CHAPTER 1

THE HISTORY OF GENETICS

Science seldom proceeds in the straightforward logical manner imagined by outsiders.

—James D. Watson, *The Double Helix: A Personal Account of the Discovery of the Structure of DNA* (1968)

Genetics is the biology of heredity, and geneticists are the scientists and researchers who study hereditary processes such as the inheritance of traits, distinctive characteristics, and diseases. Genetics considers the biochemical instructions that convey information from generation to generation.

Tremendous strides in science and technology have enabled geneticists to demonstrate that some genetic variation is related to disease, and that the ability to vary genes improves the capacity of a species to survive changes in the environment. Even though some of the most important advances in genetics research—such as deciphering the genetic code, isolating the genes that cause or predict susceptibility to certain diseases, and successfully cloning plants and animals—have occurred since the mid-twentieth century, the history of genetics study spans a period of about 150 years. As the understanding of genetics progressed, scientific research became increasingly more specific. Genetics first considered populations, then individuals, then it advanced to explore the nature of inheritance at the molecular level.

EARLY BELIEFS ABOUT HEREDITY

From the earliest recorded history, ancient civilizations observed patterns in reproduction. Animals bore offspring of the same species, children resembled their parents, and plants gave rise to similar plants. Some of the earliest ideas about reproduction, heredity, and the transmission of information from parent to child were the particulate theories developed in ancient Greece during the fourth century BC. These theories posited that information from each part of the parent had to be communicated to create the corresponding body part in the offspring. For example, the particulate theories held that information from the parent's heart, lungs, and limbs was transmitted directly from these body parts to create the offspring's heart, lungs, and limbs.

Particulate theories were attempts to explain observed similarities between parents and their children. One reason these theories were inaccurate was that they relied on observations unaided by the microscope. Microscopy (the use of or investigation with the microscope) and the recognition of cells and microorganisms did not occur until the end of the seventeenth century, when the British naturalist Robert Hooke (1635–1703) first observed cells through a microscope.

Until that time (and even for some time after) heredity remained poorly understood. During the Renaissance (from about the fourteenth to the sixteenth centuries), preformationist theories proposed that the parent's body carried highly specialized reproductive cells that contained whole, preformed offspring. Preformationist theories insisted that when these specialized cells containing the offspring were placed in suitable environments, they would spontaneously grow into new organisms with traits similar to the parent organism.

The Greek philosopher Aristotle (384–322 BC), who was such a keen observer of life that he is often referred to as the father of biology, noted that individuals sometimes resemble remote ancestors more closely than their immediate parents. He was a preformationist, positing that the male parent provided the miniature individual and the female provided the supportive environment in which it would grow. He also refuted the notion of a simple, direct transfer of body parts from parent to offspring by observing that animals and humans who had suffered mutilation or loss of body parts did not confer these losses to their offspring. Instead, he described a process that he called *epigenesist*, in which the offspring is gradually generated from an undifferentiated mass by the addition of parts.

Of Aristotle's many contributions to biology, one of the most important was his conclusion that inheritance involved the potential of producing certain characteristics rather than the absolute production of the characteristics themselves. This thinking was closer to the scientific reality of inheritance than any philosophy set forth by his predecessors. However, because Aristotle was developing his theories before the advent of microscopy, he mistakenly presumed that inheritance was conveyed via the blood. Regardless, his enduring influence is evident in the language and thinking about heredity. Even though blood is not the mode of transmission of heredity, people still refer to "blood relatives," "blood lines," and offspring as products of their own "flesh and blood."

One of the most important developments in the study of hereditary processes came in 1858, when the British naturalists Charles Darwin (1809–1882) and Alfred Russel Wallace (1823–1913) announced the theory of natural selection—the idea that members of a population who are better adapted to their environment will be the ones most likely to survive and pass their traits on to the next generation. Darwin published his theories in *On the Origin of Species by Means of Natural Selection* (1859). His work was not viewed favorably, especially by religious leaders who believed it refuted the biblical interpretation of how life on Earth began. Even in the twenty-first century the idea that life evolves gradually through natural processes is not accepted by everyone, and the dispute over creationism and evolution continues.

CELL THEORY

In 1665, when Hooke used the microscope he had designed to examine a piece of cork, he saw a honeycomb pattern of rectangles that reminded him of cells, the chambers of monks in monasteries. His observations prompted scientists to speculate that living tissue as well as nonliving tissue was composed of cells. The French scientist René Dutrochet (1776–1847) performed microscopic studies and concluded in 1824 that both plant and animal tissue was composed of cells.

In 1838 the German botanist Matthias Jakob Schleiden (1804–1881) presented his theory that all plants were constructed of cells. The following year the German cytologist Theodor Schwann (1810–1882) suggested that animals were also composed of cells. Both Schleiden and Schwann theorized that cells were all created using the same process. Even though Schleiden's hypotheses about the process of cell formation were not entirely accurate, both he and Schwann are credited with developing cell theory. Describing cells as the basic units of life, they asserted that all living things are composed of cells, the simplest forms of life that can exist independently. Their pioneering work enabled other scientists to understand accurately how cells live, such as the German pathologist Rudolf Virchow (1821–1902), who launched theories of biogenesis when he posited in 1858 that cells reproduce themselves.

Improvements in microscopy and the increasing study of cytology (the formation, structure, and function of cells) enabled scientists to identify parts of the cell. Key cell components include the nucleus, which directs all cellular activities by controlling the synthesis of proteins, and the mitochondria, which are organelles (membrane-bound cell compartments) that catalyze reactions that produce energy for the cell. Figure 1.1 is a diagram of a typical animal cell that shows its component parts, including the contents of the nucleus, where chromosomes (which contain the genes) are located.

Germplasm Theory of Heredity

Studies of cellular components, processes, and functions produced insights that revealed the connection between cytology and inheritance. The German biologist August Weissmann (1834–1914) studied medicine, biology, and zoology, and his contribution to genetics was an evolutionary theory known as the germplasm theory of heredity. Building on Darwin's idea that specific inherited characteristics are passed from one generation to the next, Weissmann asserted that the genetic code for each organism was contained in its germ cells (the cells that create sperm and eggs). The presence of genetic information in the germ cells explained how this information was conveyed, unchanged from one generation to the next.

In a series of essays about heredity published between 1889 and 1892, Weissmann observed that the amount of genetic material did not double when cells replicated, suggesting that there was some form of biological control of the chromosomes that occurred during the formation of the gametes (sperm and egg). His theory was essentially correct. Normal body growth is attributable to cell division, called mitosis, which produces cells that are genetically identical to the parent cells. The way to avoid giving offspring a double dose of heredity information is through a cell division that reduces the amount of the genetic material in the gametes by one-half. Weissmann called this process reduction division; it is now known as meiosis.

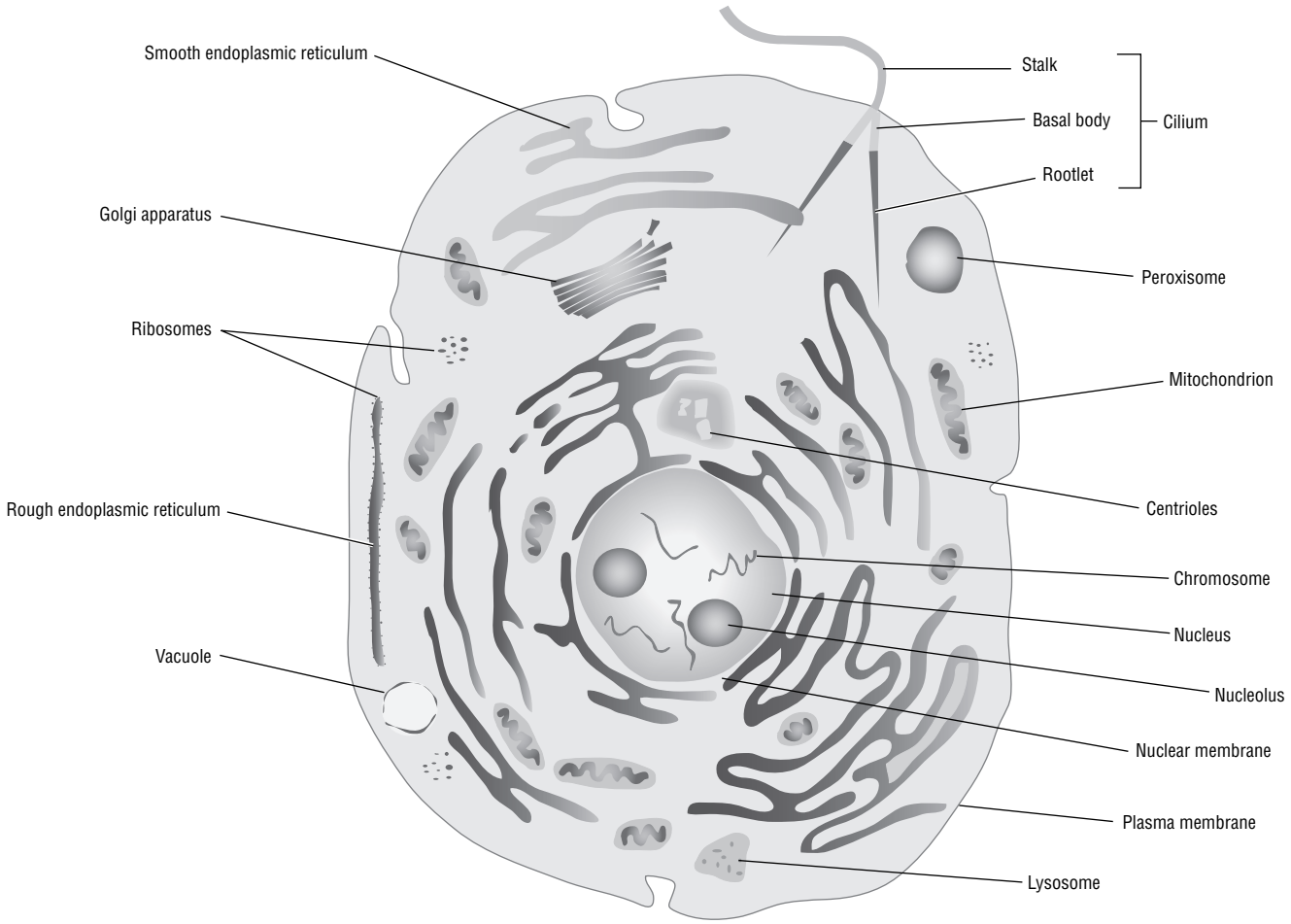
Weissmann was also the first scientist to successfully refute the members of the scientific community who believed that physical characteristics acquired through environmental exposure were passed from generation to generation. He conducted experiments in which he cut the tails off several consecutive generations of mice and observed that none of their offspring were born tailless.

A FARMER'S SON BECOMES THE FATHER OF GENETICS

Gregor Mendel (1822–1884) was born into a peasant family in what is now Hyncice, Czech Republic, and spent much of his youth working in his family's orchards and gardens. At the age of 21 he entered St. Thomas, a Roman

FIGURE 1.1

A typical animal cell



SOURCE: Richard Robinson, ed., "A Typical Animal Cell," in *Genetics*, vol. 1, *A–D*, Macmillan Reference USA, 2002

Catholic monastery, where he studied theology, philosophy, and science. His interest in botany (the scientific study of plants) and an aptitude for natural science inspired his superiors to send him to the University of Vienna, where he studied to become a science teacher. However, Mendel was not destined to become an academic, despite his abiding interest in science and experimentation. In fact, the man who was eventually called the father of genetics never passed the qualifying examinations that would have enabled him to teach science at the highest academic level. Instead, he instructed students at a technical school. He also continued to study botany and conduct research at the monastery, and from 1868 until his death in 1884 he served as its abbot.

Between 1856 and 1863 Mendel conducted carefully designed experiments with nearly 30,000 pea plants he cultivated in the monastery garden. He chose to observe pea plants systematically because they had distinct, identifiable characteristics that could not be confused. Pea plants were also ideal subjects for his experiments because their reproductive organs were surrounded by petals and usually matured before the flower bloomed. As a result, the plants self-fertilized, and each plant variety tended to be a pure breed. Mendel raised several generations of each type of plant to be certain that his plants were pure breeds. In this way, he confirmed that tall plants always produce tall offspring, and plants with green seeds and leaves always produce offspring with green seeds and leaves.

His experiments were designed to test the inheritance of a specific trait from one generation to the next. For example, to test the inheritance of the characteristic of plant height, Mendel self-pollinated several short pea plants, and the seeds they produced grew into short plants. Similarly, self-pollinated tall plants and their resulting seeds, called the first or F1 generation, grew to be tall plants. These results seemed logical. When Mendel bred tall and short plants together and all their offspring in the F1 generation were tall, he concluded that the shortness trait had disappeared. However, when he self-pollinated the F1 generation, the offspring, called the F2 generation (second generation), contained both tall and short

plants. After repeating this experiment many times, Mendel observed that in the F2 generation there were three tall plants for every short one—a 3:1 ratio.

Mendel's attention to rigorous scientific methods of observation, large sample size, and statistical analysis of the data he collected bolstered the credibility of his results. These experiments prompted him to theorize that characteristics, or traits, come in pairs—one from each parent—and that one trait will assume dominance over the other. The trait that appears more frequently is considered the stronger, or dominant, trait, whereas the one that appears less often is the recessive trait.

Focusing on plant height and other distinctive traits, such as the color of the pea pods, seed shape (smooth or wrinkled), and leaf color (green or yellow), enabled Mendel to record accurately and document the results of his plant breeding experiments. His observations about purebred plants and their consistent capacity to convey traits from one generation to the next represented a novel idea. The accepted belief of inheritance described a blending of traits, which, once combined, diluted or eliminated the original traits entirely. For example, it was believed that crossbreeding a tall and a short plant would produce a plant of medium height.

About the same time, Darwin was performing similar experiments using snapdragons, and his observations were comparable to those made by Mendel. Even though Darwin and Mendel both explained the units of heredity and variations in species in their published works, it was Mendel who was later credited with developing the groundbreaking theories of heredity.

Mendel's Laws of Heredity

> *The constant characters which appear in the several varieties of a group of plants may be obtained in all the associations which are possible according to the [mathematical] laws of combination, by means of repeated artificial fertilization.*
>
> —Gregor Mendel, "Versuche über Pflanzen-Hybriden" (1865)

From the results of his experiments, Mendel formulated and published three interrelated theories in the paper "Versuche über Pflanzen-Hybriden" ("Experiments in Plant Hybridization" [1865; translated into English in 1901]). This work established the basic tenets of heredity:

- Two heredity factors exist for each characteristic or trait.
- Heredity factors are contained in equal numbers in the gametes.
- The gametes contain only one factor for each characteristic or trait.
- Gametes combine randomly, no matter which hereditary factors they carry.
- When gametes are formed, different hereditary factors sort independently.

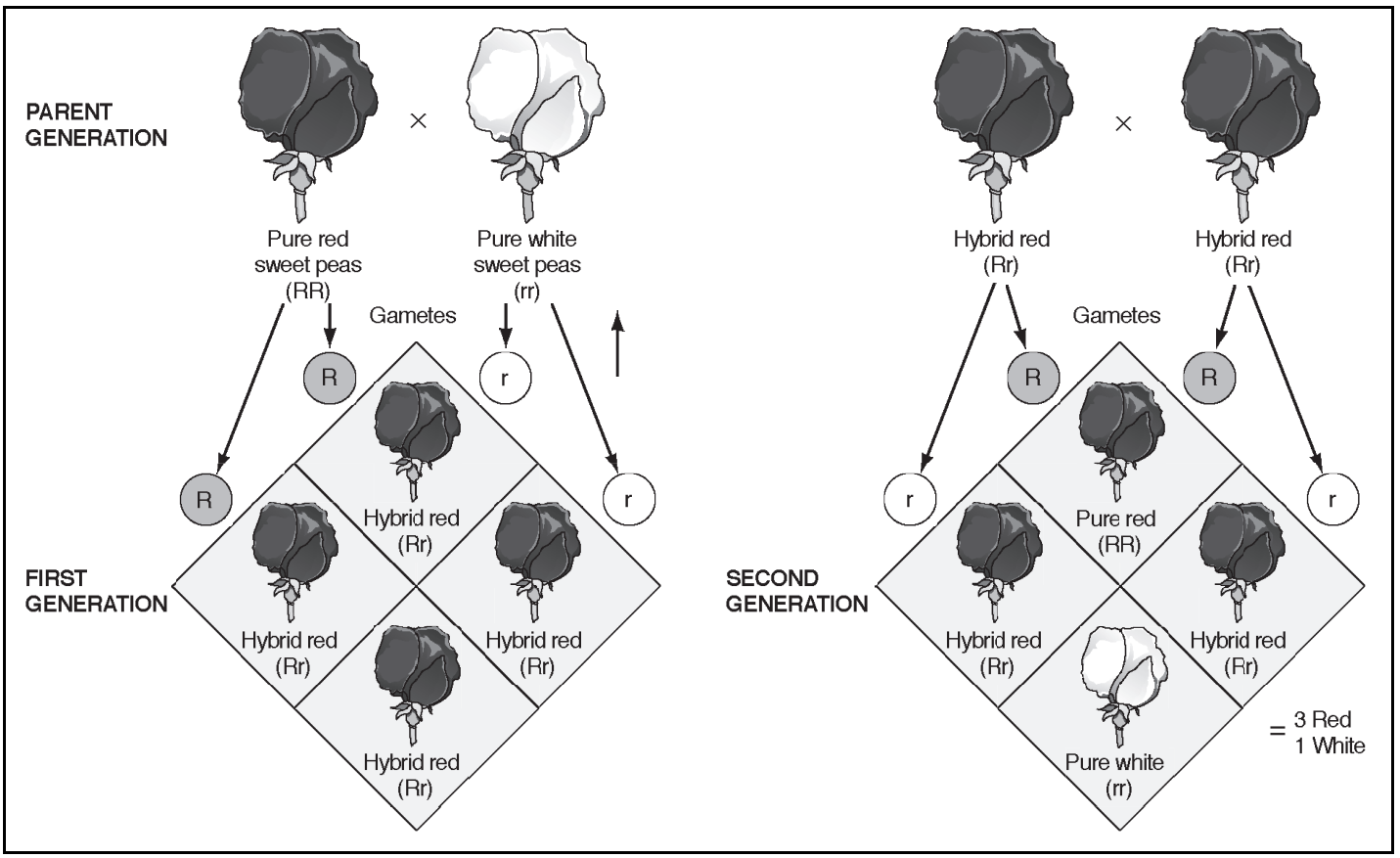
When Mendel presented his paper, it was virtually ignored by the scientific community, which was otherwise engaged in a heated debate about Darwin's theory of evolution. Years later, well after Mendel's death in 1884, his observations and assumptions were revisited and became known as Mendel's laws of heredity. His first principal of heredity, the law of segregation, stated that hereditary units, now known as genes, are always paired and that genes in a pair separate during cell division, with the sperm and egg each receiving one gene of the pair. As a result, each gene in a pair will be present in half the sperm or egg cells. In other words, each gamete receives from a parent cell only one-half of the pair of genes it carries. Because two gametes (male and female) unite to reproduce and form a new cell, the new cell will have a unique pair of genes of its own, half from one parent and half from the other.

Diagrams of genetic traits conventionally use capital letters to represent the dominant traits and lowercase letters to represent recessive traits. Figure 1.2 uses this system to demonstrate Mendel's law of segregation. The pure red sweet pea and the pure white sweet pea each have two genes—RR for the red and rr for the white. The possible outcomes of this mating in the first generation are all hybrid (a combination of two different types) red plants (Rr)—plants that all have the same outward appearance (or phenotype) as the pure red parent but that also carry the white gene. As a result, when two of the hybrid F1 generation plants are bred, there is a 50% chance that the resulting offspring will be hybrid red, a 25% chance that the offspring will be pure red, and a 25% chance that the offspring will be pure white.

Mendel also provided compelling evidence from his experiments for the law of independent assortment. This law established that each pair of genes is inherited independently of all other pairs. Figure 1.3 shows the chance distribution of any possible combination of traits. The F1 generation of tall flowering red and dwarf white sweet pea plants produced four tall hybrid red plants with the identical phenotype. However, each one has a combination of genetic information different from that of the original parent plants. The unique combination of genetic information is known as a genotype. The F2 generation, bred from two tall red hybrid flowers, produced four different phenotypes: tall with red flowers, tall with white flowers, dwarf with red flowers, and dwarf with white flowers. Both Figure 1.2 and Figure 1.3 demonstrate that recessive traits that disappear in the F1 generation may reappear in future generations in definite, predictable percentages.

The law of dominance, the third tenet of inheritance identified by Mendel, asserts that heredity factors (genes) act together as pairs. When a cross occurs between organisms that are pure for contrasting traits, only one trait, the dominant one, appears in the hybrid offspring. In Figure 1.2 all the F1 generation offspring are red—an identical phenotype to the parent plant—though they also carry the recessive white gene.

FIGURE 1.2



Mendel's law of segregation. *Hans & Cassidy, Cengage Gale.*

Mendel's contributions to the understanding of heredity were not acknowledged during his lifetime. When his efforts to reproduce the findings from his pea plant studies using hawkweed plants and honeybees did not prove successful, Mendel was dispirited. He set aside his botany research and returned to monastic life until his death. It was not until the early twentieth century, nearly 40 years after he published his findings, that the scientific community resurrected Mendel's work and affirmed the importance of his ideas.

GENETICS AT THE DAWN OF THE TWENTIETH CENTURY

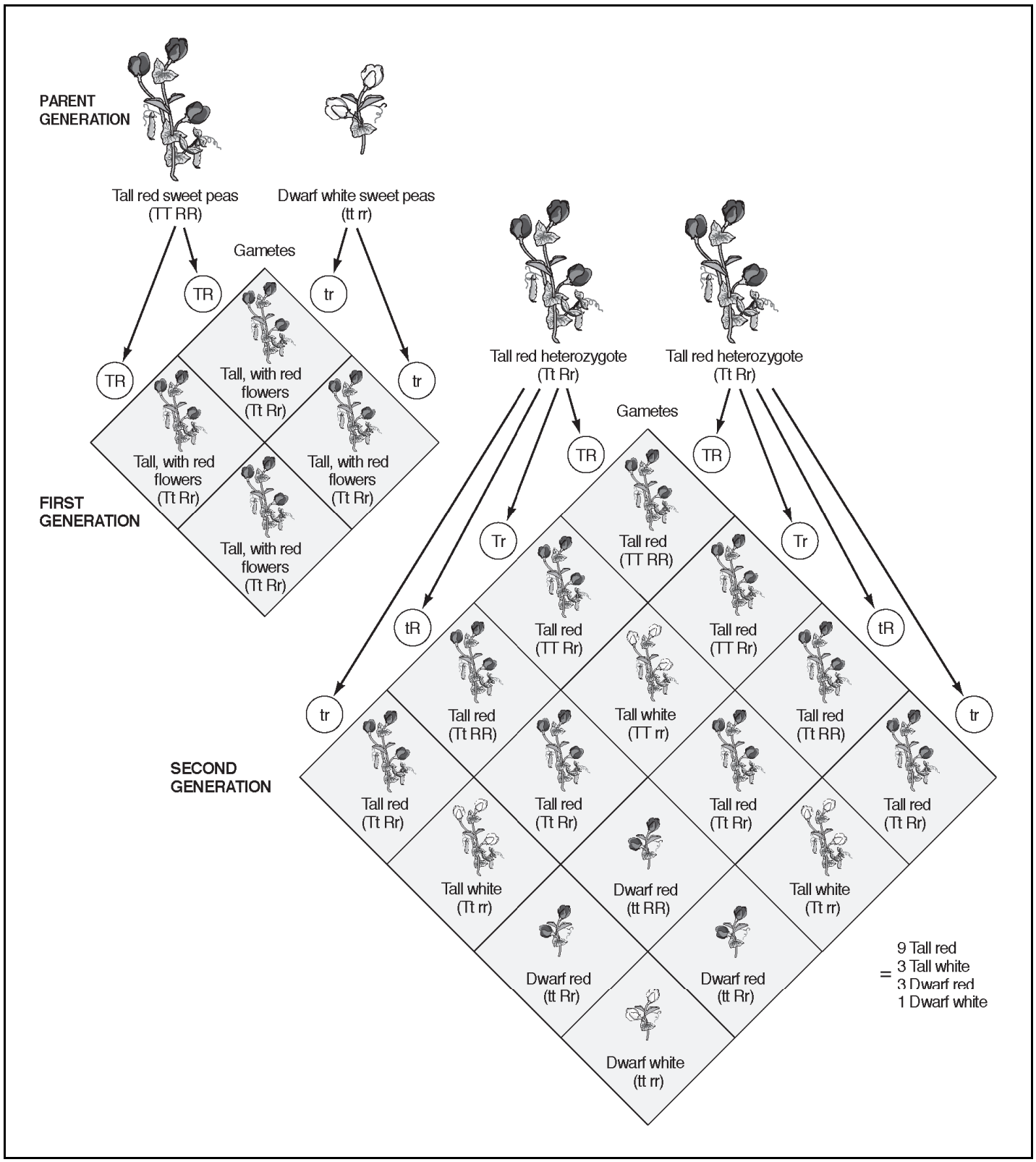
During the years following Mendel's work, understanding of cell division and fertilization increased, as did insight into the component parts of cells known as subcellular structures. For example, in 1869 the Swiss biochemist Johann Friedrich Miescher (1844–1895) looked at pus he had scraped from the dressings of soldiers wounded in the Crimean War (1853–1856). In the white blood cells from the pus, and later in salmon sperm, he identified a substance he called nuclein. In 1874 Miescher separated nuclein into a protein and an acid, and it was renamed nucleic acid. He proposed that it was the "chemical agent of fertilization."

In 1900 three scientists—Karl Erich Correns (1864–1933), Hugo Marie de Vries (1848–1935), and Eric von Tschermak-Seysenegg (1871–1962)—independently rediscovered and verified Mendel's principals of heredity, and Mendel's contributions to modern genetics were finally acknowledged. In 1902 Sir Archibald E. Garrod (1857–1936), a British physician and chemist, applied Mendel's principles and identified the first human disease attributable to genetic causes, which he called "inborn errors of metabolism." The disease was alkaptonuria, a condition in which an abnormal buildup of an acid (homogentisic acid or alkapton) accumulates.

Seven years later, Garrod published the textbook *Inborn Errors of Metabolism* (1909), which described various disorders that he believed were caused by these inborn metabolic errors. These included albinism (a pigment disorder in which affected individuals have abnormally pale skin, hair, and eyes) and porphyria (a group of disorders resulting from abnormalities in the production of heme, a vitally important substance that carries oxygen in the blood, bone, liver, and other tissues). Garrod's was the first effort to distinguish diseases caused by bacteria from those attributable to genetically programmed enzyme deficiencies that interfered with normal metabolism.

In 1905 the British geneticist William Bateson (1861–1926) coined the term *genetics*, along with other descriptive terms used in modern genetics, including *allele* (a particular

FIGURE 1.3



Mendel's law of independent assortment. *Hans & Cassidy, Cengage Gale.*

form of a gene), *zygote* (a fertilized egg), *homozygote* (an individual with genetic information that contains two identical forms of a gene), and *heterozygote* (an individual with two different forms of a particular gene). Arguably, his most important contributions to the progress of genetics were his translations of Mendel's work from German to English and his vigorous endorsement and promotion of Mendel's principles.

In 1908 the British mathematician Godfrey Harold Hardy (1877–1947) and the German geneticist Wilhelm Weinberg (1862–1937) independently developed a mathematical formula that describes the actions of genes in populations. Their assumptions that algebraic formulas could be used to analyze the occurrence of, and reasons for, genetic variation became known as the Hardy-Weinberg equilibrium. It advanced the application of Mendel's laws of heredity from individuals to populations, and by applying Mendelian genetics to Darwin's theory of evolution, it improved geneticists' understanding of the origin of mutations and how natural selection gives rise to hereditary adaptations. The Hardy-Weinberg equilibrium enables geneticists to determine whether evolution is occurring in populations.

Chromosome Theory of Inheritance

> *Bateson is often cited for having said, "Treasure your exceptions." I believe Sturtevant's admonition would be, "Analyze your exceptions."*
>
> —Edward B. Lewis, "Remembering Sturtevant," *Genetics*, 1995

The American geneticist Walter Stanborough Sutton (1877–1916) conducted studies using grasshoppers (*Brachystola magna*) he collected at his family's farm in Kansas. Sutton was strongly influenced by reading William Bateson's work and sought to clarify the role of the chromosomes in sexual reproduction. The results of his research, published in 1902, demonstrated that chromosomes exist in pairs that are structurally similar and proved that sperm and egg cells each have one pair of chromosomes. Sutton's work advanced genetics by identifying the relationship between Mendel's laws of heredity and the role of the chromosome in meiosis.

Along with Bateson, the American geneticist Thomas Hunt Morgan (1866–1945) is often referred to as the father of classical genetics. In 1907 Morgan performed laboratory research using the fruit fly *Drosophila melanogaster*. He chose to study fruit flies because they bred quickly, had distinctive characteristics, and had just four chromosomes. The aim of his research was to replicate the genetic variation de Vries had reported from his experiments with plants and animals.

Working in a laboratory they called the "Fly Room," Morgan and his students Calvin Blackman Bridges (1889–1938), Hermann Joseph Muller (1890–1967), and Alfred H. Sturtevant (1891–1970) conducted research that unequivocally confirmed the findings and conclusions of Mendel, Bateson, and Sutton. Breeding both white- and red-eyed fruit flies, they demonstrated that all the offspring were red eyed, indicating that the white-eye gene was recessive and the red-eye gene was dominant. The offspring carried the white-eye gene but it did not appear in the F1 generation. When, however, the F1 offspring were crossbred, the ratio of red-eyed to white-eyed flies was 3:1 in the F2 generation. (A similar pattern is shown for red and white flowers in Figure 1.2.)

The investigators also observed that all the white-eyed flies were male, prompting them to investigate sex chromosomes and hypothesize about sex-linked inheritance. The synthesis of their research with earlier work produced the chromosomal theory of inheritance, the premise that genes are the fundamental units of heredity and are found in the chromosomes. It also confirmed that specific genes are found on specific chromosomes, that traits found on the same chromosome are not always inherited together, and that genes are actual physical objects. In 1915 the four researchers published *The Mechanism of Mendelian Heredity*, which detailed the results of their research, conclusions, and directions for future research.

In *The Theory of the Gene* (1926), Morgan asserted that the ability to quantify or number genes enables researchers to predict accurately the distribution of specific traits and characteristics. He contended that the mathematical principles governing genetics qualify it as science:

> That the characters of the individual are referable to paired elements (genes) in the germinal matter that are held together in a definite number of linkage groups.... The members of each pair of genes separate when germ cells mature.... Each germ cell comes to contain only one set.... These principles... enable us to handle problems of genetics in a strictly numerical basis, and allow us to predict... what will occur.... In these respects the theory [of the gene] fulfills the requirements of a scientific theory in the fullest sense.

In 1933 Morgan was awarded the Nobel Prize in Physiology or Medicine for his groundbreaking contributions to the understanding of inheritance. Muller also became a distinguished geneticist, and after pursuing research on flies to determine if he could induce genetic changes using radiation, he turned his attention to studies of twins to gain a better understanding of human genetics.

Bridges eventually discovered the first chromosomal deficiency as well as chromosomal duplication in fruit flies. He served in various academic capacities at Columbia University, the Carnegie Institution, and the California Institute of Technology and was a member of the National Academy of Sciences and a fellow of the American Association for the Advancement of Science.

Sturtevant was awarded the National Medal of Science in 1968. His most notable contribution to genetics was the detailed outline and instruction he provided about gene mapping—the process of determining the linear sequence of genes in genetic material. In 1913 he began construction of a chromosome map of the fruit fly that was completed in 1951. Because of his work in gene mapping, he is often referred to as the father of the Human Genome Project, the comprehensive map of humanity's 20,000 to 25,000 genes. His book *A History of Genetics* (1965) recounts the ideas, events, scientists, and philosophies that shaped the development of genetics.

CLASSICAL GENETICS

Another American geneticist awarded a Nobel Prize was Barbara McClintock (1902–1992), who described key methods of exchange of genetic information. Performing chromosomal studies of maize in the botany department at Cornell University, she observed colored kernels on an ear of corn that should have been clear. McClintock hypothesized that the genetic information that normally would have been conveyed to repress color had somehow been lost. She explained this loss by seeking and ultimately producing cytological proof of jumping genes, which could be released from their original position and inserted, or transposed, into a new position. This genetic phenomenon of chromosomes exchanging pieces became known as crossing over, or recombination.

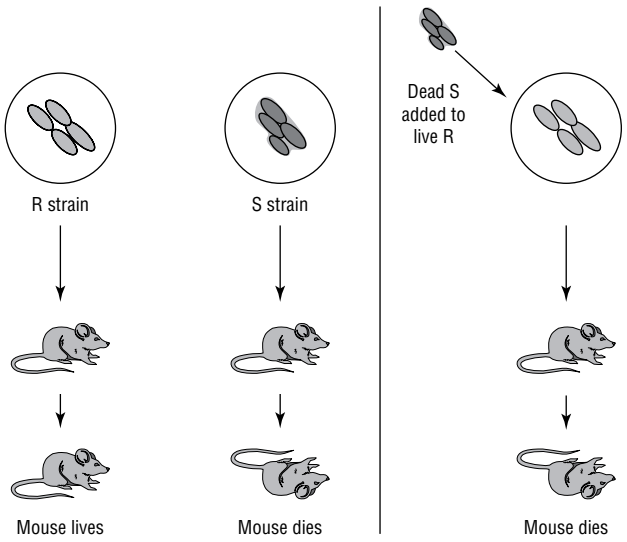
With another pioneering female researcher, Harriet Creighton (1909–2004), McClintock published a series of research studies, including a 1931 paper that offered tangible evidence that genetic information crossed over during the early stages of meiosis (cell division). Along with the 1983 Nobel Prize in Physiology or Medicine, McClintock received the prestigious Albert Lasker Basic Medical Research Award in 1981, making her the most celebrated female geneticist in history.

During the same period, the British microbiologist Frederick Griffith (1879–1941) performed experiments with *Streptococcus pneumoniae*, demonstrating that the ability to cause deadly pneumonia in mice could be transferred from one strain of bacteria to another. Griffith observed that the hereditary ability of bacteria to cause pneumonia could be altered by a transforming principle. Even though Griffith mistakenly believed the transforming factor was a protein, his observation offered the first tangible evidence linking deoxyribonucleic acid (DNA, the molecule that carries the genetic code) to heredity in cells. His experiment provided a framework for researching the biochemical basis of heredity in bacteria. In 1944 the Canadian biologist Oswald Theodore Avery (1877–1955), along with the American microbiologist Colin Munro Macleod (1909–1972) and the American bacteriologist Maclyn McCarty (1911–2005), performed studies demonstrating that Griffith's transforming factor was DNA rather than simply a protein. Among the experiments Avery, Macleod, and McCarty performed was one similar to Griffith's, which confirmed that DNA from one strain of bacteria could transform a harmless strain of bacteria into a deadly strain. (See Figure 1.4.) Their findings gave credence to the premise that DNA was the molecular basis for genetic information.

Nearly half of the twentieth century was devoted to classical genetics research and the development of increasingly detailed and accurate descriptions of genes and their transmission. In 1929 the American organic chemist Phoebus A. Levene (1869–1940) isolated and discovered the structure of the individual units of DNA. Called nucleotides, the molecular building blocks of DNA are composed of deoxyribose (a sugar molecule), a phosphate molecule, and four types of nucleic acid bases. (See Figure 1.5.)

FIGURE 1.4

Oswald Avery's experiments with DNA from *Pneumococcus* bacteria



SOURCE: Richard Robinson, ed., "Oswald Avery's Experiments Showed That DNA from Dead S Strain of *Pneumococcus* Bacteria Could Transform a Harmless Strain into a Deadly Strain," in *Genetics*, vol. 1, *A–D*, Macmillan Reference USA, 2002

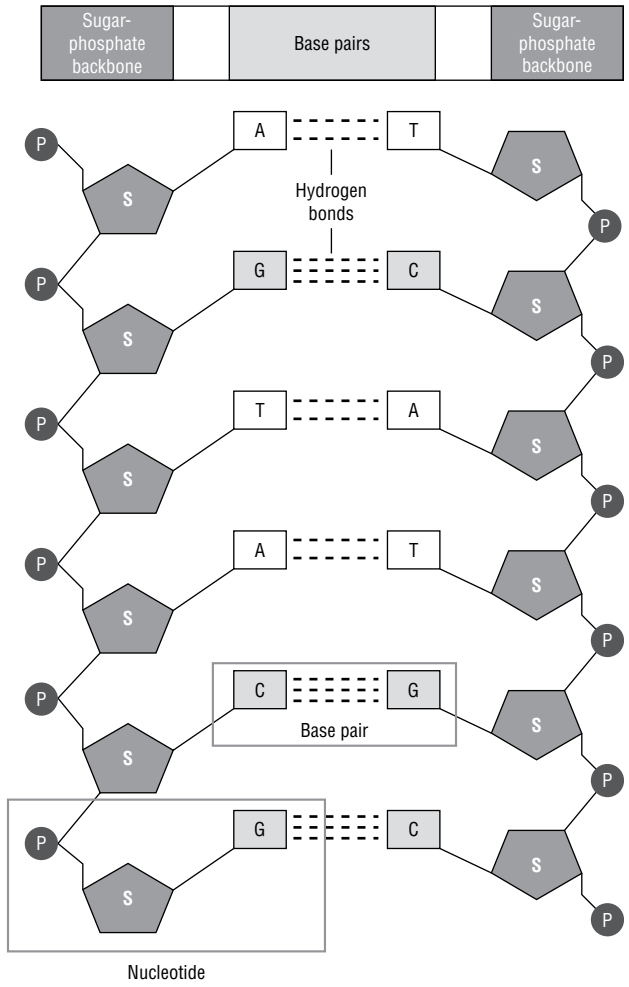
Also in 1929 Theophilus Shickel Painter (1889–1969), an American cytologist, made the first estimate of the number of human chromosomes. His count of 48 was off by only 2—25 years later researchers were able to stain and view human chromosomes microscopically to determine that they number 46. Analysis of chromosome number and structure would become pivotal to medical diagnosis of diseases and disorders associated with altered chromosomal numbers or structure.

Another milestone in the first half of the twentieth century was the determination by the American chemist Linus Pauling (1901–1994) that sickle-cell anemia (the presence of oxygen-deficient, abnormal red blood cells that cause affected individuals to suffer from obstruction of capillaries, resulting in pain and potential organ damage) was caused by the change in a single amino acid (a building block of protein) of hemoglobin (the oxygen-bearing, iron-containing protein in red blood cells). Pauling's work paved the way for research showing that genetic information is used by cells to direct the synthesis of protein and that mutation (a change in genetic information) can directly cause a change in a protein. This explains hereditary genetic disorders such as sickle-cell anemia.

From 1950 to 1952 the American geneticists Martha Cowles Chase (1927–2003) and Alfred Day Hershey (1908–1997) conducted experiments that provided definitive proof that DNA was genetic material. In research that would be widely recounted as the "Waring blender experiment," the investigators dislodged virus particles that infect bacteria by

FIGURE 1.5

Building blocks of deoxyribonucleic acid (DNA)



SOURCE: "Deoxyribonucleic Acid (DNA)," in *Talking Glossary of Genetic Terms*, U.S. Department of Health and Human Services, National Institutes of Health, National Human Genome Research Institute, Division of Intramural Research, http://www.genome.gov/Pages/Hyperion//DIR/VIP/Glossary/Illustration/nucleotide.shtml (accessed September 2, 2008)

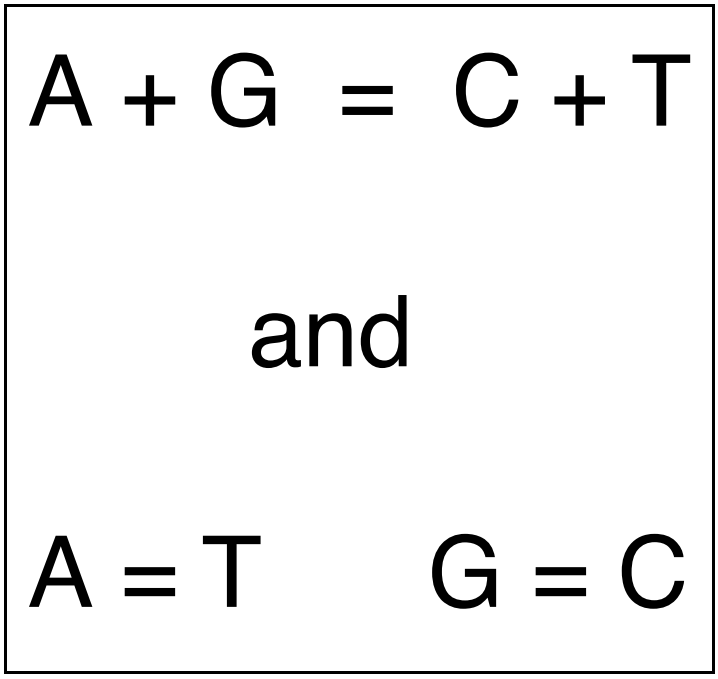
spinning them in a blender and found that the viral DNA, and not the viral protein, that remains inside the bacteria directed the growth and multiplication of new viruses.

MODERN GENETICS EMERGES

The period of classical genetics focused on refining and improving the structural understanding of DNA. In contrast, modern genetics seeks to understand the processes of heredity and how genes work.

Many historians consider 1953—the year that the American geneticist James D. Watson (1928–) and the British biophysicist Francis Crick (1916–2004) famously described the structure of DNA—as the birth of modern genetics. It is important, however, to remember that Watson and Crick's

FIGURE 1.6



Chargaff's rules. *Argosy Publishing, Cengage Gale.*

historic accomplishment was not the discovery of DNA—Miescher had identified nucleic acid in cells nearly a century earlier. Similarly, even though Watson and Crick earned recognition and public acclaim for their landmark research, it would not have been possible without the efforts of their predecessors and colleagues such as the British biophysicist Maurice Wilkins (1916–2004) and the British molecular biologist Rosalind Elsie Franklin (1920–1958). Wilkins and Franklin were the molecular biologists who in 1951 obtained sharp X-ray diffraction photographs of DNA crystals, revealing a regular, repeating pattern of molecular building blocks that correspond to the components of DNA. (Wilkins shared the Nobel Prize with Watson and Crick, but Franklin was ineligible to share the prize because she died in 1958, four years before it was awarded.)

Another pioneer in biochemistry, the Austrian Erwin Chargaff (1905–2002), also provided information about DNA that paved the way for Watson and Crick. Chargaff suggested that DNA contained equal amounts of the four nucleotides: the nitrogenous (containing nitrogen, a nonmetallic element that constitutes almost four-fifths of the air by volume) bases adenine (A) and thymine (T), and guanine (G), and cytosine (C). In DNA there is always one A for each T, and one G for each C. This relationship became known as base pairing or Chargaff's rules, which also includes the observation that the ratio of AT to GC varies from species to species but remains consistent across different cell types within each species. (See Figure 1.6.)

Watson and Crick

Watson is an American geneticist known for his willingness to grapple with big scientific challenges and his

expansive view of science. In *The Double Helix: A Personal Account of the Discovery of the Structure of DNA* (1968), he chronicles his collaboration with Crick to create an accurate model of DNA. He credits his inclination to take intellectual risks and venture into uncharted territory as his motivation for this ambitious undertaking.

Watson was just 25 years old when he announced the triumph that was hailed as one of the greatest scientific achievements of the twentieth century. Following this remarkable accomplishment, Watson served on the faculty of Harvard University for two decades and assumed the directorship and then the presidency of the Cold Spring Harbor Laboratory in Long Island, New York. From 1989 to 1992 he headed the National Institutes of Health's (NIH) Human Genome Project, the effort to sequence (or discover the order of) the entire human genome.

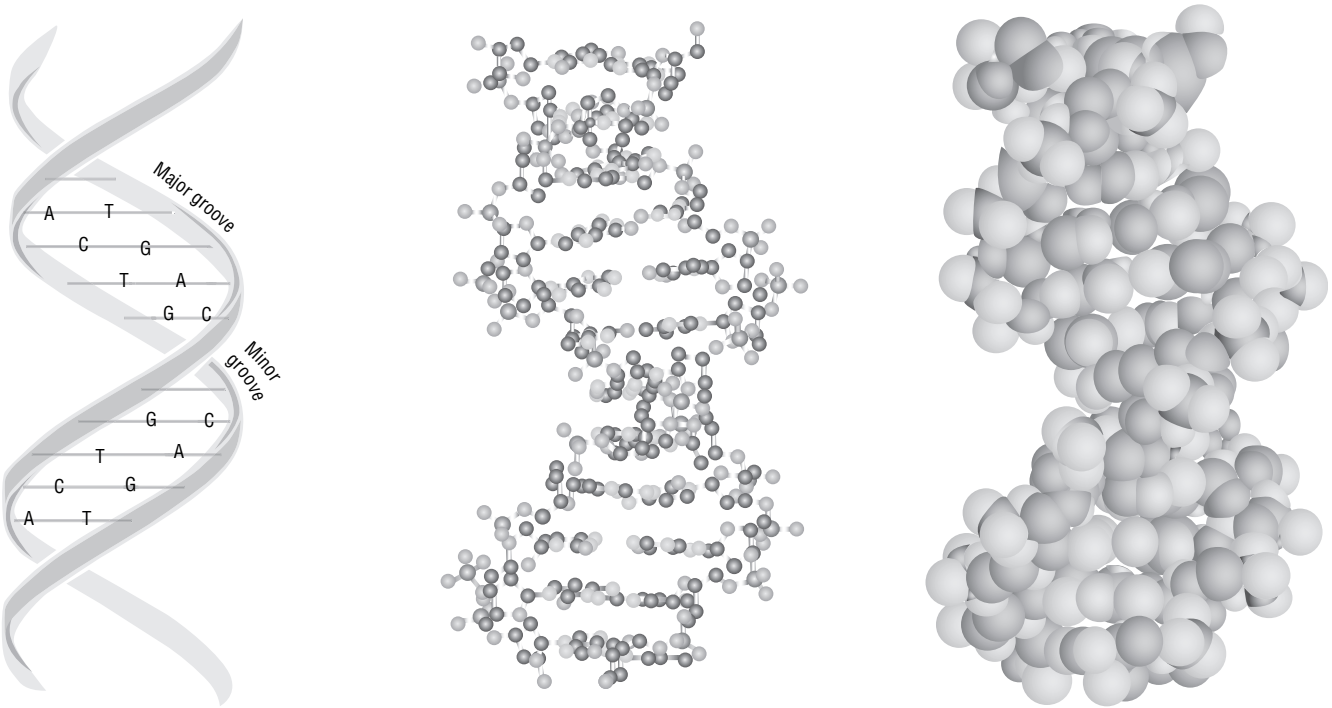
Crick was a British scientist who had studied physics before turning his attention to biochemistry and biophysics. He became interested in discovering the structure of DNA, and when in 1951 Watson came to work at the Cavendish Laboratory in Cambridge, England, the two scientists decided to work together to unravel the structure of DNA.

After his landmark accomplishment with Watson, Crick continued to study the relationship between DNA and genetic coding. He is credited with predicting the ways in which proteins are created and formed, a process known as protein synthesis. During the mid-1970s Crick turned his attention to the study of brain functions, including vision and consciousness, and assumed a professorship at the Salk Institute for Biological Studies in San Diego, California. Like Watson, he received many professional awards and accolades for his work, and besides the scientific papers he and Watson coauthored, he wrote four books. Published a decade before his death in 2004, Crick's last book, *The Astonishing Hypothesis: The Scientific Search for the Soul* (1994), detailed his ideas and insights about human consciousness.

WATSON AND CRICK MODEL OF DNA. Using the X-ray images of DNA created by Franklin and Wilkins, who also worked in the Cavendish Laboratory, Watson and Crick worked out and then began to build models of DNA. Crick contributed his understanding of X-ray diffraction techniques and imaging and relied on Watson's expertise in genetics. In 1953 Watson and Crick published the paper "Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid" (*Nature*, vol. 171, no. 4356, April 25, 1953), which contained the famously understated first lines, "We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest." Watson and Crick then described the shape of a double helix, an elegant structure that resembles a latticework spiral staircase. (See Figure 1.7.)

FIGURE 1.7

Canonical B–DNA double helix models



SOURCE: Richard Robinson, ed., "Figure 3. Canonical B–DNA Double Helix," in *Genetics*, vol. 1, *A–D*, Macmillan Reference USA, 2002

Their model enabled scientists to better understand functions such as carrying hereditary information to direct protein synthesis, replication, and mutation at the molecular level. The three-dimensional Watson and Crick model consists of two strings of nucleotides connected across like a ladder. Each rung of the ladder contains an A-T pair or a G-C pair, which is consistent with Chargaff's rule that there is an A for every T and a G for every C in DNA. (See Figure 1.7.) Watson and Crick posited that changes in the sequence of nucleotide pairs in the double helix would produce mutations.

MILESTONES IN MODERN GENETICS

Geneticists and other researchers made remarkable strides during the second half of the twentieth century. In 1956 the American biochemist Vernon M. Ingram (1924–2006), who would soon be recognized as the father of molecular medicine, identified the single base difference between normal and sickle-cell hemoglobin. The implications of his finding that the mutation of a single letter in the DNA genetic code was sufficient to cause a hereditary medical disorder were far reaching. This greater insight into the mechanisms of sickle-cell disease suggested directions for research into prevention and treatment. It prompted research that uncovered other diseases with similar causes, such as hemophilia (an inherited blood disease associated with insufficient clotting factors and excessive bleeding) and cystic fibrosis (an inherited disease of the mucous glands that produces problems associated with the lungs and pancreas). Just three years later, the first human chromosome abnormality was identified: people with Down syndrome were found to have an extra chromosome, demonstrating that it is a genetic disorder that may be diagnosed by direct examination of the chromosomes.

Ingram's work has been the foundation for current research to map genetic variations that affect human health. For example, in 1989, more than 30 years after Ingram's initial work, the gene for cystic fibrosis was identified and a genetic test for the gene mutation was developed.

Using radioactive labeling to track each strand of the DNA in bacteria, the American molecular biologist Matthew Stanley Meselson (1930–) and the American geneticist Franklin W. Stahl (1929–) demonstrated with an experiment in 1958 that the replication of DNA in bacteria is semiconservative. Semiconservative replication occurs as the double helix unwinds at several points and knits a new strand along each of the old strands. Meselson and Stahl's experiment revealed that one strand remained intact and combined with a newly synthesized strand when DNA replicated, precisely as Watson and Crick's model predicted. In other words, each of the two new molecules created contains one of the two parent strands and one new strand.

In the early 1960s Crick, the American biochemist Marshall Nirenberg (1927–), the Russian-born American physicist George Gamow (1904–1968), and other researchers performed experiments that detected a direct relationship between DNA nucleotide sequences and the sequence of the amino acid building blocks of proteins. They determined that the 4 nucleotide letters (A, T, C, and G) may be combined into 64 different triplets. The triplets are code for instructions that determine the amino acid structure of proteins. Ribosomes are cellular organelles (membrane-bound cell compartments) that interpret a sequence of genetic code three letters at a time and link together amino acid building blocks of proteins specified by the triplets to construct a specific protein. The 64 triplets of nucleotides that can be coded in the DNA—which are copied during cell division, infrequently mutate, and are read by the cell to direct protein synthesis—make up the universal genetic code for all cells and viruses.

Origins of Genetic Engineering

The late 1960s and early 1970s were marked by research that would lay the groundwork for modern genetic engineering technology. In 1966 DNA was found to be present not only in chromosomes but also in the mitochondria. The first single gene was isolated in 1969, and the following year the first artificial gene was created. In 1972 the American biochemist Paul Berg (1926–) developed a technique to splice DNA fragments from different organisms and created the first recombinant DNA, or DNA molecules formed by combining segments of DNA, usually from different types of organisms. In 1980 Berg was awarded the Nobel Prize in Chemistry for this achievement, which is now referred to as recombinant DNA technology.

In 1976 an artificial gene inserted into a bacterium functioned normally. The following year DNA from a virus was fully decoded, and three researchers, working independently, developed methods to sequence DNA—in other words, to determine how the building blocks of DNA (the nucleotides A, C, G, and T) are ordered along the DNA strand. In 1978 bacteria were engineered to produce insulin, a pancreatic hormone that regulates carbohydrate metabolism by controlling blood glucose levels. Just four years later, the Eli Lilly pharmaceutical company marketed the first genetically engineered drug: a type of human insulin grown in genetically modified bacteria.

In 1980 the U.S. Supreme Court decision in *Diamond v. Chakrabarty* (447 U.S. 303) permitted patents for genetically modified organisms; the first one was awarded to the General Electric Company for bacteria to assist in clearing oil spills. The following year, a gene was transferred from one animal species to another. In 1983 the first artificial chromosome was created. In the same year, the marker—the usually dominant gene or trait that serves to identify genes or traits linked with it—for Huntington's disease (an inherited disease that affects the functioning of both the body and brain) was identified; in 1993 the disease gene was identified.

In 1984 the observation that some nonfunctioning DNA is different in each individual launched research to refine tools and techniques developed by the British geneticist Sir Alec John Jeffreys (1950–) at the University of Leicester in England that perform genetic fingerprinting. Initially, the technique was used to determine the paternity of children, but it rapidly gained acceptance among forensic medicine specialists, who are often called on to assist in the investigation of crimes and interpret medicolegal issues.

The 1985 invention of the polymerase chain reaction (PCR), which amplifies (or produces many copies of) DNA, enabled geneticists, medical researchers, and forensic specialists to analyze and manipulate DNA from the smallest samples. PCR allowed biochemical analysis of even trace amounts of DNA. In *A Short History of Genetics and Genetic Engineering* (2003, http://www.dna50.com/dna50.swf), Ricki Lewis and Bernard Possidente describe the American biochemist Kary B. Mullis's (1944–) development of PCR as the "genetic equivalent of a printing press," with the potential to revolutionize genetics in the same way that the printing press had revolutionized mass communications.

Five years later, in 1990, the first gene therapy was administered. Gene therapy introduces or alters genetic material to compensate for a genetic mistake that causes disease. The patient was a four-year-old girl with the inherited immunodeficiency disorder adenine deaminase deficiency. If left untreated, the deficiency is fatal. Given along with conventional medical therapy, the gene therapy treatment was considered effective. The 1999 death of another gene therapy patient, as a result of an immune reaction to the treatment, tempered enthusiasm for gene therapy and prompted medical researchers to reconsider its safety and effectiveness.

Cloning (the production of genetically identical organisms) was performed first with carrots. A cell from the root of a carrot plant was used to generate a new plant. By the early 1950s scientists had cloned tadpoles, and during the 1970s attempts were under way to clone mice, cows, and sheep. These clones were created using embryos, and many did not produce healthy offspring, offspring with normal life spans, or offspring with the ability to reproduce. In 1993 researchers at George Washington University in Washington, D.C., cloned nearly fifty human embryos, but their experiment was terminated after just six days.

In 1996 the British embryologist Ian Wilmut (1944–) and his colleagues at the Roslin Institute in Scotland successfully cloned the first adult mammal that was able to reproduce. Dolly the cloned sheep, named for the country singer Dolly Parton, focused public attention on the practical and ethical considerations of cloning.

Human Genome Project and More

The term *genetics* refers to the study of a single gene at a time, and *genomics* is the study of all genetic information contained in a cell. The Human Genome Project (HGP) set as one of its goals the determination of the entire nucleotide sequence of the more than 3 billion bases of DNA contained in the nucleus of a human cell. Initial discussions about the feasibility and value of conducting the HGP began in 1986. The following year the first automated DNA sequencer was produced commercially. Automated sequencing, which enabled researchers to decode millions, as opposed to thousands, of letters of genetic code per day, was a pivotal technological advance for the HGP, which began in 1987 under the auspices of the U.S. Department of Energy (DOE).

In 1988 the HGP was relocated to the NIH, and Watson was recruited to direct the project. The following year the NIH opened the National Center for Human Genome Research, and a committee composed of professionals from the NIH and the DOE was named to consider ethical, social, and legal issues that might arise from the project. In 1990 the project began in earnest, with work on preliminary genetic maps of the human genome and four other organisms believed to share many genes with humans.

During the early 1990s several new technologies were developed that further accelerated progress in analyzing, sequencing, and mapping sections of the genome. The advisability of granting private biotechnology firms the right to patent specific genes and DNA sequences was hotly debated. In April 1992 Watson resigned as director of the project to express his vehement disapproval of the NIH decision to patent human gene sequences. Later that year preliminary physical and genetic maps of the human genome were published.

The American geneticist Francis S. Collins (1950–) of the NIH was named as the director of the HGP in April 1993, and international efforts to assist were under way in England, France, Germany, Japan, and other countries. In 1995, when Stanford researchers released DNA chip technology that simultaneously analyzes genetic information representing thousands of genes, the development promised to speed the project to completion even before the anticipated date of 2005.

In 1995 investigators at the Institute for Genomic Research published the first complete genome sequence for any organism: the bacterium *Haemophilus influenzae*, with nearly 2 million genetic letters and 1,000 recognizable genes. In 1997 a yeast genome, *Saccharomyces cerevisiae*, composed of about 6,000 genes, was sequenced, and later that year the genome of the bacterium *Escherichia coli*, also known as *E. coli*, which contains approximately 4,600 genes, was sequenced.

In 1998 the genome of the first multicelled animal, the nematode worm *Caenorhabditis elegans*, was sequenced, containing approximately 18,000 genes. The following year the first complete sequence of a human chromosome (number 22) was published by the HGP. In 2000 the genome of the fruit

fly *Drosophila melanogaster*, which Morgan and his colleagues had used to study genetics nearly a century earlier, was sequenced by the private firm Celera Genomics. The fruit fly sequence contains about 13,000 genes, with many sequences matching already identified human genes that are associated with inherited disorders.

In 2000 the first draft of the human genome was announced, and it was published in 2001. Also in 2000 the first plant genome, *Arabidopsis thaliana*, was sequenced. This feat spurred research in plant biology and agriculture. Even though tomatoes that had been genetically engineered for longer shelf life had been marketed during the mid-1990s, agricultural researchers began to see new possibilities to enhance crops and food products. For example, in 2000 plant geneticists developed genetically engineered rice that manufactured its own vitamin A. Many researchers believe the genetically enhanced strain of rice holds great promise in terms of preventing vitamin A deficiency in developing countries.

The 2001 publication of the human genome estimated that humans have between 30,000 and 35,000 genes. The HGP was completed in 2003, the same year that Cold Spring Harbor Laboratory held educational events to commemorate and celebrate the fiftieth anniversary of the discovery of the double helical structure of DNA. In October 2004 human gene count estimates were revised downward to between 20,000 and 25,000. During 2005 and 2006 sequencing of more than 10 human chromosomes was completed, including the human X chromosome, which is one of the two sex chromosomes; the other is the Y chromosome.

In 2006 Roger D. Kornberg (1947–), an American structural biologist at Stanford University, was awarded the Nobel Prize in Chemistry for determining the intricate way in which information in the DNA of a gene is copied to provide the instructions for building and running a living cell. In 2007 the Nobel Prize in Physiology or Medicine was awarded jointly to Mario R. Capecchi (1937–), Sir Martin J. Evans (1941–), and Oliver Smithies (1925–), acknowledging their landmark discoveries about the use of embryonic stem cells (undifferentiated cells from the embryo that have the potential to become a wide variety of specialized cell types) to introduce gene modifications in mice, and their development of a technique known as gene targeting that is used to inactivate single genes. The postgenomic era began with a firestorm of controversies about the direction of genetic research, human cloning, stem cell research, and genetically modified food and crops.