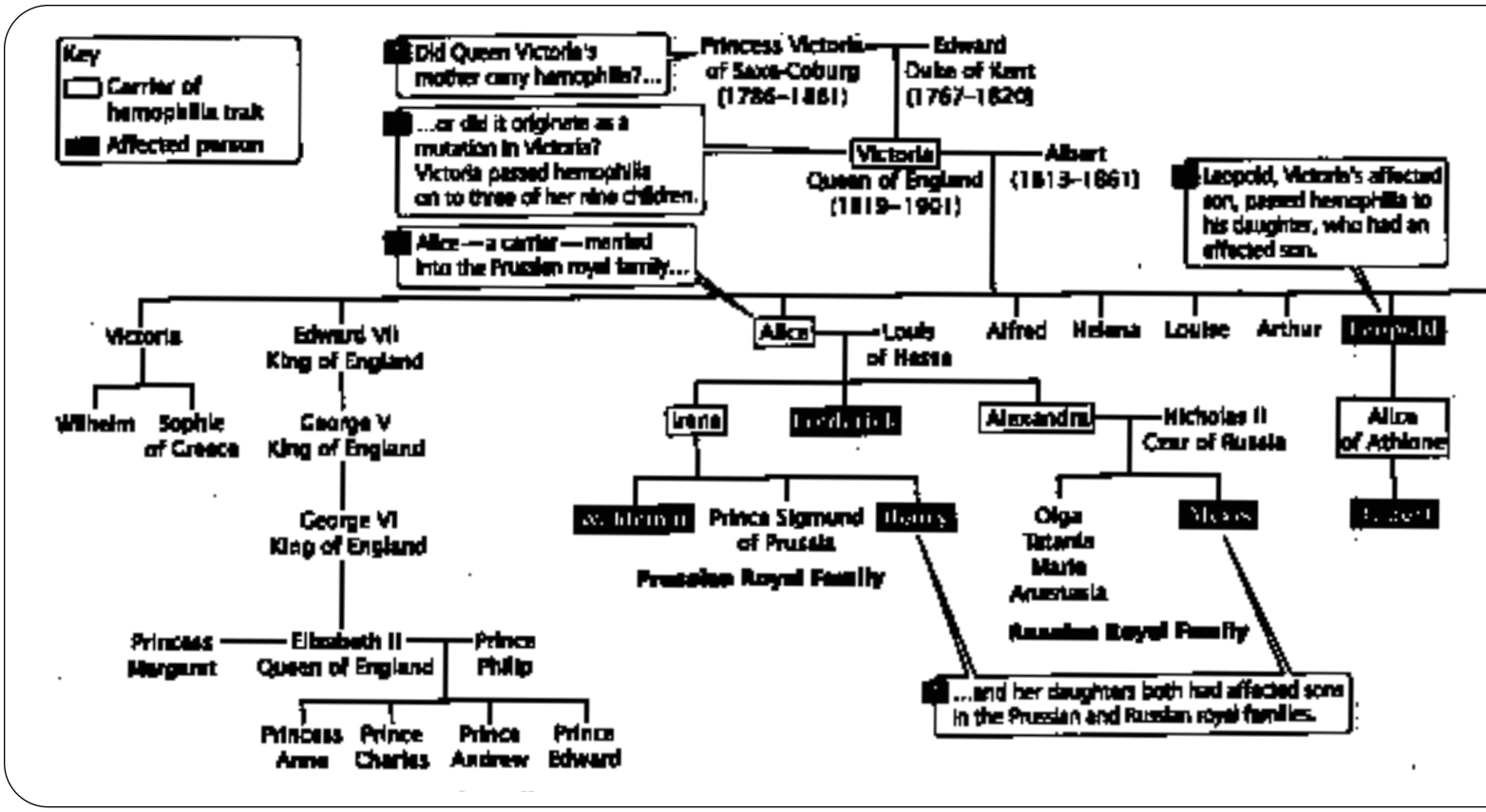
Alexis, heir to the Russian throne, and his father Tsar Nicholas Romanoff II. (Hulton/Archive by Getty Images.)

Royal Hemophilia and Romanov DNA

On August 12, 1904, Tsar Nicholas Romanov II of Russia wrote in his diary: "A great never-to-be forgotten day when the mercy of God has visited us so clearly." That day Alexis, Nicholas's first son and heir to the Russian throne, had been born.

At birth, Alexis was a large and vigorous baby with yellow curls and blue eyes, but at 6 weeks of age he began spontaneously hemorrhaging from the navel. The bleeding persisted for several days and caused great alarm. As he grew and began to walk, Alexis often stumbled and fell, as all children do. Even his small scrapes bled profusely, and minor bruises led to significant internal bleeding. It soon became clear that Alexis had hemophilia.

Hemophilia results from a genetic deficiency of blood clotting. When a blood vessel is severed, a complex cascade of reactions swings into action, eventually producing a protein called fibrin. Fibrin molecules stick together to form a clot, which stems the flow of blood. Hemophilia, marked by slow clotting and excessive bleeding, is the result if any one of the factors in the clotting cascade is missing or faulty. In those with hemophilia, life-threatening blood loss can occur with minor injuries, and spontaneous bleeding into joints erodes the bone with crippling consequences.



1.1 Hemophilia was passed down through the royal families of Europe.

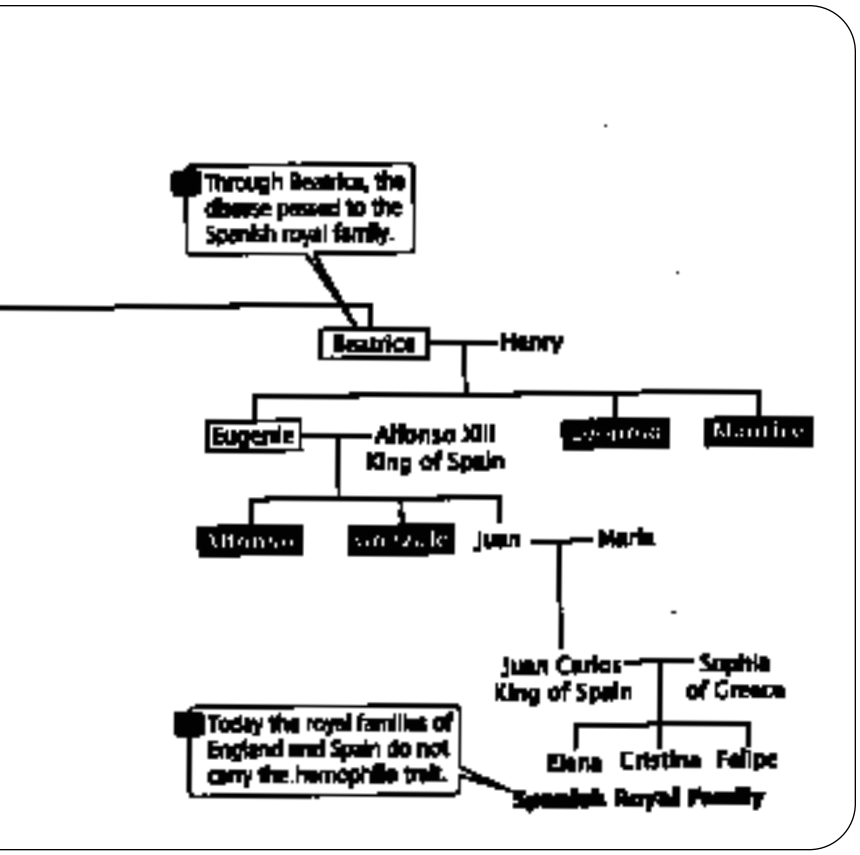
Alexis suffered from classic hemophilia, which is caused by a defective copy of a gene on the X chromosome. Females possess two X chromosomes per cell and may be unaffected carriers of the gene for hemophilia. A carrier has one normal version and one defective version of the gene; the normal version produces enough of the clotting factor to prevent hemophilia. A female exhibits hemophilia only if she inherits two defective copies of the gene, which is rare. Because males have a single X chromosome per cell, if they inherit a defective copy of the gene, they develop hemophilia. Consequently, hemophilia is more common in males than in females.

Alexis inherited the hemophilia gene from his mother, Alexandra, who was a carrier. The gene appears to have originated with Queen Victoria of England (1819–1901), (FIGURE 1.1). One of her sons, Leopold, had hemophilia and died at the age of 31 from brain hemorrhage following a minor fall. At least two of Victoria's daughters were carriers; through marriage, they spread the hemophilia gene to the royal families of Prussia, Spain, and Russia. In all, 10 of Queen Victoria's male descendants suffered from hemophilia. Six female descendants, including her granddaughter Alexandra (Alexis's mother), were carriers.

Nicholas and Alexandra constantly worried about Alexis's health. Although they prohibited his participation in sports and other physical activities, cuts and scrapes were inevitable, and Alexis experienced a number of severe bleeding episodes. The royal physicians were helpless during these crises—they had no treatment that would stop the bleeding. Gregory Rasputin, a monk and self-proclaimed "miracle worker," prayed over Alexis during one bleeding crisis, after which Alexis made a remarkable recovery. Rasputin then gained considerable influence over the royal family.

At this moment in history, the Russian Revolution broke out. Bolsheviks captured the tsar and his family and held them captive in the city of Ekaterinburg. On the night of July 16, 1918, a firing squad executed the royal family and their attendants, including Alexis and his four sisters. Eight days later, a protsarist army fought its way into Ekaterinburg. Although army investigators searched vigorously for the bodies of Nicholas and his family, they found only a few personal effects and a single finger. The Bolsheviks eventually won the revolution and instituted the world's first communist state.

Historians have debated the role that Alexis's illness may have played in the Russian Revolution. Some have argued that the revolution was successful because the tsar and Alexandra were distracted by their son's illness and under the influence of Rasputin. Others point out that many factors contributed to the overthrow of the tsar. It is probably naive to attribute the revolution entirely to one sick boy, but it is



clear that a genetic defect, passed down through the royal family, contributed to the success of the Russian Revolution.

More than 80 years after the tsar and his family were executed, an article in the *Moscow News* reported the discovery of their skeletons outside Ekaterinburg. The remains had first been located in 1979; however, because of secrecy surrounding the tsar's execution, the location of the graves was not made public until the breakup of the Soviet government in 1989. The skeletons were eventually recovered and examined by a team of forensic anthropologists, who concluded that they were indeed the remains of the tsar and his wife, three of their five children, and the family doctor, cook, maid, and footman. The bodies of Alexis and his sister Anastasia are still missing.

To prove that the skeletons were those of the royal family, mitochondrial DNA (which is inherited only from the mother) was extracted from the bones and amplified with a molecular technique called the polymerase chain reaction (PCR). DNA samples from the skeletons thought to belong to Alexandra and the children were compared with DNA taken from Prince Philip of England, also a direct descendant of Queen Victoria. Analysis showed that mitochondrial DNA from Prince Philip was identical with that from these four skeletons.

DNA from the skeleton presumed to be Tsar Nicholas was compared with that of two living descendants of the Romanov line. The samples matched at all but one nucleotide position: the living relatives possessed a cytosine (C) residue at this position, whereas some of the skeletal DNA possessed a thymine (T) residue and some possessed a C. This difference could be due to normal variation in the DNA; so experts concluded that the skeleton was almost certainly that of Tsar Nicholas. The finding remained controversial, however, until July 1994, when the body of Nicholas's younger brother Georgij, who died in 1899, was exhumed. Mitochondrial DNA from Georgij also contained both C and T at the controversial position, proving that the skeleton was indeed that of Tsar Nicholas.

This chapter introduces you to genetics and reviews some concepts that you may have encountered briefly in a preceding biology course. We begin by considering the importance of genetics to each of us, to society at large, and to students of biology. We then turn to the history of genetics, how the field as a whole developed. The final part of the chapter reviews some fundamental terms and principles of genetics that are used throughout the book.

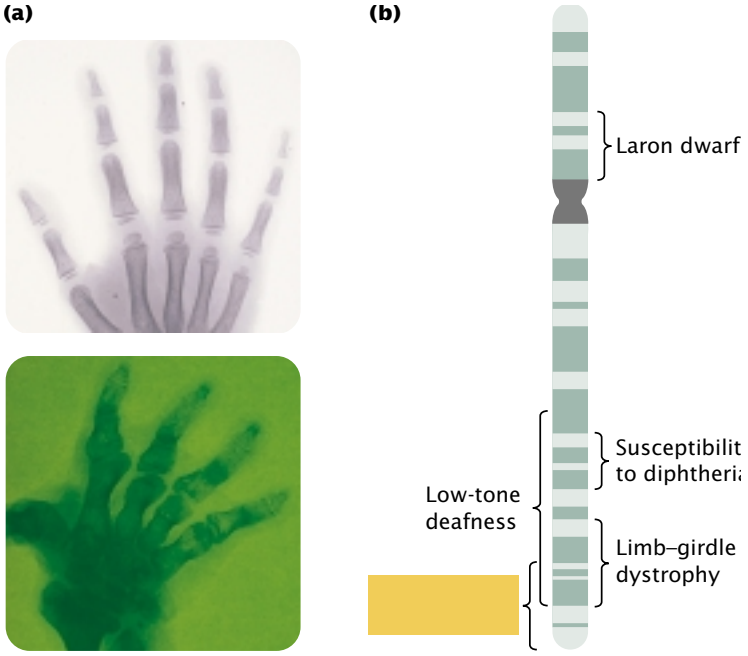
There has never been a more exciting time to undertake the study of genetics than now. Genetics is one of the frontiers of science. Pick up almost any major newspaper or news magazine and chances are that you will see something related to genetics: the discovery of cancer-causing genes; the use of gene therapy to treat diseases; or reports of possible hereditary influences on intelligence, personality, and sexual orientation. These findings often have significant economic and ethical implications, making the study of genetics relevant, timely, and interesting.

www.whfreeman.com/pierce More information about the history of Nicholas II and other tsars of Russia and about hemophilia

The Importance of Genetics

Alexis's hemophilia illustrates the important role that genetics plays in the life of an individual. A difference in one gene, of the 35,000 or so genes that each human possesses, changed Alexis's life, affected his family, and perhaps even altered history. We all possess genes that influence our lives. They affect our height and weight, our hair color and skin pigmentation. They influence our susceptibility to many diseases and disorders **(FIGURE 1.2)** and even contribute to our intelligence and personality. Genes are fundamental to who and what we are.

Although the science of genetics is relatively new, people have understood the hereditary nature of traits and have "practiced" genetics for thousands of years. The rise of agriculture began when humans started to apply genetic principles to the domestication of plants and animals. Today, the major crops and animals used in agriculture have undergone extensive genetic alterations to greatly increase their yields and provide many desirable traits, such as disease and pest



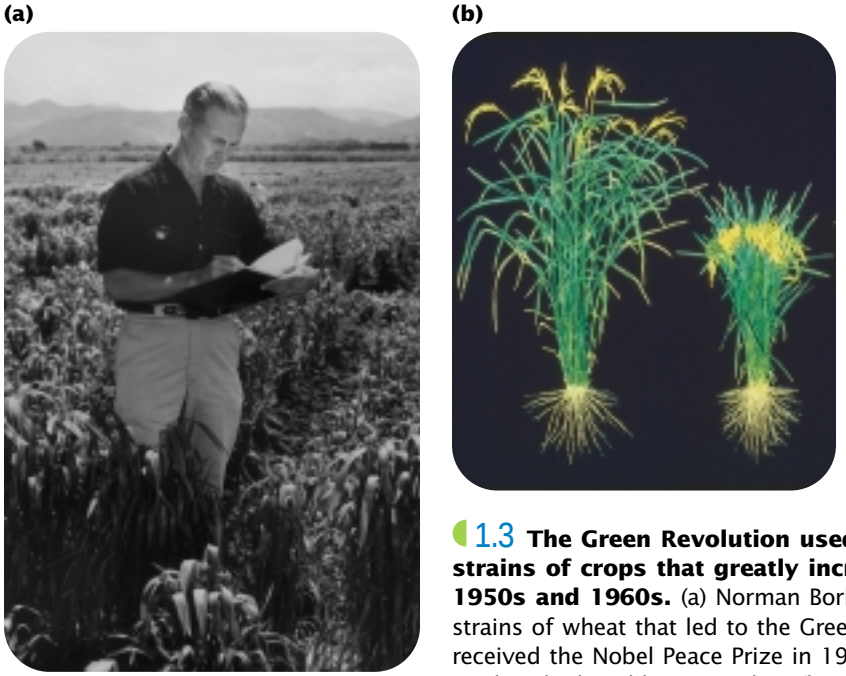
1.2 Genes influence susceptibility to many diseases and disorders. (a) X-ray of the hand of a person suffering from diastrophic dysplasia (bottom), a hereditary growth disorder that results in curved bones, short limbs, and hand deformities, compared with an X-ray of a normal hand (top). (b) This disorder is due to a defect in a gene on chromosome 5. Other genetic disorders encoded by genes on chromosome 5 also are indicated by braces. (Part a: top, Biophoto Associates/Science Source Photo Researchers; bottom, courtesy of Eric Lander, Whitehead Institute, MIT.)

resistance, special nutritional qualities, and characteristics that facilitate harvest. The Green Revolution, which expanded global food production in the 1950s and 1960s, relied heavily on the application of genetics (FIGURE 1.3). Today, genetically engineered corn, soybeans, and other crops constitute a significant proportion of all the food produced worldwide.

The pharmaceutical industry is another area where genetics plays an important role. Numerous drugs and food additives are synthesized by fungi and bacteria that have been genetically manipulated to make them efficient producers of these substances. The biotechnology industry employs molecular genetic techniques to develop and mass-produce substances of commercial value. Growth hormone, insulin, and clotting factor are now produced commercially by genetically engineered bacteria (FIGURE 1.4). Techniques of molecular genetics have also been used to produce bacteria that remove minerals from ore, break down toxic chemicals, and inhibit damaging frost formation on crop plants.

Genetics also plays a critical role in medicine. Physicians recognize that many diseases and disorders have a hereditary component, including well-known genetic disorders such as sickle-cell anemia and Huntington disease as well as many common diseases such as asthma, diabetes, and hypertension. Advances in molecular genetics have allowed important insights into the nature of cancer and permitted the development of many diagnostic tests. Gene therapy—the direct alteration of genes to treat human diseases—has become a reality.

www.whfreeman.com/pierce Information about biotechnology, including its history and applications

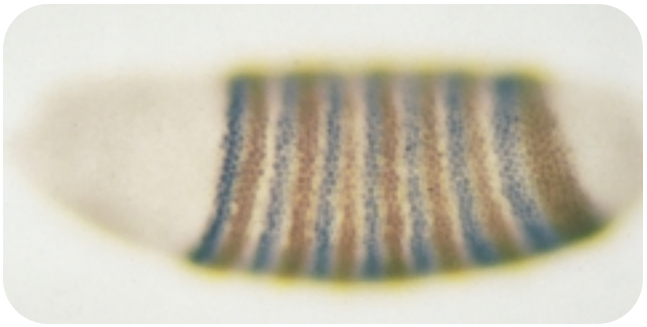


1.3 The Green Revolution used genetic techniques to develop new strains of crops that greatly increased world food production during the 1950s and 1960s. (a) Norman Borlaug, a leader in the development of new strains of wheat that led to the Green Revolution, and a family in Ghana. Borlaug received the Nobel Peace Prize in 1970. (b) Traditional rice plant (top) and modern, high-yielding rice plant (bottom). (Part a, UPI/Corbis-Bettman; part b, IRRI.)

1.4 The biotechnology industry uses molecular genetic methods to produce substances of economic value. In the apparatus shown, growth hormone is produced by genetically engineered bacteria. (James Holmes/Celltech Ltd./Science Photo Library/Photo Researchers.)

The Role of Genetics in Biology

Although an understanding of genetics is important to all people, it is critical to the student of biology. Genetics provides one of biology's unifying principles: all organisms use nucleic acids for their genetic material and all encode their genetic information in the same way. Genetics undergirds the study of many other biological disciplines. Evolution, for example, is genetic change taking place through time; so the study of evolution requires an understanding of basic genetics. Developmental biology relies heavily on genetics: tissues and organs form through the regulated expression of genes (**Figure 1.5**). Even such fields as taxonomy, ecology, and animal behavior are making increasing use of genetic methods. The study of almost any field of biology or medicine is incomplete without a thorough understanding of genes and genetic methods.



1.5 The key to development lies in the regulation of gene expression. This early fruit-fly embryo illustrates the localized production of proteins from two genes, *ftz* (stained gray) and *eve* (stained brown), which determine the development of body segments in the adult fly. (Peter Lawrence, 1992. *The Making of a Fly,* Blackwell Scientific Publications.)

Genetic Variation Is the Foundation of Evolution

Life on Earth exists in a tremendous array of forms and features that occupy almost every conceivable environment. All life has a common origin (see Chapter 2); so this diversity has developed during Earth's 4-billion-year history. Life is also characterized by adaptation: many organisms are exquisitely suited to the environment in which they are found. The history of life is a chronicle of new forms of life emerging, old forms disappearing, and existing forms changing.

Life's diversity and adaptation are a product of evolution, which is simply genetic change through time. Evolution is a two-step process: first, genetic variants arise randomly and, then, the proportion of particular variants increases or decreases. Genetic variation is therefore the foundation of all evolutionary change and is ultimately the basis of all life as we know it. Genetics, the study of genetic variation, is critical to understanding the past, present, and future of life.

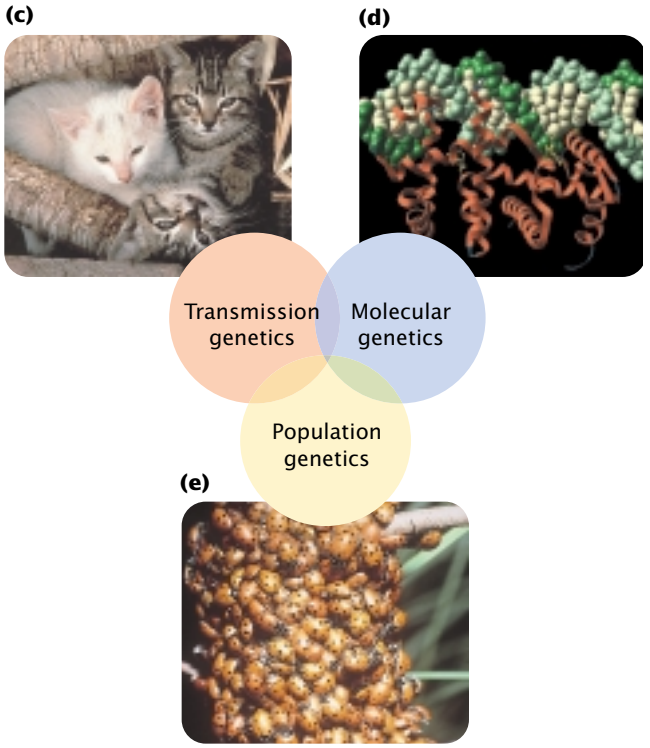
Concepts

Heredity affects many of our physical features as well as our susceptibility to many diseases and disorders. Genetics contributes to advances in agriculture, pharmaceuticals, and medicine and is fundamental to modern biology. Genetic variation is the foundation of the diversity of all life.

Divisions of Genetics

Traditionally, the study of genetics has been divided into three major subdisciplines: transmission genetics, molecular genetics, and population genetics (**Figure 1.6**). Also known as classical genetics, **transmission genetics** encompasses the basic principles of genetics and how traits are passed from one generation to the next. This area addresses the relation between chromosomes and heredity, the arrangement of genes on chromosomes, and gene mapping. Here the focus is on the individual organism—how an individual organism inherits its genetic makeup and how it passes its genes to the next generation.

Molecular genetics concerns the chemical nature of the gene itself: how genetic information is encoded, replicated, and expressed. It includes the cellular processes of replication, transcription, and translation—by which genetic information is transferred from one molecule to another—and gene



1.6 Genetics can be subdivided into three interrelated fields. (Top left, Alan Carey/Photo Researchers; top right, MONA file M0214602 tif; bottom, J. Alcock/Visuals Unlimited.)

regulation—the processes that control the expression of genetic information. The focus in molecular genetics is the gene—its structure, organization, and function.

Population genetics explores the genetic composition of groups of individual members of the same species (populations) and how that composition changes over time and space. Because evolution is genetic change, population genetics is fundamentally the study of evolution. The focus of population genetics is the group of genes found in a population.

It is convenient and traditional to divide the study of genetics into these three groups, but we should recognize that the fields overlap and that each major subdivision can be further divided into a number of more specialized fields, such as chromosomal genetics, biochemical genetics, quantitative genetics, and so forth. Genetics can alternatively be subdivided by organism (fruit fly, corn, or bacterial genetics), and each of these organisms can be studied at the level of transmission, molecular, and population genetics. Modern genetics is an extremely broad field, encompassing many interrelated subdisciplines and specializations.

Concepts

The three major divisions of genetics are transmission genetics, molecular genetics, and population genetics. Transmission genetics examines the principles of heredity; molecular genetics deals with the gene and the cellular processes by which genetic information is transferred and expressed; population genetics concerns the genetic composition of groups of organisms and how that composition changes over time and space.

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A Brief History of Genetics

Although the science of genetics is young—almost entirely a product of the past 100 years—people have been using genetic principles for thousands of years.

Prehistory

The first evidence that humans understood and applied the principles of heredity is found in the domestication of plants and animals, which began between approximately 10,000 and 12,000 years ago. Early nomadic people depended on hunting and gathering for subsistence but, as human populations grew, the availability of wild food resources declined. This decline created pressure to develop new sources of food; so people began to manipulate wild plants and animals, giving rise to early agriculture and the first fixed settlements.

Initially, people simply selected and cultivated wild plants and animals that had desirable traits. Archeological evidence of the speed and direction of the domestication process demonstrates that people quickly learned a simple but crucial rule of heredity: like breeds like. By selecting and breeding individual plants or animals with desirable traits, they could produce these same traits in future generations.

The world's first agriculture is thought to have developed in the Middle East, in what is now Turkey, Iraq, Iran, Syria, Jordan, and Israel, where domesticated plants and animals were major dietary components of many populations by 10,000 years ago. The first domesticated organisms included wheat, peas, lentils, barley, dogs, goats, and sheep. Selective breeding produced woollier and more manageable goats and sheep and seeds of cereal plants that were larger and easier to harvest. By 4000 years ago, sophisticated genetic techniques were already in use in the Middle East. Assyrians and Babylonians developed several hundred varieties of date palms that differed in fruit size, color, taste, and time of ripening. An Assyrian bas-relief from 2880 years ago depicts the use of artificial fertilization to control crosses between date palms (FIGURE 1.7). Other crops and domesticated animals were developed by cultures in Asia, Africa, and the Americas in the same period.

1.7 Ancient peoples practiced genetic techniques in agriculture. (Top) Comparison of ancient (left) and modern (right) wheat. (Bottom) Assyrian bas-relief sculpture showing artificial pollination of date palms at the time of King Assurnasirpalli II, who reigned from 883–859 B.C. (Top left and right, IRRI; bottom, Metropolitan Museum of Art, gift of John D. Rockefeller Jr., 1932.

Concepts

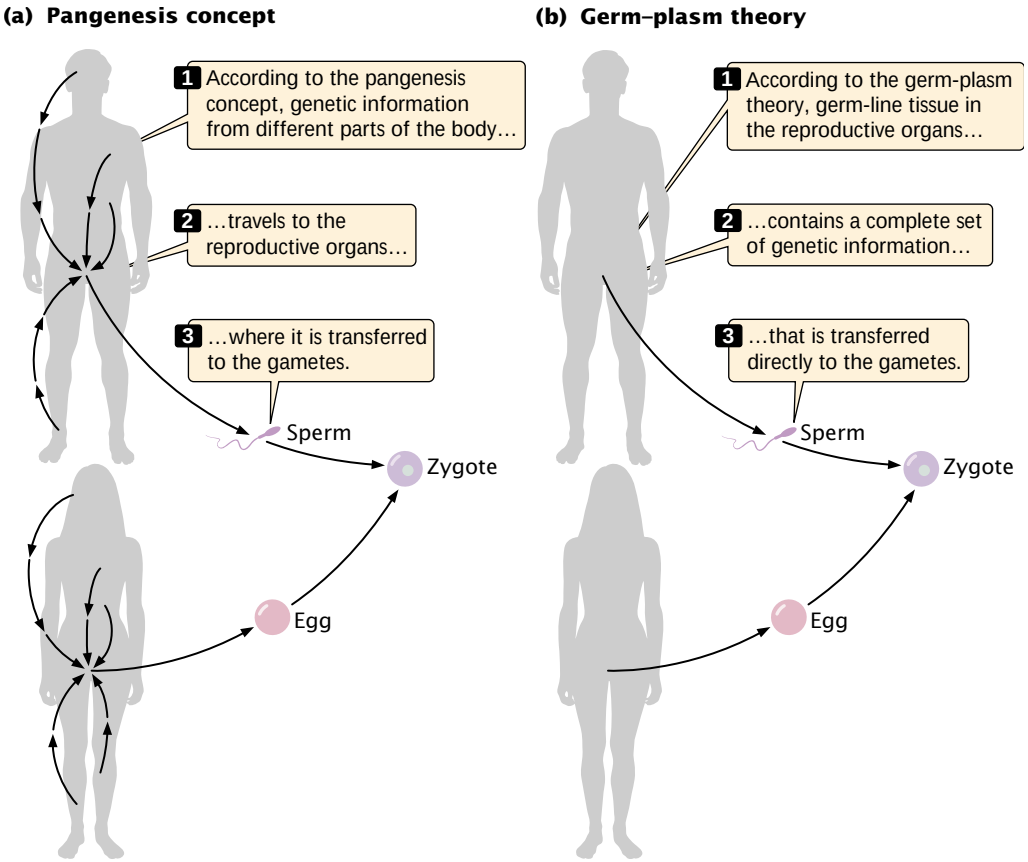
Humans first applied genetics to the domestication of plants and animals between approximately 10,000 and 12,000 years ago. This domestication led to the development of agriculture and fixed human settlements.

Early Written Records

Ancient writings demonstrate that early humans were aware of their own heredity. Hindu sacred writings dating to 2000 years ago attribute many traits to the father and suggest that differences between siblings can be accounted for by effects from the mother. These same writings advise that one should avoid potential spouses having undesirable traits that might be passed on to one's children. The Talmud, the Jewish book of religious laws based on oral traditions dating back thousands of years, presents an uncannily accurate understanding of the inheritance of hemophilia. It directs that, if a woman bears two sons who die of bleeding after circumcision, any additional sons that she bears should not be circumcised; nor should the sons of her sisters be circumcised, although the sons of her brothers should. This advice accurately depicts the X-linked pattern of inheritance of hemophilia (discussed further in Chapter 6).

The ancient Greeks gave careful consideration to human reproduction and heredity. The Greek physician Alcmaeon (circa 520 B.C.) conducted dissections of animals and proposed that the brain was not only the principle site of perception, but also the origin of semen. This proposal sparked a long philosophical debate about where semen was produced and its role in heredity. The debate culminated in the concept of **pangenesis,** which proposed that specific particles, later called gemmules, carry information from various parts of the body to the reproductive organs, from where they are passed to the embryo at the moment of conception **(Figure 1.8a)**. Although incorrect, the concept of pangenesis was highly influential and persisted until the late 1800s.

Pangenesis led the ancient Greeks to propose the notion of the **inheritance of acquired characteristics,** in which traits acquired during one's lifetime become incorporated into one's hereditary information and are passed on to



1.8 Pangenesis, an early concept of inheritance, compared with the modern germ-plasm theory.

offspring; for example, people who developed musical ability through diligent study would produce children who are innately endowed with musical ability. The notion of the inheritance of acquired characteristics also is no longer accepted, but it remained popular through the twentieth century.

The Greek philosopher Aristotle (384–322 B.C.) was keenly interested in heredity. He rejected the concepts of both pangenesis and the inheritance of acquired characteristics, pointing out that people sometimes resemble past ancestors more than their parents and that acquired characteristics such as mutilated body parts are not passed on. Aristotle believed that both males and females made contributions to the offspring and that there was a struggle of sorts between male and female contributions.

Although the ancient Romans contributed little to the understanding of human heredity, they successfully developed a number of techniques for animal and plant breeding; the techniques were based on trial and error rather than any general concept of heredity. Little new was added to the understanding of genetics in the next 1000 years. The ancient ideas of pangenesis and the inheritance of acquired characteristics, along with techniques of plant and animal breeding, persisted until the rise of modern science in the seventeenth and eighteenth centuries.

The Rise of Modern Genetics

Dutch spectacle makers began to put together simple microscopes in the late 1500s, enabling Robert Hooke (1653–1703) to discover cells in 1665. Microscopes provided naturalists with new and exciting vistas on life, and perhaps it was excessive enthusiasm for this new world of the very small that gave rise to the idea of **preformationism.** According to preformationism, inside the egg or sperm existed a tiny miniature adult, a *homunculus*, which simply enlarged during development. Ovists argued that the homunculus resided in the egg, whereas spermists insisted that it was in the sperm (◖ FIGURE 1.9). Preformationism meant that all traits would be inherited from only one parent—from the father if the homunculus was in the sperm or from the mother if it was in the egg. Although many observations suggested that offspring possess a mixture of traits from both parents, preformationism remained a popular concept throughout much of the seventeenth and eighteenth centuries.

Another early notion of heredity was **blending inheritance,** which proposed that offspring are a blend, or mixture,

The New Genetics
ETHICS • SCIENCE • TECHNOLOGY

Mapping the Human Genome—Where does it lead, and what does it mean?

by Arthur L. Caplan and Kelly A. Carroll

In June 2000, scientists from the Human Genome Project and Celera Genomics stood at a podium with former President Bill Clinton to announce a stunning achievement—they had successfully constructed a sequence of the entire huan genome. Soon this process of identifying and sequencing each and every human gene became characterized as "mapping the human genome". As with maps of the physical world, the map of the human genome provides a picture of locations, terrains, and structures. But, like explorers, scientists must continue to decipher what each location on the map can tell us about diseases, human health, and biology. The map accelerates this process, as it allows researchers to identify key structural dimensions of the gene they are exploring, and reminds them where they have been and where they have yet to explore.

What does the map of the human genome depict? when researchers discuss the sequencing of the genome, they are describing the identification of the patterns and order of the 3 billion human DNA base pairs. While this provides valuable information about overall structure and the evolution of humans in relation to other organisms, researchers really wanted the key information encoded in just 2% of this enormous map—the information that makes most of the proteins that compose you and me. Comprised of DNA, genes are the basic units of heredity; they hold all of the information required to make the proteins that regulate most life functions, from digesting food to battling diseases. Proteins stand as the link between genes and pharmaceutical drug development, they show which genes are being expressed at any given moment, and provide information about gene function.

Knowing our genes will lead to greater understanding and radically improved treatment of many diseases. However, sequencing the entire human genome, in conjunction with sequencing of various nonhuman genomes under the same project, has raised fundamental questions about what it means to be human. After all, fruit flies possess about one-third the number of genes as humans, and an ear of corn has approximately the same number of genes as a human! In addition, the overall DNA sequence of a chimpanzee is about 99% the same as the human genome sequence. As the genomes of other species become available, the similarities to the human genome in both structure and sequence pattern will continue to be identified. At a basic level, the discovery of so many commonalities and links and ancestral trees with other species adds credence to principles of evolution and Darwinism.

Some of the most anticipated developments and potential benefits of the Human Genome Project directly affect human health; researchers, practicing physicians, and the general public eagerly await the development of targeted pharmaceutical agents and more specific diagnostic tests. Pharmacogenomics is at the intersection of genetics and pharmacology; it is the study of how one's genetic makeup will affect his or her response to various drugs. In the future, medicine will potentially be safer, cheaper, and more disease specific, all while causing fewer side effects and acting more effectively, the first time around.

There are however some hard ethical questions that follow in the wake of new genetic knowledge. Patients will have to undergo genetic testing in order to match drugs to their genetic makeup. Who will have access to these result—just the health care practitioner, or the patient's insurance company, employer/school, and/or family members? While the tests were administered for one case, will the information derived from them be used for other purposes, such as for identification of other conditions/future diseases, or even in research studies?

How should researchers conduct studies in pharmacogenomics? Often they need to group study subjects by some kind of identifiabe traits that they believe will assist in separating groups of drugs, and in turn they separate people into populations. The order of almost all of the DNA base pairs (99.9%) is exactly the same in all humans. So, this leaves a small window of difference. There is potential for stigmatization of individuals and groups, of people based on race and ethnicity inherent in genomic research and analysis. As scientists continue drug development, they must be careful to not further such ideas, especially as studies of nuclear DNA indicate that there is often more genetic variation within "races" or cultures, than between "races" or cultures. Stigmatization or discrimination can occur through genetic testing and human subjects research on populations.

These are just a few of the ethical issues arising out of one development of the Human Genome Project. The potential applications of genome research are staggering, and the mapping is just the beginning. Realizing this was simply a starting point, the draft sequences of the human genome released in February 2001 by the publicly funded Human Genome Project and the private company, Celera Genomics, are freely available on the Internet. A long road lies ahead, where scientists will be charged with exploring and understanding the functions of and relationships between genes and proteins. With such exploration comes a responsibility to acknowledge and address the ethical, legal, and social implications of this exciting research.

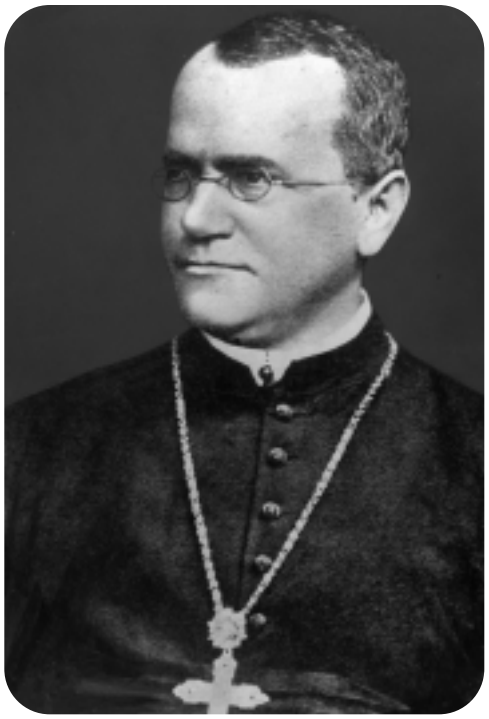
1.9 **Preformationism was a popular idea of inheritance in the seventeenth and eighteenth centuries.** Shown here is a drawing of a homunculus inside a sperm. (Science VU/Visuals Unlimited.)

of parental traits. This idea suggested that the genetic material itself blends, much as blue and yellow pigments blend to make green paint. Once blended, genetic differences could not be separated out in future generations, just as green paint cannot be separated out into blue and yellow pigments. Some traits do *appear* to exhibit blending inheritance; however, we realize today that individual genes do not blend.

Nehemiah Grew (1641–1712) reported that plants reproduce sexually by using pollen from the male sex cells. With this information, a number of botanists began to experiment with crossing plants and creating hybrids. Foremost among these early plant breeders was Joseph Gottleib Kölreuter (1733–1806), who carried out numerous crosses and studied pollen under the microscope. He observed that many hybrids were intermediate between the parental varieties. Because he crossed plants that differed in many traits, Kölreuter was unable to discern any general pattern of inheritance. In spite of this limitation, Kölreuter's work set the foundation for the modern study of genetics. Subsequent to his work, a number of other botanists began to experiment with hybridization, including Gregor Mendel (1822–1884) (FIGURE 1.10), who went on to discover the basic principles of heredity. Mendel's conclusions, which were unappreciated for 45 years, laid the foundation for our modern understanding of heredity, and he is generally recognized today as the father of genetics.

Developments in cytology (the study of cells) in the 1800s had a strong influence on genetics. Robert Brown (1773–1858) described the cell nucleus in 1833. Building on the work of others, Matthis Jacob Schleiden (1804–1881) and Theodor Schwann (1810–1882) proposed the concept of the **cell theory** in 1839. According to this theory, all life is composed of cells, cells arise only from preexisting cells, and the cell is the fundamental unit of structure and function in living organisms. Biologists began to examine cells to see how traits were transmitted in the course of cell division.

Charles Darwin (1809–1882), one of the most influential biologists of the nineteenth century, put forth the theory of evolution through natural selection and published his ideas in *On the Origin of Species* in 1856. Darwin recognized that heredity was fundamental to evolution, and he



1.10 **Gregor Mendel was the founder of modern genetics.** Mendel first discovered the principles of heredity by crossing different varieties of pea plants and analyzing the pattern of transmission of traits in subsequent generations. (Hulton/Archive by Getty Images.)

conducted extensive genetic crosses with pigeons and other organisms. However, he never understood the nature of inheritance, and this lack of understanding was a major omission in his theory of evolution.

In the last half of the nineteenth century, the invention of the microtome (for cutting thin sections of tissue for microscopic examination) and the development of improved histological stains stimulated a flurry of cytological research. Several cytologists demonstrated that the nucleus had a role in fertilization. Walter Flemming (1843–1905) observed the division of chromosomes in 1879 and published a superb description of mitosis. By 1885, it was generally recognized that the nucleus contained the hereditary information.

Near the close of the nineteenth century, August Weismann (1834–1914) finally laid to rest the notion of the inheritance of acquired characteristics. He cut off the tails of mice for 22 consecutive generations and showed that the tail length in descendants remained stubbornly long. Weismann proposed the **germ-plasm theory,** which holds that the cells in the reproductive organs carry a complete set of genetic information that is passed to the gametes (see Figure 1.8b).

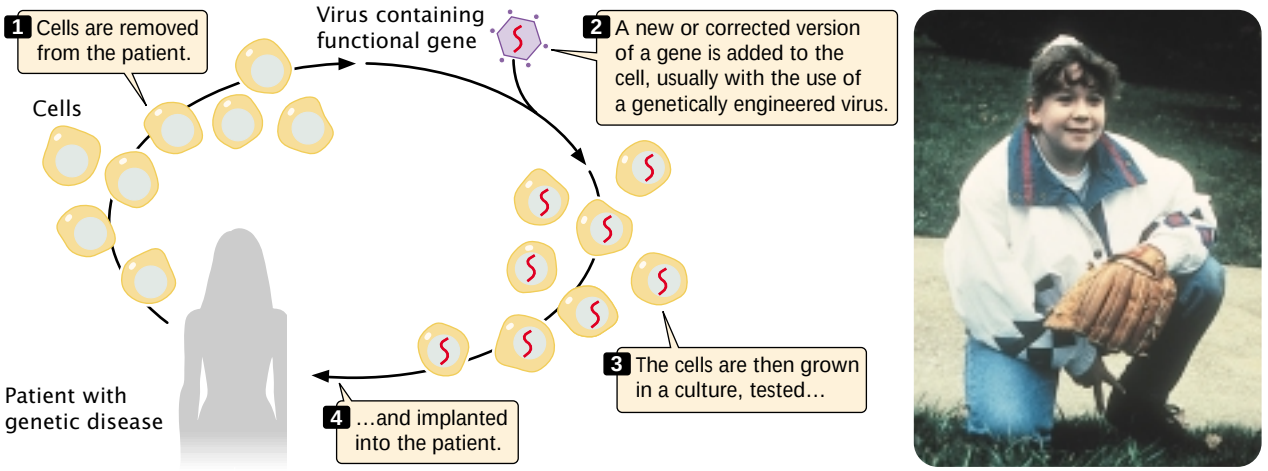
Twentieth-Century Genetics

The year 1900 was a watershed in the history of genetics. Gregor Mendel's pivotal 1866 publication on experiments with pea plants, which revealed the principles of heredity, was "rediscovered," as discussed in more detail in Chapter 3. The significance of his conclusions was recognized, and other biologists immediately began to conduct similar genetic studies on mice, chickens, and other organisms. The results of these investigations showed that many traits indeed follow Mendel's rules.

Walter Sutton (1877–1916) proposed in 1902 that genes are located on chromosomes. Thomas Hunt Morgan (1866–1945) discovered the first genetic mutant of fruit flies in 1910 and used fruit flies to unravel many details of transmission genetics. Ronald A. Fisher (1890–1962), John B. S. Haldane (1892–1964), and Sewall Wright (1889–1988) laid the foundation for population genetics in the 1930s.

Geneticists began to use bacteria and viruses in the 1940s; the rapid reproduction and simple genetic systems of these organisms allowed detailed study of the organization and structure of genes. At about this same time, evidence accumulated that DNA was the repository of genetic information. James Watson (b. 1928) and Francis Crick (b. 1916) described the three-dimensional structure of DNA in 1953, ushering in the era of molecular genetics.

By 1966, the chemical structure of DNA and the system by which it determines the amino acid sequence of proteins had been worked out. Advances in molecular genetics led to the first recombinant DNA experiments in 1973, which touched off another revolution in genetic research. Walter Gilbert (b. 1932) and Frederick Sanger (b. 1918) developed methods for sequencing DNA in 1977. The polymerase chain reaction, a technique for quickly amplifying tiny amounts of DNA, was developed by Kary Mullis (b. 1944) and others in 1986. In 1990, gene therapy was used for the first time to treat human genetic disease in the United States (FIGURE 1.11), and the Human Genome Project was launched. By 1995, the first complete DNA sequence of a free-living organism—the bacterium *Haemophilus influenzae*—was determined, and the first complete sequence of a eukaryotic organism (yeast) was reported a year later. At the beginning of the twenty-first century, the human genome sequence was determined, ushering in a new era in genetics.



1.11 Gene therapy applies genetic engineering to the treatment of human diseases. (J. Coate, MDBD/Science VU/Visuals Unlimited.)

The Future of Genetics

The information content of genetics now doubles every few years. The genome sequences of many organisms are added to DNA databases every year, and new details about gene structure and function are continually expanding our knowledge of heredity. All of this information provides us with a better understanding of numerous biological processes and evolutionary relationships. The flood of new genetic information requires the continuous development of sophisticated computer programs to store, retrieve, compare, and analyze genetic data and has given rise to the field of bioinformatics, a merging of molecular biology and computer science.

In the future, the focus of DNA-sequencing efforts will shift from the genomes of different species to individual differences within species. It is reasonable to assume that each person may some day possess a copy of his or her entire genome sequence. New genetic microchips that simultaneously analyze thousands of RNA molecules will provide information about the activity of thousands of genes in a given cell, allowing a detailed picture of how cells respond to external signals, environmental stresses, and disease states. The use of genetics in the agricultural, chemical, and health-care fields will continue to expand; some predict that biotechnology will be to the twenty-first century what the electronics industry was to the twentieth century. This ever-widening scope of genetics will raise significant ethical, social, and economic issues.

This brief overview of the history of genetics is not intended to be comprehensive; rather it is designed to provide a sense of the accelerating pace of advances in genetics. In the chapters to come, we will learn more about the experiments and the scientists who helped shape the discipline of genetics.

www.whfreeman.com/pierce More information about the history of genetics

Concepts

Developments in plant hybridization and cytology in the eighteenth and nineteenth centuries laid the foundation for the field of genetics today. After Mendel's work was rediscovered in 1900, the science of genetics developed rapidly and today is one of the most active areas of science.

Basic Concepts in Genetics

Undoubtedly, you learned some genetic principles in other biology classes. Let's take a few moments to review some of these fundamental genetic concepts.

Cells are of two basic types: eukaryotic and prokaryotic- Structurally, cells consist of two basic types, although, evolutionarily, the story is more complex (see Chapter 2). Prokaryotic cells lack a nuclear membrane and possess no membrane-bounded cell organelles, whereas eukaryotic cells are more complex, possessing a nucleus and membrane-bounded organelles such as chloroplasts and mitochondria.

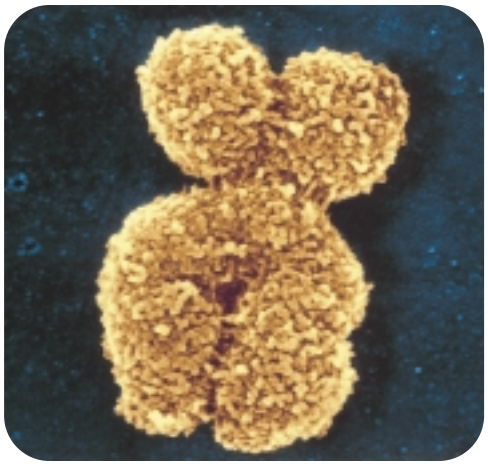
A gene is the fundamental unit of heredity- The precise way in which a gene is defined often varies. At the simplest level, we can think of a gene as a unit of information that encodes a genetic characteristic. We will enlarge this definition as we learn more about what genes are and how they function.

Genes come in multiple forms called alleles- A gene that specifies a characteristic may exist in several forms, called alleles. For example, a gene for coat color in cats may exist in alleles that encode either black or orange fur.

Genes encode phenotypes- One of the most important concepts in genetics is the distinction between traits and genes. Traits are not inherited directly. Rather, genes are inherited and, along with environmental factors, determine the expression of traits. The genetic information that an individual organism possesses is its genotype; the trait is its phenotype. For example, the A blood type is a phenotype; the genetic information that encodes the blood type A antigen is the genotype.

Genetic information is carried in DNA and RNA- Genetic information is encoded in the molecular structure of nucleic acids, which come in two types: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Nucleic acids are polymers consisting of repeating units called nucleotides; each nucleotide consists of a sugar, a phosphate, and a nitrogenous base. The nitrogenous bases in DNA are of four types (abbreviated A, C, G, and T), and the sequence of these bases encodes genetic information. Most organisms carry their genetic information in DNA, but a few viruses carry it in RNA. The four nitrogenous bases of RNA are abbreviated A, C, G, and U.

Genes are located on chromosomes- The vehicles of genetic information within the cell are chromosomes **(FIGURE 1.12)**, which consist of DNA and associated proteins. The cells of each species have a characteristic number of chromosomes; for example, bacterial cells normally possess a single chromosome; human cells possess 46; pigeon cells possess 80. Each chromosome carries a large number of genes.



1.12 Genes are carried on chromosomes.
(Biophoto Associates/Science Source/Photo Researchers.)

Chromosomes separate through the processes of mitosis and meiosis- The processes of mitosis and meiosis ensure that each daughter cell receives a complete set of an organism's chromosomes. Mitosis is the separation of replicated chromosomes during the division of somatic (nonsex) cells. Meiosis is the pairing and separation of replicated chromosomes during the division of sex cells to produce gametes (reproductive cells).

Genetic information is transferred from DNA to RNA to protein- Many genes encode traits by specifying the structure of proteins. Genetic information is first transcribed from DNA into RNA, and then RNA is translated into the amino acid sequence of a protein.

Mutations are permanent, heritable changes in genetic information- Gene mutations affect only the genetic information of a single gene; chromosome mutations alter the number or the structure of chromosomes and therefore usually affect many genes.

Some traits are affected by multiple factors- Some traits are influenced by multiple genes that interact in complex ways with environmental factors. Human height, for example, is affected by hundreds of genes as well as environmental factors such as nutrition.

Evolution is genetic change- Evolution can be viewed as a two-step process: first, genetic variation arises and, second, some genetic variants increase in frequency, whereas other variants decrease in frequency.

www.whfreeman.com/pierce A glossary of genetics terms

Connecting Concepts Across Chapters

This chapter introduces the study of genetics, outlining its history, relevance, and some fundamental concepts. One of the themes that emerges from our review of the history of genetics is that humans have been interested in, and using, genetics for thousands of years, yet our understanding of the mechanisms of inheritance are relatively new. A number of ideas about how inheritance works have been proposed throughout history, but many of them have turned out to be incorrect. This is to be expected, because science progresses by constantly evaluating and challenging explanations. Genetics, like all science, is a self-correcting process, and thus many ideas that are proposed will be discarded or modified through time.

CONCEPTS SUMMARY

- Genetics is central to the life of every individual: it influences our physical features, susceptibility to numerous diseases, personality, and intelligence.
- Genetics plays important roles in agriculture, the pharmaceutical industry, and medicine. It is central to the study of biology.
- Genetic variation is the foundation of evolution and is critical to understanding all life.
- The study of genetics can be divided into transmission genetics, molecular genetics, and population genetics.
- The use of genetics by humans began with the domestication of plants and animals.
- The ancient Greeks developed the concept of pangenesis and the concept of the inheritance of acquired characteristics. Ancient Romans developed practical measures for the breeding of plants and animals.
- In the seventeenth century, biologists proposed the idea of preformationism, which suggested that a miniature adult is present inside the egg or the sperm and that a person inherits all of his or her traits from one parent.
- Another early idea, blending inheritance, proposed that genetic information blends during reproduction and offspring are a mixture of the parental traits.
- By studying the offspring of crosses between varieties of peas, Gregor Mendel discovered the principles of heredity.
- Darwin developed the concept of evolution by natural selection in the 1800s, but he was unaware of Mendel's work and was not able to incorporate genetics into his theory.

- Developments in cytology in the nineteenth century led to the understanding that the cell nucleus is the site of heredity.
- In 1900, Mendel's principles of heredity were rediscovered. Population genetics was established in the early 1930s, followed closely by biochemical genetics and bacterial and viral genetics. Watson and Crick discovered the structure of DNA in 1953, which stimulated the rise of molecular genetics.
- Advances in molecular genetics have led to gene therapy and the Human Genome Project.
- Cells come in two basic types: prokaryotic and eukaryotic.
- Genetics is the study of genes, which are the fundamental units of heredity.
- The genes that determine a trait are termed the genotype; the trait that they produce is the phenotype.
- Genes are located on chromosomes, which are made up of nucleic acids and proteins and are partitioned into daughter cells through the process of mitosis or meiosis.
- Genetic information is expressed through the transfer of information from DNA to RNA to proteins.
- Evolution requires genetic change in populations.

IMPORTANT TERMS

transmission genetics (p. 5)
molecular genetics (p. 5)
population genetics (p. 6)
pangenesis (p. 7)
inheritance of acquired characteristics (p. 7)
preformationism (p. 8)
blending inheritance (p. 8)
cell theory (p. 10)
germ-plasm theory (p. 11)

COMPREHENSION QUESTIONS

Answers to questions and problems preceded by an asterisk will be found at the end of the book.

1. Outline some of the ways in which genetics is important to each of us.
* 2. Give at least three examples of the role of genetics in society today.
3. Briefly explain why genetics is crucial to modern biology.
* 4. List the three traditional subdisciplines of genetics and summarize what each covers.
5. When and where did agriculture first arise? What role did genetics play in the development of the first domesticated plants and animals?
* 6. Outline the notion of pangenesis and explain how it differs from the germ-plasm theory.
* 7. What does the concept of the inheritance of acquired characteristics propose and how is it related to the notion of pangenesis?
* 8. What is preformationism? What did it have to say about how traits are inherited?
9. Define blending inheritance and contrast it with preformationism.
10. How did developments in botany in the seventeenth and eighteenth centuries contribute to the rise of modern genetics?
11. How did developments in cytology in the nineteenth century contribute to the rise of modern genetics?
*12. Who first discovered the basic principles that laid the foundation for our modern understanding of heredity?
13. List some advances in genetics that have occurred in the twentieth century.
*14. Briefly define the following terms: **(a)** gene; **(b)** allele; **(c)** chromosome; **(d)** DNA; **(e)** RNA; **(f)** genetics; **(g)** genotype; **(h)** phenotype; **(i)** mutation; **(j)** evolution.
15. What are the two basic cell types (from a structural perspective) and how do they differ?
16. Outline the relations between genes, DNA, and chromosomes.

APPLICATION QUESTIONS AND PROBLEMS

*17. Genetics is said to be both a very old science and a very young science. Explain what is meant by this statement.
18. Find at least one newspaper article that covers some aspect of genetics. Briefly summarize the article. Does this article focus on transmission, molecular, or population genetics?
19. The following concepts were widely believed at one time but are no longer accepted as valid genetic theories. What experimental evidence suggests that these concepts are incorrect and what theories have taken their place?
(a) pangenesis; **(b)** the inheritance of acquired characteristics; **(c)** preformationism; **(d)** blending inheritance.

CHALLENGE QUESTIONS

20. Describe some of the ways in which your own genetic makeup affects you as a person. Be as specific as you can.
21. Pick one of the following ethical or social issues and give your opinion on this issue. For background information, you might read one of the articles on ethics listed and marked with an asterisk in Suggested Readings at the end of this chapter.

    (a) Should a person's genetic makeup be used in determining his or her eligibility for life insurance?

    (b) Should biotechnology companies be able to patent newly sequenced genes?

    (c) Should gene therapy be used on people?

    (d) Should genetic testing be made available for inherited conditions for which there is no treatment or cure?

    (e) Should governments outlaw the cloning of people?

SUGGESTED READINGS

Articles on ethical issues in genetics are preceded by an asterisk.

*American Society of Human Genetics Board of Directors and the American College of Medical Genetics Board of Directors. 1995. Points to consider: ethical, legal, pyschosocial implications of genetic testing in children. *American Journal of Human Genetics* 57:1233–1241.

An official statement on some of the ethical, legal, and psychological considerations in conducting genetic tests on children by two groups of professional geneticists.

Dunn, L. C. 1965. *A Short History of Genetics.* New York: McGraw-Hill.

An excellent history of major developments in the field of genetics.

*Friedmann, T. 2000. Principles for human gene therapy studies. *Science* 287:2163–2165.

An editorial that outlines principles that serve as the foundation for clinical gene therapy.

Kottak, C. P. 1994. *Anthropology: The Exploration of Human Diversity,* 6th ed. New York: McGraw-Hill.

Contains a summary of the rise of agriculture and initial domestication of plants and animals.

Lander, E. S., and R. A. Weinberg. 2000. Genomics: journey to the center of biology. *Science* 287:1777–1782.

A succinct history of genetics and, more specifically, genomics written by two of the leaders of modern genetics.

McKusick, V. A. 1965. The royal hemophilia. *Scientific American* 213(2):88–95.

Contains a history of hemophilia in Queen Victoria's descendants.

Massie, R. K. 1967. *Nicholas and Alexandra.* New York: Atheneum.

One of the classic histories of Tsar Nicholas and his family.

Massie, R. K. 1995. *The Romanovs: The Final Chapter.* New York: Random House.

Contains information about the finding of the Romanov remains and the DNA testing that verified the identity of the skeletons.

*Rosenberg, K., B. Fuller, M. Rothstein, T. Duster, et al. 1997. Genetic information and workplace: legislative approaches and policy challenges. *Science* 275:1755–1757.

Deals with the use of genetic information in employment.

*Shapiro, H. T. 1997. Ethical and policy issues of human cloning. *Science* 277:195–196.

Discussion of the ethics of human cloning.

Stubbe, H. 1972. *History of Genetics: From Prehistoric Times to the Rediscovery of Mendel's Laws.* Translated by T. R. W. Waters. Cambridge, MA: MIT Press.

A good history of genetics, especially for pre-Mendelian genetics.

Sturtevant, A. H. 1965. *A History of Genetics.* New York: Harper and Row.

An excellent history of genetics.

*Verma, I. M., and N. Somia. 1997. Gene therapy: promises, problems, and prospects. *Nature* 389:239–242.

An update on the status of gene therapy.