# Introduction and Historical Perspective

*"Nothing in biology makes sense except in the light of evolution."*

Theodosius Dobzhansky

## OVERVIEW

Behavioral genetics aims to understand the genetic mechanisms that enable the nervous system to direct appropriate interactions between organisms and their social and physical environments. Early scientific explorations of animal behavior defined the fields of experimental psychology and classical ethology. Behavioral genetics has emerged as an interdisciplinary science at the interface of experimental psychology, classical ethology, genetics, and neuroscience. This chapter provides a brief overview of the emergence of experimental psychology and ethology, followed by a historical perspective of how concepts of natural selection and principles of heredity were combined by the founders of the modern evolutionary synthesis into the sciences of population and quantitative genetics. Subsequently, population genetic, quantitative genetic and molecular genetic principles could be applied to experimental psychology, behavioral ecology, and behavioral neuroscience, to give rise to the modern field of behavioral genetics. We will highlight some of the major historical milestones and controversies. We indicate how the past history of the field has laid the foundation for examining the genetic architectures of behaviors in the genomic era. This historical perspective provides an important reference frame for understanding past, current, and future trends and issues in behavioral genetics.

## THE RISE OF THE MODERN FIELD OF BEHAVIORAL GENETICS

Behaviors are mediated by the nervous system in response to environmental conditions. From a genetics perspective, behaviors are complex traits determined by networks of multiple segregating genes that are influenced by the environment. Both genetic factors and neural circuits can be modified by the developmental history of the organism, its physiology – from cellular to systems levels – and by the social and physical environment. Finally, behaviors are shaped through evolutionary forces of natural selection that optimize survival and reproduction (Figure 1.1). Truly, the study of behavior provides us with a window through which we can view much of biology.

Understanding behaviors requires a multidisciplinary perspective, with regulation of gene expression at its core. The emerging field of behavioral genetics is still taking shape and its boundaries are still being defined. Behavioral genetics has evolved through the merger of experimental psychology and classical **ethology** with evolutionary biology and genetics, and also incorporates aspects of neuroscience (Figure 1.2). To gain a perspective on the current definition of this field, it is helpful to survey some of the historical milestones of experimental psychology and the study of animal behavior, together with the development of the concept of evolution through natural selection and its coalescence with Mendel's principles of heredity, which gave rise to the fields of quantitative and population genetics. These are the critical cornerstones of today's behavioral genetics. In the following sections we will provide broad overviews of the development of each of these disciplines to show, at the end of this chapter, how they can be brought together to study the link between genes, brain, and behavior.

## Experimental Psychology and Animal Behavior

Since time immemorial philosophers and naturalists have been intrigued by animal behaviors. Twenty-three centuries ago Xenophon, a disciple of Socrates, wrote a treatise on *The Art of Horsemanship* which covers basic aspects of horse husbandry and training, while paying great attention to their behaviors. Studies on animal behavior, however, remained descriptive and **anthropocentric** (interpreted in terms of human experience) for much of recorded history. Human emotions and cultural values were projected onto animals, some of which were considered intrinsically noble (lions, horses), loyal (dogs), or repugnant (snakes), and discussions on the relative intelligence of species generated fruitless debates.

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**FIGURE 1.1** A schematic representation of the scope of behavioral genetics. Both developmental and physiological factors modify gene expression, neural circuits, and interactions between them as they mediate the expression of an appropriate behavior. Interactions with the physical and social environment provide feedback information that can alter gene expression and neural circuitry to modify expression of the behavior, again in the context of the organism's physiology and development. The behavior itself becomes an instrument of evolution that acts on the genome through changes in allele frequencies under the forces of natural selection.
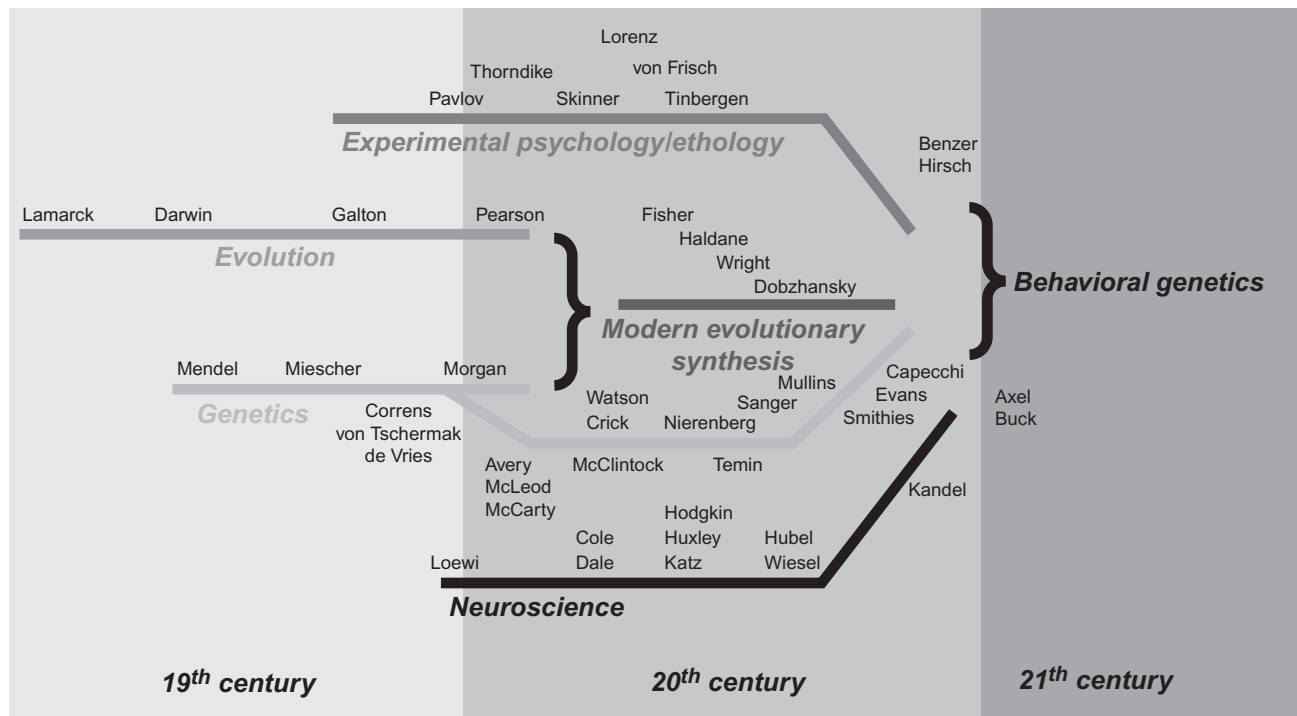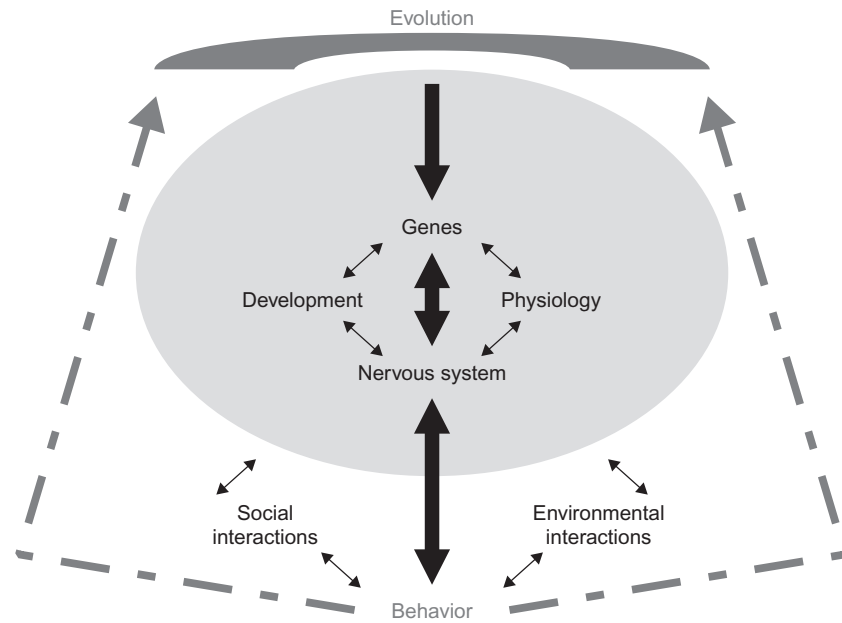


**FIGURE 1.2** Historic time course of the convergence of experimental psychology, ethology, evolution, genetics, and neuroscience to enable the multi-disciplinary study of genes, brain, and behavior through behavioral genetics. A sampling of names of pioneers who made seminal discoveries and who will be mentioned later in this chapter is indicated. Note that this list is not exhaustive.

Studies in which a behavior could be modified in a predictable manner and subjected to scientific scrutiny did not begin in earnest until the end of the nineteenth and beginning of the twentieth century, when a Russian scientist, Ivan Pavlov, living in Leningrad, studied gastric function in dogs by analyzing their salivary secretions in response to food (Figure 1.3). Pavlov noticed that dogs would salivate in anticipation of food. He found that he could elicit this salivation response reliably by administering a distinct auditory or visual stimulus that would signal anticipation of a subsequent food reward. Although it is generally believed that Pavlov rang a bell when training his dogs, his writings do not mention a bell, but rather whistles, metronomes, tuning forks, and a variety of other stimuli (no bell

FIGURE 1.3 Ivan Pavlov (left); one of Pavlov's dogs (right) preserved in the Pavlov Museum.



FIGURE 1.4 A typical "Skinner" box in which a pigeon learns that it will receive a food grain reward when it pecks on a spot of bright light.

was found in his carefully-preserved laboratory after his death in 1936). Pavlov called the responses of his dogs' **conditional reflexes**, now generally referred to as **classical conditioning** or **associative learning**. His observations are reminiscent of Aristotle's assessment that "When two things commonly occur together, the appearance of one will bring the other to mind." Pavlov's studies heralded the birth of experimental and comparative psychology.

Intrigued by the debate about whether animals have innate intelligence or develop responses by trial and error, Edward Thorndike, an American scientist and contemporary of Pavlov, conducted experiments in which he measured the time it would take for cats to escape from a puzzle box. He constructed learning curves that showed that cats do not have an innate understanding, but rather learn gradually through trial and error in which each previous success improves performance in a subsequent trial. In his 1911 book *Animal Intelligence* Thorndike lambasted prevailing notions of animal intelligence of his time: "In the first place, most of the books do not give us a psychology, but rather a eulogy of animals. They have all been about animal intelligence, never about animal stupidity."

Pavlov's and Thorndike's experiments laid the foundation for subsequent experimentation by the influential American scientist Burrhus Frederic Skinner, who developed the paradigm of **operant conditioning** as a contrast to the classical conditioning experiments of Pavlov. Operant conditioning results in behavioral modification through positive reinforcement. Skinner's favorite animal, which remains a model for experimental psychologists today, was the pigeon (Figure 1.4). Skinner reasoned that when a hungry pigeon would receive a food reward, it might associate the food with the execution of a particular behavior and repeat that behavior. Skinner observed that pigeons would repeat behaviors they had exhibited by chance when food rewards were delivered at random. In his article "*Superstition*" *in the Pigeon*, Skinner wrote "One bird was conditioned to turn counter-clockwise about the cage, making two or three turns between reinforcements. Another repeatedly thrust its head into one of the upper corners of the cage. A third developed a "tossing" response, as if placing its head beneath an invisible bar and lifting it repeatedly. Two birds developed a pendulum motion of the head and body, in which the head was extended forward and swung from right to left with a sharp movement followed by a somewhat slower return."

Operant conditioning paradigms are still widely used in experimental psychology, and usually employ a paradigm

in which an animal is trained to press a lever to obtain a food reward. Skinner argued that whereas positive reinforcement was an effective way for modifying behaviors, **negative reinforcement**, i.e. punishment, was ineffective for long-term behavioral modification, as, in his view, the subject would not modify the behavior that caused the punishment, but rather seek ways to avoid the punishing consequence. For example, some may argue that the risk of imprisonment does not deter criminal behavior, but rather encourages criminals to devise schemes that avoid the consequence of imprisonment. Skinner advocated the use of operant conditioning in raising children, and argued that positive reinforcement would be a method for improving society. His idealistic and unconventional views of **social engineering** have, however, been controversial.

Like Pavlov, Thorndike, and other experimental psychologists of his time, Skinner did not consider genetic influences on behavior, but espoused the view that behaviors could be entirely controlled by the environment. Skinner's studies provided fuel for the **nature versus nurture** debate that still smolders today, even though the notion that both genetic and environmental factors contribute to the manifestation of behaviors has gained wide acceptance.

## Ethology: The Early Years

While Skinner and his contemporaries studied animal behaviors in the laboratory, two Austrian scientists, Konrad Lorenz and Karl von Frisch, and a Dutch biologist, Nikolaas Tinbergen, began to apply careful experimental approaches to animals in the natural environment. Together they laid the foundations for ethology, the study of animal behavior and the modern field of behavioral ecology. The collective contributions of Lorenz, von Frisch, and Tinbergen, for which they shared the 1973 Nobel Prize, was their pioneering experimental approaches to uncover fundamental principles that would apply not only to a single species, but would find widespread relevance.

Born in Vienna, where he worked as professor at the University of Vienna from 1928 to 1935, Konrad Lorenz formulated the idea of **fixed action patterns** of instinctive behaviors. According to Lorenz, such stereotyped behaviors are set in motion by an **innate releasing mechanism**, which elicits a fixed sequence of behavioral events. Courtship and mating rituals, and nest building of birds, are examples of such behaviors. Lorenz also popularized the notion of **imprinting**, originally described by the nineteenth century English scientist Douglas Spalding. (Note that this concept of psychological imprinting, in which an animal learns the characteristics of its parents, should not be confused with the term "imprinting" used by molecular biologists to indicate inactivation of genes on one parental chromosome through DNA modification.) Lorenz observed that when he hatched greylag geese in his laboratory, the

goslings would imprint on him instead of on a natural parent, and they would follow him around (Figure 1.5). The major contributions Konrad Lorenz made to experimental psychology are clouded by the history of his political activities. He joined the Nazi party in 1938 and the Wehrmacht (German armed forces) in 1941. He spent four years in a Russian prison camp from 1944 to 1948. In later years he apologized for his Nazi past and spent his remaining scientific career at the Max Planck Institute for Behavioral Physiology at Seewiesen in Bavaria.

Karl von Frisch, working in Munich, dedicated much of his life to the study of bees. He designed clever experiments in which he placed food sources on colored pieces of paper which he surrounded by papers with different matched shades of gray to demonstrate that bees had color vision. In addition to documenting the sensitivity of honeybees to color, ultraviolet, and polarized light, von Frisch was intrigued by the common observation that after a bee had found a distant food source, many more bees would soon gather around the food. It seemed as if the original forager had somehow communicated its location to other members of the hive, and recruited additional foragers. Karl von Frisch set out to discover how this communication might occur, and discovered that when a bee located a food source in the vicinity of the hive it would perform a flight pattern which he described as a "round dance." When the food source was remote from the hive, bees would perform a more intricate flight pattern that consisted of elaborate figure-of-eight movements, known as the "waggle dance" (Figure 1.6). By experimentally manipulating the location of the food source with respect to the hive and carefully observing the behavior of the bees, von Frisch showed that the waggle dance communicates accurate information about both the direction and the distance of the food source. Furthermore, as the position of the sun shifts during the day the angle of the waggle dance would



**FIGURE 1.5**    Konrad Lorenz and his imprinted geese.

shift accordingly, but the endogenous biological clock of the bees entrained to the light–dark cycle would compensate appropriately, so that the information on the location of the food source could be communicated accurately at different times during the day. This is essential, as bees use polarized light vectors for navigation. The elegant experiments by von Frisch explained a complex social communication system that elicits distinct behavioral patterns.

Nikolaas ("Niko") Tinbergen became motivated to study animal behavior when Konrad Lorenz visited the Dutch University of Leiden, where Tinbergen had a minor faculty position (Figure 1.7). Lorenz would have a lasting influence throughout Tinbergen's career, most of which was spent at Oxford University. Tinbergen became best known for his early studies on reflex behaviors in sea gulls
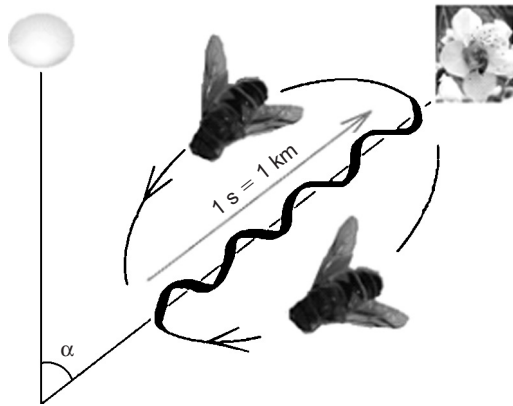


**FIGURE 1.6**  The waggle dance of honeybees elucidated by Karl von Frisch. The angle from the sun indicates the direction toward the food source. The duration of the waggle part of the dance encodes the distance. Approximately one second of dance corresponds to one kilometer of distance. The bee adjusts the angle of its dance to the position of the sun, depending on the time of day.



**FIGURE 1.7**  Nikolaas Tinbergen.

on the Dutch island of Texel, and the breeding behavior of three-spined stickleback fishes. For example, he observed that sea gulls will only recognize an egg when it is in their nest. When the egg is moved only slightly from the nest, the bird will not relate to it. However, birds will accept "fake eggs," even of the wrong shape, such as a square, as long as it has certain color characteristics. Tinbergen became well-known for formulating a set of what he considered critical questions that should be addressed to the study of any behavior, and that relate respectively to function, causation, development, and evolution of the behavior: what is the impact of the behavior on the animal's survival and reproduction; what stimuli elicit the behavior, and how can these behavioral responses be modified by learning; how do behaviors change with age and to what extent are early critical periods essential for development of the behavior; and how do similar behaviors compare between related species and how have they arisen in the course of evolution? These questions poignantly defined the field of ethology, and remain relevant today. Tinbergen's appreciation for comparative studies of behaviors and their relationship to evolution, and his interest in adaptation set him apart from other ethologists of his day and link him, at least conceptually, to the earlier exploits of Charles Darwin, who a century earlier had formulated the theory of natural selection.

## Charles Darwin and the Theory of Natural Selection

The first notion of the evolution of species was reported in 1809 by Jean-Baptiste Pierre Antoine de Monet, Chevalier de Lamarck, more commonly known as Jean-Baptiste Lamarck (Figure 1.8). In his *Philosophie Zoologique* Lamarck proposed that beneficial changes acquired during an organism's lifetime could be passed on to its progeny and that over successive generations this process would alter the organism's characteristics. This theory of inheritance of acquired traits invoked a teleological process of evolution (i.e. a process that saw design or purpose in nature). For example, according to Lamarck, giraffes would stretch their necks to be better able to reach increasingly higher foliage and this change would be transmitted to their progeny. Although the Lamarckian theory of evolution has been discredited decisively, it should be noted that at his time no theoretical framework existed to explain the diversity of species and their different adaptations to their environments, and that the notion of gradual changes of species over time was a novel concept.

Charles Darwin was born in 1809, the same year Lamarck published his theory of inheritance of acquired traits. Darwin initially went to the University of Edinburgh to study medicine, but could not stand the sight of surgery and instead became a naturalist under the tutelage

## Box 1.1  A political war against science

The rise to power of Trofim Denisovich Lysenko (1898–1976) during the Stalin years of the Soviet Union provides an example of how resistance to scientific progress can have disastrous consequences (Figure A). Born to a Ukrainian peasant family, and working initially at an agricultural station in Azerbaijan, Lysenko claimed that he could increase grain yields by cold-treating seeds and that the benefits of this cold treatment could be inherited by future generations of the grain. This idea is a typical example of the theory of Jean Baptiste Lamarck on "inheritance of acquired characteristics," which had already been discredited by scientists in Western Europe.



**FIGURE A**  Trofim Denisovich Lysenko.

Under a repressive communist regime that felt pressure to increase agricultural production to feed the large Soviet population, Lysenko's pragmatic approach, which went against already-established genetic principles, was favorably viewed by Stalin, and he was appointed director of the Institute of Genetics of the USSR Academy of Sciences. While bragging about mostly imaginary agricultural successes, Lysenko began a campaign to discredit the science of genetics, and persecuted prominent Soviet biologists, including the previous director of the Institute of Genetics, the well-respected botanist and geneticist Nikolai Vavilov, who was fired, arrested, and eventually died from malnutrition in prison during the German siege of Leningrad in 1943. Lysenko's relentless rule of terror led to the repression, expulsion, imprisonment, and death of hundreds of scientists, and to the demise of genetics in the USSR. His ill-conceived pseudoscientific ideas and farming techniques ultimately had disastrous consequences for both Soviet science and agriculture. Lysenko's influence persisted during the reign of Khrushchev, and it was not until after Khrushchev's fall from power in 1964 that Lysenko was finally ousted and modern science was allowed to reclaim its place in the Soviet Union. The period of Lysenkoism in the USSR is a vivid example of the profound importance of scientific infrastructure to a society, and highlights the dangers of sacrificing sound scientific technology and theory to political ideology.



**FIGURE 1.8**  Jean-Baptiste Lamarck.

of Robert Edmund Grant, who supported the theories of Lamarck. In 1827, when it became clear that the young Darwin had no interest in the practice of medicine, his father sent him to Christ's College at the University of Cambridge to prepare him for a career as a clergyman. Members of the clergy could look forward to a comfortable lifestyle, and were often avid naturalists as they considered it their duty to "explore the wonders of God's creation." At Cambridge, Darwin fell under the influence of the naturalist John Stevens Henslow, who arranged for him to travel as a gentleman's companion and naturalist with captain Robert FitzRoy on the *HMS Beagle* for a two-year expedition to explore the South American coast. The voyage turned into a five-year expedition during which Charles Darwin collected a vast amount of specimens. Among others, he noted that distinct species of mockingbirds, tortoises, and finches inhabited different islands in the Galapagos Islands. The fauna of the Galapagos Islands would later become a cornerstone of evidence for his theory of evolution, especially the 14 species of finches that displayed distinctly different beak morphologies, functionally adapted to their different food sources – insects, grubs, leaves, seeds or fruit – and which have since become known as "Darwin's finches" (Figure 1.9). After his return to England, Darwin quickly reached a position of
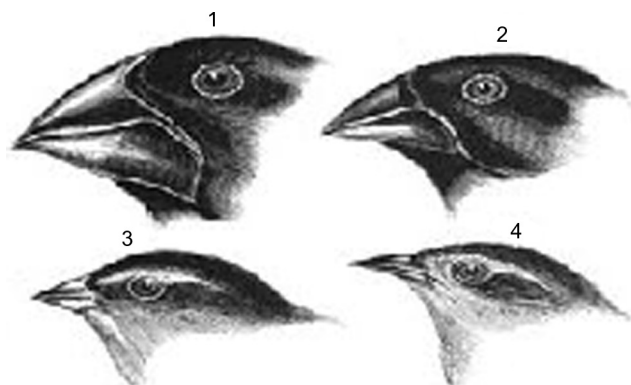
**FIGURE 1.9** Drawings of finches from the Galapagos Islands as they appear in Charles Darwin's book *The Voyage of the Beagle* (1839). 1. *Geospiza magnirostris*; 2. *Geospiza fortis*; 3. *Geospiza parvula*; 4. *Certhidea olivacea*.

prominence in the scientific and social elite. In subsequent years he would develop his theory that species evolve as a consequence of natural selection that favors survival and procreation of the best adapted individuals. (This process of evolution by natural selection is aptly described by the phrase, **survival of the fittest**, first used by Herbert Spencer in 1864 in reference to Darwin's theory.) Darwin was well aware of the controversies his theory entailed, as it dispensed with the need for a divine creator and made no fundamental distinction between man and other animals. He avoided the term **evolution**, although his book *On the Origin of Species by Means of Natural Selection* ends with the words "endless forms most beautiful and most wonderful have been, and are being, evolved." His theory on the origin of species was not published until 1859 spurred on by his friend, the prominent geologist Charles Lyell.

While Darwin developed his ideas of natural selection, another naturalist, Alfred Russell Wallace, traveled extensively in the East Indies (Figure 1.10). Wallace had previously met and corresponded with Darwin. In 1858, Wallace solicited Darwin's opinion on an essay, entitled *On the Tendency of Varieties to Depart Indefinitely From the Original Type*. Darwin was astounded. Wallace had arrived independently at the same theory of the origin of species. In a letter to Charles Lyell, Darwin wrote: "He could not have made a better short abstract! Even his terms now stand as heads of my chapters!" Fearing that Wallace would forestall publication of his own discoveries, Darwin quickly completed his book, and both Darwin's and Wallace's findings were presented together by Lyell and Sir Joseph Dalton Hooker at a meeting of the Linnaean Society of London on 1 July, 1858. Darwin, being a well-respected member of the scientific establishment, received priority credit (Figure 1.11). Nonetheless, both men remained good friends.

Both Darwin and Wallace were influenced by Thomas Malthus' *An Essay on the Principle of Population*, which was published in 1798 and painted a grim picture for the



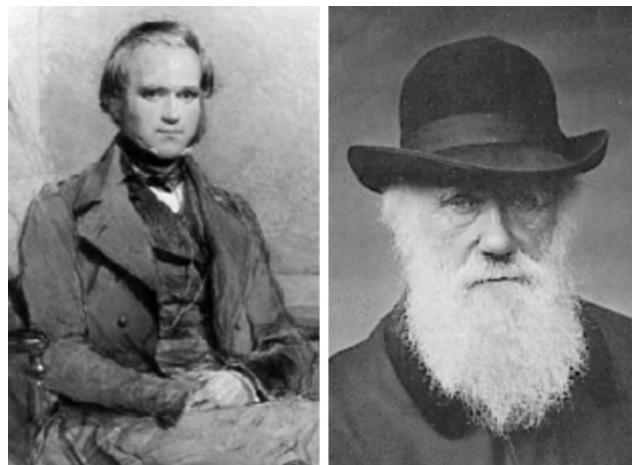**FIGURE 1.10** Alfred Russell Wallace in 1862.



**FIGURE 1.11** The young Darwin (left), already a member of the scientific elite, and a classic image of the old Darwin (right), as he appeared in 1880.

future of mankind. Malthus predicted that population growth would outrun food supply, creating a scenario of intraspecies competition in line with the ideas of Wallace and Darwin. Darwin's theories were controversial from the moment *The Origin of Species* was published (Figure 1.12). Adam Sedgwick, a Cambridge geologist and former tutor of Darwin, wrote to him: "If I did not think you a good tempered and truth loving man I should not tell you that … I have read your book with more pain than pleasure. Parts of it I admired greatly; parts I laughed at till
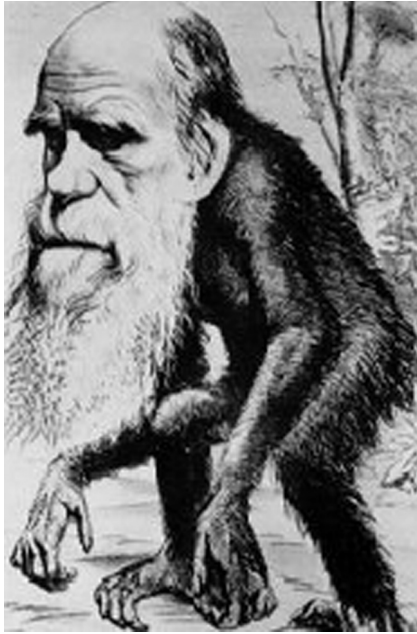
**FIGURE 1.12**   A satirical cartoon of Charles Darwin as a monkey, which appeared in *Hornet* magazine, reflecting the way he was often ridiculed by his adversaries.



**FIGURE 1.13**   The title page of the 1859 edition of *On the Origin of Species*.

my sides were almost sore; other parts I read with absolute sorrow; because I think them utterly false and grievously mischievous."

Among the fierce supporters of Darwin's theory was Thomas Huxley, who would acquire the nickname "Darwin's bulldog" for his eloquent and aggressive defenses of Darwin's theory of natural selection. During subsequent years natural selection became firmly established as a mechanism for the evolution of species. It has become a central tenet in biology, and represents one of few inviolate laws in the life sciences, not unlike the basic law of gravity in physics (Figure 1.13).

## Mendel and the Discovery of Heredity

While Darwin and Wallace were developing their theories of natural selection, an obscure Austrian monk, Gregor Mendel, performed experiments that would lay the foundation for the science of genetics in what is today the city of Brno in the Czech Republic. Gregor Mendel (Figure 1.14) was born in Heinzendorf in 1822. Early in his life he developed a great interest in the natural sciences. He was ordained a priest in 1847, and entered the Augustinian monastery of St Thomas in Brno. The monastery of St Thomas was not only a spiritual center, but also an intellectual center with a large library, which encouraged the exploration of art, philosophy, and the natural sciences.

Recognizing his talents, the abbot of the monastery sent Mendel to the University of Vienna to study physics, chemistry, zoology, and botany. In 1856, after his return to the monastery in Brno, Mendel began his famous experiments
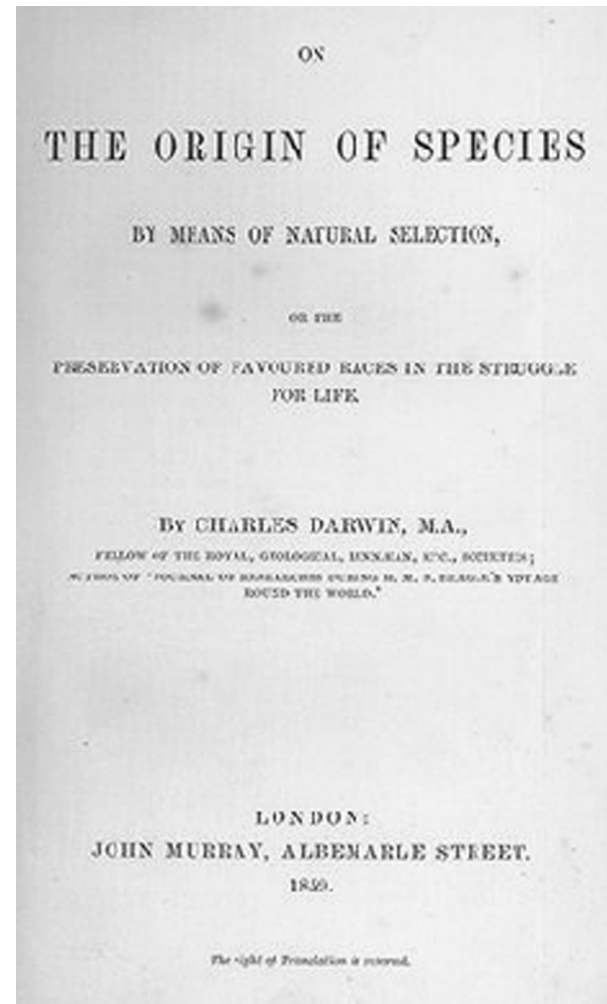


**FIGURE 1.14**   Gregor Mendel.

**FIGURE 1.15**   Monks of the monastery of St Thomas in 1862. Gregor Mendel is the second standing from the right.

on garden peas (*Pisum sativum*), which he cultivated in the small monastery garden (Figure 1.15). Peas were excellent subjects for his experiments on plant hybridization as they are easy to cultivate and the anatomy of their flowers prevents cross-pollination. Another key to Mendel's success was his decision to examine only distinctive physical traits that could be categorically classified. He carefully controlled his experiments, and noted that some of the characters did not permit "sharp and certain separations" as they showed "differences of the 'more or less' nature." (These would later become known as **quantitative traits**.) He therefore selected seven characteristics which "stand out clearly and definitely in the plants." These were round or wrinkled seeds, yellow or green seeds, inflated or wrinkled seed pods, green or yellow seed pods, purple or white flowers, flowers along the stem or at the tip, and tall or dwarf plants.

Mendel observed that these traits are passed from parents to their offspring according to set ratios. He reasoned that individuals possess two sets of factors that underlie each of these traits, one from each parent. He found that a particular characteristic was sometimes expressed (dominant) and sometimes concealed (recessive), but that recessive traits would reappear in the second generation in predictable ratios, and dominant characters appeared in that second generation three times as frequently as recessive characters. He also observed that the different traits generally segregated independently. For example, a pea may develop seeds that are round and yellow, wrinkled and yellow, round and green, or wrinkled and green.

In 1865, Mendel presented his results to the Brno Society for the Study of Natural Science, and in 1866 he published his *Versuche über Pflanzenhybriden* (*Research on Plant Crosses*). He distributed about 40 copies of this paper to individuals he thought would be interested in his observations, but his work was largely ignored. The only person who understood the significance of his findings was Carl Nägeli, Professor of Botany at the University of



**FIGURE 1.16**   The statue of Mendel in the courtyard of the monastery of St Thomas in Brno.

Munich, who encouraged him to perform similar experiments on his pet plant, hawkweed. Unfortunately, Mendel was not aware that hawkweed also reproduces asexually, and to his disappointment could not reproduce his observations with the peas in hawkweed.

In 1867, Mendel became abbot of the monastery of St Thomas. His work on heredity was forgotten until it was rediscovered in 1900 simultaneously by three European botanists, Carl Correns, Erich von Tschermak, and Hugo de Vries, who independently searched the literature, stumbled on Mendel's *Versuche*, and realized that Mendel had published their observations 34 years earlier. Thereafter, Mendel became known as the "Father of Genetics," (Figures 1.16 and 1.17) even though the term *genetics* (from the Greek "to give birth") was not used until 1905 for the first time by William Bateson in a personal letter to Adam Sedgwick. The terms **gene**, **genotype** and **phenotype** were first coined by Wilhelm Johansen in 1909.

**FIGURE 1.17**    The plaque above Mendel's grave with an inscription that reads "Scientist and biologist, in charge of the Augustinian monastery in Old Brno. He discovered the laws of heredity in plants and animals. His knowledge provides a permanent scientific basis for recent progress in genetics."

Mendel's success stemmed from his careful note-taking, his aptitude for mathematics and statistical analysis, and his ability to think creatively. He was one of the first to apply statistical data analysis to biological observations.

## Pioneers of Biometrics

A half-cousin of Charles Darwin, Sir Francis Galton, was an unusually talented scientist who, at the age of six, studied Latin and Greek and read Shakespeare for pleasure (Figure 1.18). Like Charles Darwin, Galton enjoyed traveling and made extensive journeys through the Middle East and Africa, which he chronicled for the Royal Geographic Society. Galton was strongly influenced by Darwin's book *On the Origin of Species* and, being virtually obsessed with counting and measuring, was intrigued by the observed variation in human characteristics. He was intrigued by the question of whether human abilities were hereditary or environmental, and was the first to coin the phrase "nature versus nurture." He devised questionnaires which he circulated among the 190 Fellows of the Royal Society requesting information about family characteristics to assess whether scientific capability was innate. Recognizing the limitations of this experiment, he used a similar questionnaire approach in twin studies, being the first to recognize twins as an invaluable resource for studies on genetic variation of human characteristics. He also proposed adoption studies, to tease out hereditary effects from environmental effects. Despite his innovative studies, Galton was not able to conclusively resolve the nature versus nurture issue, which would kindle a polarized debate in the scientific community for another century.
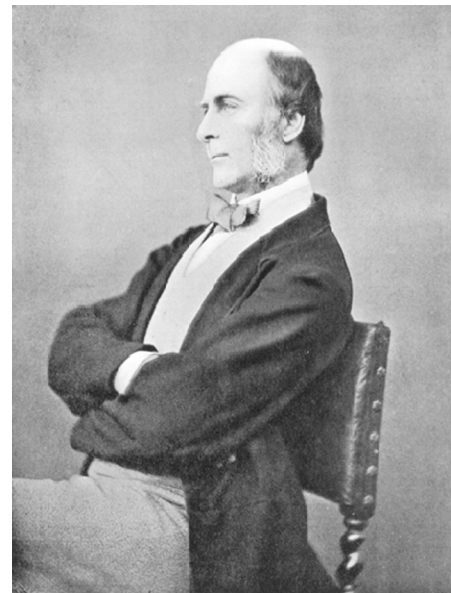


**FIGURE 1.18**    Sir Francis Galton.

Based on his results, Galton became convinced that the human population could be improved by encouraging marriages between "appropriate" individuals. He advocated that incentives should be provided for early marriages between members of higher social rank. The notion that government interference in directing human reproduction to improve society was acceptable became known as **eugenics**, a term Galton invented. As the notion of eugenics is based on subjective judgements of what constitutes a better individual, and since eugenics principles have been
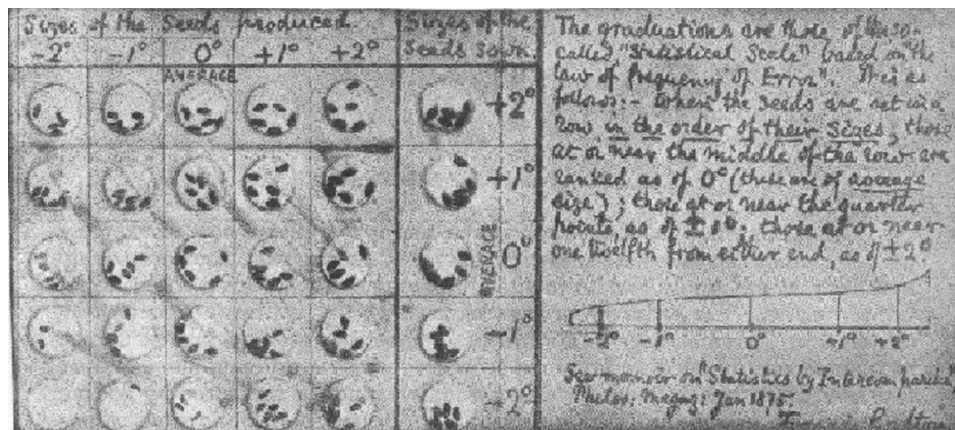
**FIGURE 1.19**  Francis Galton's description of his experiments with pea seeds, dated 1875.

used to justify genocide, for example by the Nazis during the Holocaust, the concept of eugenics fell into disrepute during the second half of the twentieth century, and is now widely regarded as unethical and scientifically flawed.

In 1877, Galton sent seven batches of sweet pea seeds to a group of friends, who planted them and sent offspring seeds back to Galton (Figure 1.19). When Galton measured the mean diameters of the parents and offspring seeds he noticed that they correlated, and that when these measures were plotted against each other the points were distributed around a straight line. He coined the term **co-relation**, which could be measured by the **coefficient of regression** represented by the slope of the line. Galton's graph of seed sizes represented the first regression line (Figure 1.20).

Galton discovered the statistical principle of **regression toward the mean**, where above-average parental phenotypes tend to regress to average phenotypic values in the offspring, as genes recombine and favorable combinations of alleles are lost. Galton also constructed histograms, and described and analyzed for the first time the **normal distribution**. Another of Galton's notable contributions was his study on fingerprints. Although he was not the first to realize the individual uniqueness of fingerprints and its potential applications to forensic science, Galton estimated the probability of two persons having the same fingerprint, and by placing fingerprinting on a solid scientific basis opened the way for its use in criminal courts.

One might wonder why Galton, despite his meticulous measurements and his mathematical genius, did not make the same breakthrough observations of the principles of heredity as Gregor Mendel. The reason is that whereas Mendel had deliberately chosen categorical traits, Galton examined continuous traits that were complex and arose from multiple interacting genes. His statistical analyses laid the foundation for the field that would become known as **quantitative genetics**.

The analysis of measurements of biological parameters, which became known as **biometrics**, was enthusiastically
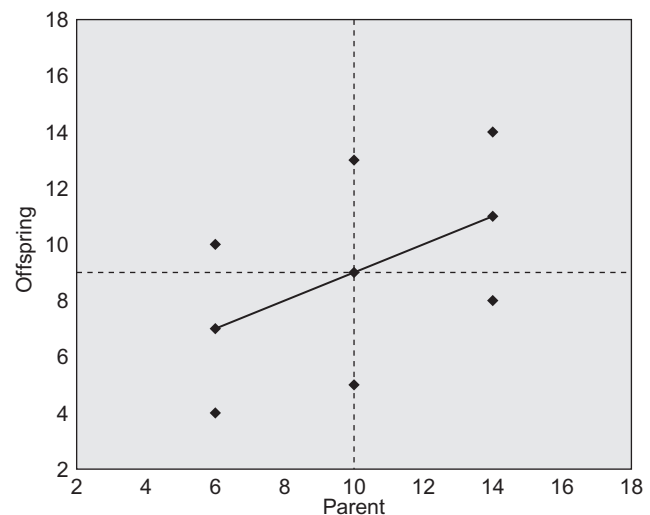


**FIGURE 1.20**  Galton's correlation between the diameters of sweet pea seeds from parents and offspring. The slope of the regression line is exactly 0.50. Many of the points are closer to the offspring pea size mean of 9 on the *y*-axis than to the parental pea size mean of 10 on the *x*-axis, which gave rise to Galton's concept of regression toward the mean.

embraced by Karl Pearson, Galton's protégé and intellectual heir, who after Galton's death in 1911 became the first professor of eugenics at the University of London (Figure 1.21). Pearson was a person of internal contradictions, in that he was a Marxist socialist, yet at the same time a strong advocate for eugenics, to the extent of espousing profoundly racist theories. He loathed the working class and advocated "war" against "inferior races." He remains, however, well-known for his important work which refined Galton's concepts of linear regression and correlation, and his classification of probability distributions. The **Pearson product–moment correlation coefficient**, a frequently-used statistic for estimating correlations, is named after him. The biometrics movement around the turn of the twentieth century provided a statistical basis for the modern evolutionary synthesis, which would soon follow.

**FIGURE 1.21**  Karl Pearson (left) with the 87-year-old Francis Galton.



**FIGURE 1.22**  Thomas Hunt Morgan.

## THE MODERN EVOLUTIONARY SYNTHESIS

The **modern evolutionary synthesis**, also referred to as neo-Darwinism, provided major conceptual advances in the history of science by combining Darwin's theory of natural selection with Mendel's discoveries of the basic mechanisms of inheritance, and by developing statistical techniques that would enable quantitative descriptions of **complex traits** and of **gene flow** in populations. Evolution by natural selection was predicted to proceed through the occasional occurrence of mutations that would confer advantages to the individuals harboring them. Soon after the rediscovery of Gregor Mendel's work in 1900, a Kentucky-born scientist working at Columbia University, Thomas Hunt Morgan (Figure 1.22), attempted to identify such mutations while studying the fruit fly, *Drosophila melanogaster*. In 1910 Morgan discovered a mutant fly which had white eyes instead of the usual red eyes. He referred to this mutant as "*white*," thereby starting the tradition of naming *Drosophila* genes after their mutant phenotypes. When Morgan crossed white-eyed males with red-eyed females, he noticed that the offspring were all red-eyed, indicating that the mutation was recessive. When he subsequently crossbred the offspring, the white-eyed phenotype reappeared, but only in males, indicating that the trait was **sex-linked** (Figure 1.23). Morgan went on to identify many more fly mutants, and his work established *Drosophila* as an important genetic model organism. Morgan postulated that genes were carried on chromosomes, on which they would be linearly arrayed. Furthermore, he deduced that the amount of crossing-over between adjacent genes differs, and that crossover frequency could be used as a measure of the distance separating genes on a chromosome. His student, Alfred Sturtevant, created
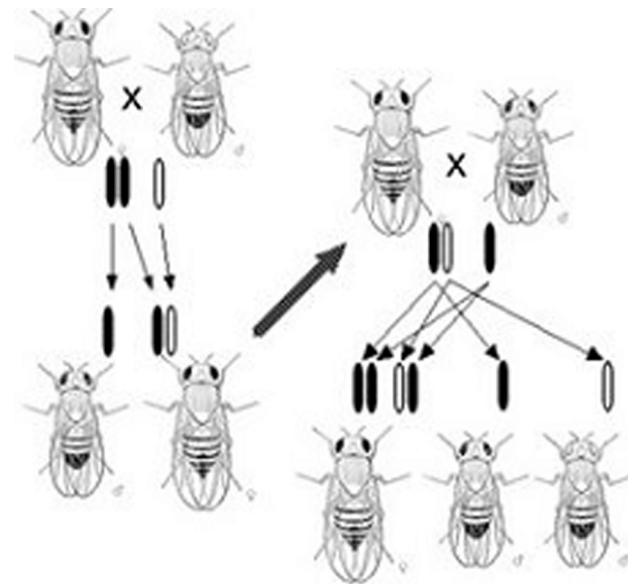


**FIGURE 1.23**  Sex-linked inheritance of the *white* allele; the smaller flies represent males. The open symbol designates the X-chromosome with the *white* allele. Males are XY (the Y-chromosome is not shown).

what is often considered the first genetic **linkage map**. The English geneticist J.B.S. Haldane later suggested that the unit of genetic recombination should be named the **morgan** in his honor. Morgan's concepts influenced the work of George Beadle and Edward Tatum, who showed in the early 1940s that individual mutations induced by X-rays in the bread mold, *Neurospora crassa*, caused changes in specific metabolic enzymes. This work laid the foundation for their **one gene**, **one enzyme hypothesis**.

**FIGURE 1.24**   Barbara McClintock.



Sewall Wright in 1954



J.B.S. (John Burdon Sanderson) Haldane



R.A. Fisher in 1956

**FIGURE 1.25**   Three prominent contributors to the modern evolutionary synthesis.

In the 1920s, Barbara McClintock, working on maize, developed a technique to visualize maize chromosomes, and studied the process of genetic recombination through crossing-over during meiosis (Figure 1.24). Later, between 1948 and 1950, McClintock discovered mobile elements in maize that would give rise to unstable **mosaic phenotypes**. The discovery of transposition mediated by such mobile elements – also known as jumping genes or **transposons** – would have a significant impact on later studies using other organisms, where transposition would become the principal tool for introducing mutations (see Chapter 9). McClintock understood the importance of transposons on modulation of gene action and in evolution long before transposition was generally recognized as an important genetic mechanism.

The major concept that emerged from the modern evolutionary synthesis was that genes provide the units for natural selection, and that changes in allele frequencies represent the mechanism for evolution. This was clearly formulated by Theodosius Dobzhansky, a Russian immigrant scientist who worked with Morgan at Columbia University and moved with him to the California Institute of Technology in 1928. In his 1937 book *Genetics and the Origin of Species*, Dobzhansky defined evolution as "a change in the frequency of an allele within a gene pool." This concept became a central tenet of **population genetics**, a science that arose as a result of the modern evolutionary synthesis.
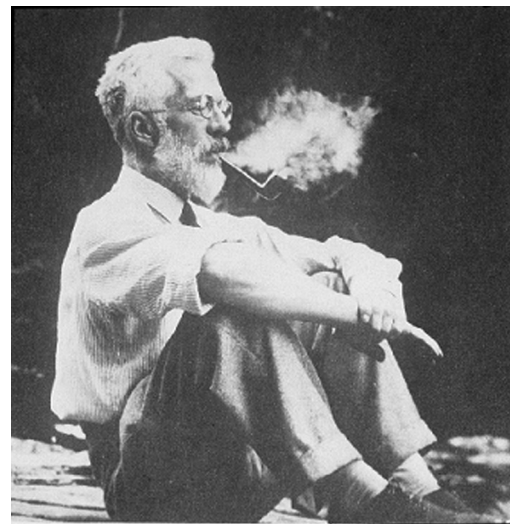
Although a number of prominent scientists contributed to the modern evolutionary synthesis, three central protagonists stand out: Ronald A. Fisher; J. B. S. Haldane; and Sewall Wright (Figure 1.25). Fisher devised methods to partition variance observed in experimental data sets in different sources, a technique that became known as **analysis of variance** (ANOVA), which remains a central analytical tool in experimental biology. Fisher also invented the **maximum likelihood estimation method**, a technique extensively used today in gene-mapping studies. One of Fisher's major insights was the notion that the probability that a mutation increases the fitness of an organism decreases with the severity of the mutation. He also pointed out that larger populations that carry more variation have a greater chance of survival than small populations with a restricted gene pool. Fisher developed many of the concepts that form the foundation for the field of population genetics. Like his predecessors, Fisher was a fervent believer in eugenics, although he did not share the extreme prejudices of Karl Pearson.

J.B.S. Haldane, an English geneticist descended from Scottish aristocrats, published a book in 1932, *The Causes of Evolution*, which explained natural selection in evolution as a consequence of Mendelian genetics in mathematical terms. He remains perhaps best known for **Haldane's rule**,

which states that when one sex is absent, rare or sterile, in the F1 offspring of two different animal races, that sex is the heterozygous (**heterogametic**) sex. Haldane's rule has implications for speciation, because if a sex-linked gene necessary for fertility or viability in two subspecies is absent from the homozygous chromosome and not transmitted to offspring with the heterozygous sex, fertility and viability of the F1 hybrids will be reduced. As speciation progresses, ultimately, the two subspecies will no longer be able to interbreed and become different species. Whereas Darwin and the early evolutionary biologists' distinguished species based on morphological criteria, the twentieth-century biologist Ernst Mayr defined different species by their inability to interbreed. Darwin's finches, from the Galapagos Islands, can, in fact, interbreed in captivity.

While Fisher and Haldane were developing their theories in Britain, major contributions to the developing field of population genetics were being made at the University of Chicago by Sewall Wright. Wright studied the effect of inbreeding on fitness, and realized that statistical variation of alleles of a gene that change their frequencies in a population during successive generations of inbreeding would lead to fixation to homozygosity of one of the alleles, a phenomenon known as **genetic drift**. The fixed alleles would not necessarily be beneficial but could, in fact, lead to a reduction in fitness, known as **inbreeding depression**. Genetic drift is more pronounced the smaller the population size. For example, this has become a major concern in the management of endangered species. Wright defined the **inbreeding coefficient**, and his work laid important theoretical foundations for investigators like Jay Lush and Alan Robertson, who were instrumental in applying genetic principles to animal and plant breeding. Wright also introduced the concept of **adaptive landscapes** into evolutionary biology. These are three-dimensional graphical representations in which peaks represent genotypes with high reproductive success (fitness) separated by valleys. Wright's concept implies that, for a genotype to evolve from its present fitness value to a phenotype with higher fitness, it must accumulate detrimental mutations that will eventually allow it to cross through an adaptive valley of lower fitness to another nearby peak.

A contentious issue that remained throughout the modern evolutionary synthesis period was the question of whether evolution proceeds through gradual changes, as envisioned by Charles Darwin, or through mutations of large effect, like those observed by Thomas Hunt Morgan, and whether complex traits are determined by a few genes of large effect, or by an infinite number of genes, that each contribute only a small effect (the **infinitesimal model**). The latter issue was addressed convincingly by Alan Robertson at the University of Edinburgh, who proposed that much of the variation in complex traits can be accounted for by a limited number of genes with large effects, and a larger number of genes with minor effects,

striking a now widely-accepted compromise between the two alternative theories.

## THE RISE OF MOLECULAR GENETICS

One of the greatest discoveries in modern science was the elucidation of the structure of DNA. DNA (deoxyribonucleic acid) was discovered in 1868 by a Swiss biologist, Friedrich Miescher, who isolated it from nuclei of pus cells he found in discarded surgical bandages. As strange as it may seem today, in the early twentieth century there was debate as to whether DNA or proteins would represent the genetic material. This issue was conclusively resolved in 1943, when Oswald Avery, Colin MacLeod, and Maclyn McCarty at the Rockefeller University showed that they could transform an inactive strain of *Streptococcus pneumoniae* into a virulent strain by incorporating DNA isolated from virulent bacteria into the inactive strain. Furthermore, in 1952, Alfred Hershey and Martha Chase showed that when bacteria are infected with bacteriophage T2, it is the viral DNA and not its protein that is injected into the bacteria and directs viral replication.

The structure of DNA was discovered in 1953 by an American geneticist, James Watson, and an English physicist, Francis Crick, working together at the University of Cambridge (Figure 1.26). In formulating a model for DNA, Watson and Crick first arrived at the wrong conclusion, a triple helix with the bases on the outside. Meanwhile, Linus Pauling in the United States had come up with a similar model. Watson and Crick realized that it would only be a
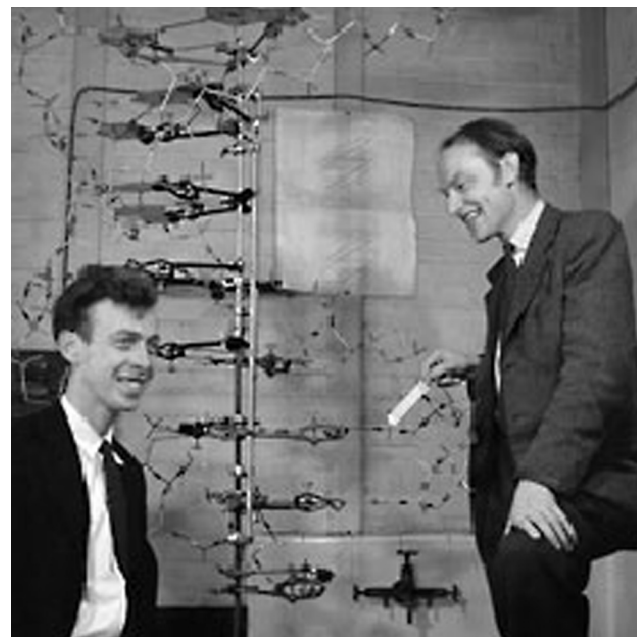


**FIGURE 1.26**  A photograph taken by Antony Barrington Brown in 1953 of Watson (left) and Crick (right) with their DNA model.

matter of months for Pauling to realize that the triple helix model was chemically unfavorable, and that they had only a short time to solve the structure of DNA. Pauling had intended to visit London, but was denied a visa by the US State Department as his antinuclear sympathies were viewed unfavorably during the McCarthy period. If Pauling's visit to London had taken place, and if he would have had access to the same critical information as Watson and Crick, he might have derived at the same structure of DNA earlier. This critical information consisted, in part, of an X-ray photograph taken by Rosalind Franklin, who was performing comprehensive X-ray diffraction studies on DNA. Her now-famous photograph 51 (Figure 1.27) was shown to James Watson by Franklin's supervisor Maurice Wilkins without Franklin's knowledge, an act which has been considered by many as unethical. Photograph 51 provided the last bit of information needed by Watson and Crick to derive their model for the structure of DNA. Previously, Erwin Chargaff had reported that the molar concentration of adenine always equaled that of thymidine, and that the amount of guanine always equaled that of cytosine. Using cardboard models of the four bases, Watson had noticed that the sizes of the adenine–thymidine and guanine–cytosine base pairs were similar in size. These facts, together with the X-ray diffraction pattern in Franklin's photograph, allowed Watson and Crick to describe a model in which adenine–thymidine and guanine–cytosine base pairs were located on the inside of a double helix, with the phosphate backbone exposed on the outside. Moreover, the helical strands were antiparallel and, when taken apart, could each serve as a blueprint for replication of the other. Furthermore, based simply on arithmetic considerations, Crick hypothesized that three nucleotides would specify an amino acid and that, consequently, the genetic code would be degenerate as there would be 64 possible three-nucleotide codons to encode only 20 amino acids. The genetic code was subsequently unraveled by Marshall Nirenberg and his coworkers between 1961 and 1965. The notion that proteins are encoded by an mRNA that is synthesized from a DNA template became known as the **central dogma** in molecular biology. The central dogma has largely held up, although it was modified in 1971 by Howard Temin who showed that RNA viruses can direct the synthesis of DNA from an RNA template, an exception to the central dogma.

In a videotaped message to the participants of the Nineteenth International Congress of Genetics in Melbourne (Australia) in 2003, which marked the fiftieth anniversary of Watson and Crick's discovery of the structure of DNA, Francis Crick described their discovery and asserted that he and Watson were fully aware of the impact their work would have, but that they never could have imagined that one day whole genomes could be sequenced, since they believed at that time that sequencing DNA would be extremely difficult. The first method for DNA sequencing was developed in 1975 by Frederick Sanger. With the advent of improved methodologies and automatic sequencers, high-throughput DNA sequencing for whole-genome analyses became a reality near the end of the twentieth century.

Recombinant DNA technology was pioneered by Paul Berg and others in California in the early 1970s. Propagation of engineered DNA constructs in bacteria allowed such constructs to be multiplied (cloned) in large amounts. Another major breakthrough in DNA technology came in 1983, when a young Californian scientist, Kary B. Mullis, introduced the **polymerase chain reaction** (PCR), which uses a thermostable DNA polymerase that can withstand multiple heat cycles necessary to separate and re-anneal DNA strands, and is active at a temperature of 72°C (Figure 1.28). PCR allows the amplification of precisely-identified DNA sequences, even if present in minute amounts, to sizable quantities. It is now a standard tool in the molecular biologist's toolkit. DNA cloning reached another milestone in 1997, when a Scottish investigator in Edinburgh, Ian Wilmut, announced that he had cloned a sheep from an adult cell from the udder of a six-year-old
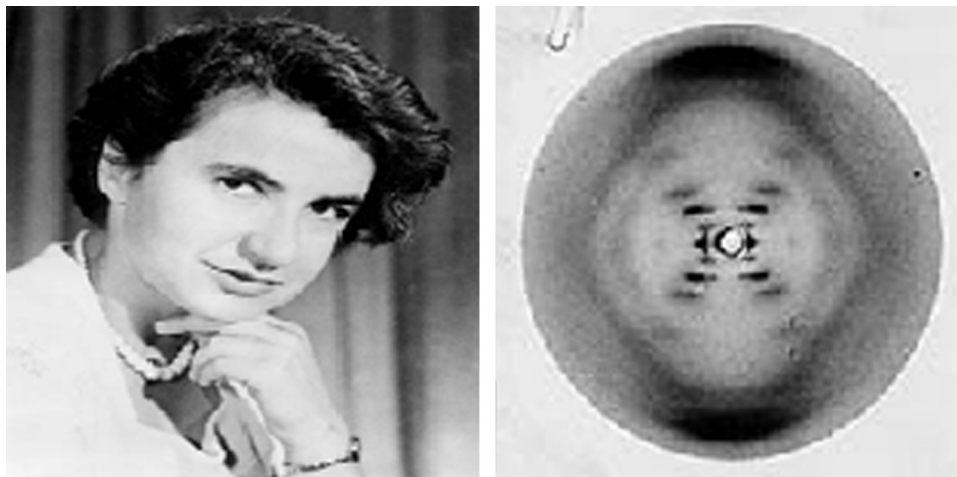


**FIGURE 1.27** Rosalind Franklin (left) and her famous photograph 51 showing the X-ray diffraction pattern of DNA that enabled Watson and Crick to deduce its structure (right).
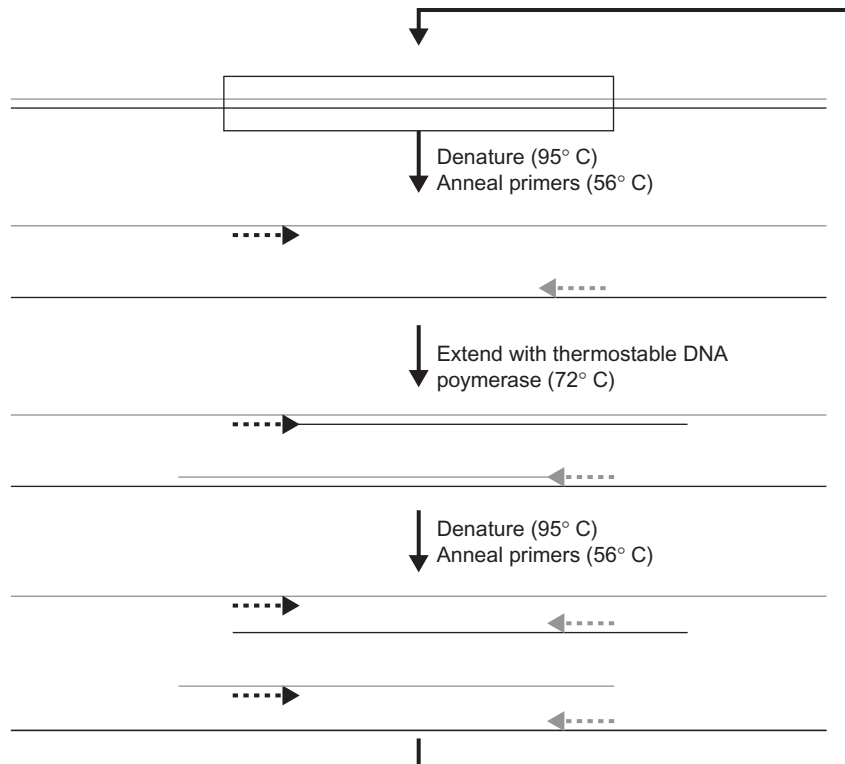
**FIGURE 1.28** The polymerase chain reaction. The black rectangle indicates the target DNA sequence. The DNA strands are separated by heating at 95°C, and oligonucleotide primers, indicated by the dotted arrows, are allowed to anneal to the two antiparallel DNA strands at each side of the target sequence at an optimal temperature, in this example 56°C. The temperature is then raised to 72°C. At this temperature, a thermostable DNA polymerase – isolated from bacteria that grow in hot geothermal springs – is optimally active and can synthesize complementary DNA from each primer. Since this enzyme survives the denaturation temperature of 95°C, the process can be repeated. Repeating this cycle 20 or more times in a thermal cycler will lead to exponential amplification of the target sequence.

ewe. The cloned sheep was named Dolly (after the US country singer Dolly Parton), and her creation was soon followed by that of cloned mice, cows, and pigs. This led to a controversy that is still hotly debated regarding the possibility of human cloning, which many consider unethical as well as premature, in part because potential adverse health effects remain uncertain.

The impressive growth of molecular genetics provided a much-needed molecular framework for the study of quantitative traits, which during the modern evolutionary synthesis were described mostly statistically. As will become clear in this book, behavioral genetics requires both molecular and quantitative genetic approaches.

## A BRIEF HISTORY OF NEUROSCIENCE

While the modern evolutionary synthesis was in full swing, the field of neuroscience was being born. In the 1920s and 1930s, classical experiments by Otto Loewi and Sir Henry Hallett Dale led to the identification of the first **neurotransmitters**, acetylcholine and adrenaline, and Dale coined the terms **cholinergic** and **adrenergic** to describe their often antagonistic physiological effects (Figure 1.29). During the following decades the repertoire of neurotransmitters expanded dramatically to include a host of other bioamines, amino acids and their derivatives, and peptides.

Using home-built oscilloscopes and amplifiers, early electrophysiologists studied how neurons generate electrical



**FIGURE 1.29** Early pioneers in neuroscience.

impulses to encode and convey information. The first **action potential** was recorded by Kenneth C. Cole and H. J. Curtis in 1939 (Figure 1.30). Working at Cambridge in the 1930s and 1940s, Sir Andrew Fielding Huxley and Alan Lloyd Hodgkin developed the **voltage-clamp method** (explained in Chapter 2) that enabled them to explain the ionic basis of the action potential as the sequential opening and closing of "gates" that are selectively permeable to sodium and potassium. At the same time, a controversy arose as to whether **synaptic transmission**, that is, communication between one cell and another in the nervous

**FIGURE 1.30**   The first action potential showing a transient increase in membrane conductance, recorded by K.C. Cole.



**FIGURE 1.31**   Sir Bernard Katz.



**FIGURE 1.32**   Linda Buck receiving the 2004 Nobel Prize from His Majesty King Carl Gustav XVI of Sweden, for her discovery of odorant receptors and the organization of the olfactory system.

system, was electrical, as proposed by John Eccles, or chemical, as advocated by Sir Bernard Katz (Figure 1.31). The controversy was resolved in the 1950s when Katz demonstrated that synaptic transmission at the neuromuscular junction was due to the release of discrete packages (**quanta**) of acetylcholine from the **presynaptic cell**, which would elicit changes in the membrane potential of the muscle fiber (the **postsynaptic cell**) after diffusing across a **synaptic cleft**. Soon after, the advent of electron microscopy consolidated the existence of a physical separation at the synapse.

The subsequent development of increasingly more sophisticated neuroanatomical tracer and imaging techniques, and extracellular, intracellular, and multicellular recording methods have led to an explosion of information about neural circuitry in the brain, and its relationship to physiological and behavioral functions. Among many noteworthy achievements are the studies by Eric Kandel and his colleagues at Columbia University who developed a seemingly unlikely invertebrate model for learning, the sea slug *Aplysia californica* (see also Chapter 14). This simple organism exhibits a defensive gill withdrawal reflex when a jet of water is sprayed against its siphon. This response can be paired with an electric shock to the tail, so that subsequent electric shocks will elicit stronger gill withdrawal responses, a characteristic example of reinforcement through classical conditioning, not unlike the salivation responses elicited by Pavlov in his dogs. The neural circuitry that underlies this response, as well as evolutionarily conserved mechanisms that control alterations in gene expression during learning, could be identified and characterized. Landmark discoveries in sensory neurobiology included the organization of the visual cortex and elucidation of how visual information is processed by deconstructing aspects of the image along parallel neural pathways, for which David Hubel and Tornsten Wiesel received the 1981 Nobel Prize, and the discovery of a large multigene family of odorant receptors and the functional organization of the olfactory system, for which Linda Buck and Richard Axel received the 2004 Nobel Prize (Figure 1.32).

In addition to great advances in understanding the neural mechanisms that mediate sensory information processing, **sensory-motor integration** and motor control, complex cognitive brain functions once thought intractable, have become amenable to scientific scrutiny. Such processes include learning and consolidation and retrieval of memory, fear, attention, and even such seemingly esoteric perceptions as empathy and appreciation of music.

Whereas advances in neurobiology paralleled developments in genetics, and occurred contemporaneously with the exploits of the early ethologists, there was relatively little conceptual cross-talk between these disciplines, other than the application of molecular genetic techniques. Neurogenetics – although recognized as a subdiscipline – was not a major focus of behavioral neuroscience.

This changed with the availability of whole-genome sequences and genomics technologies near the end of the twentieth century, which has spurred a profound and widespread interest in exploring the link between the genome and the nervous system. The concept of "genes, brain, and behavior" – that is, how genes enable the nervous system to respond to environmental cues and elicit an appropriate behavior – has become the central focus of behavioral biology. Although this book focuses on genetic aspects of behavior, appreciating the neural circuits that express behaviors is indispensable. Fundamental neurobiological principles are described in greater detail in Chapter 3, and auxiliary neurobiological information is provided in text boxes in subsequent chapters.

## THE EMERGENCE OF BEHAVIORAL GENETICS

The classical ethologists and early experimental psychologists demonstrated that behaviors were not of such intractable complexity that they could not be studied using carefully-designed experimental approaches. Behavioral biology has developed since then along two parallel tracks that have only recently begun to interconnect. On the one hand, advances in neurobiology, including the ability to record electrophysiologically from multiple neurons simultaneously in real-time in live behaving animals, have rapidly identified neural circuits that contribute to the manifestation of a wide range of behaviors. On the other hand, geneticists have begun to investigate how spatial and temporal patterns of expression of ensembles of genes enable the activity of such neural circuits to allow the organism to sense and respond to changes in its environment. Until the advent of technologies that enabled whole-genome analyses, genetic studies lagged behind the neurobiological approaches. The present **genomic era** can look forward to the coalescence of both approaches into **neurogenomics** applications that will monitor activity of the nervous system, while at the same time assessing the transcriptional, translational, and post-translational dynamics of the genome that supports this activity.

**Artificial selection** has long been the standard procedure by which animal breeders improve livestock by selecting individuals of extreme phenotypes as parents for each successive generation (e.g. milk yield in dairy cows). The earliest artificial selection experiment in behavioral genetics was reported by R.C. Tryon in 1942, by selecting rats based on their ability to negotiate a maze. Poor performers were labeled "dull" and good performers were designated "bright." Tryon observed a substantial difference in maze running ability in two selected lines after only seven generations of selecting "bright" and "dull" lines by breeding the best and worst maze-running rats with others of similar abilities. However, subsequent studies showed that the performance of dull rats could be improved dramatically by rearing them in an enriched environment, with a variety of objects to explore and ample social interactions. These studies provided one of the first well-documented examples of **genotype-by-environment interaction** on a behavioral trait, since manifestation of the genetic difference between the dull and bright strains is dependent on the environmental conditions in which the rats are reared.

Another noteworthy early and pioneering experiment in behavioral genetics was performed in the 1960s by J. Hirsch, on **geotaxis** in *Drosophila*. Flies are positively geotactic, that is, they move upwards against the force of gravity. Hirsch constructed a vertical maze, in which he could introduce flies on one side in the center of the maze and watch them move toward a light source at the other side of the maze. The maze consisted of sequential branch points, each of which required flies to make a decision to move upward or downward. They would emerge at nine different vertical locations at the other side of the maze. Hirsch selected flies that emerged near the top of the maze, and flies that emerged near the bottom of the maze, and subjected them to iterative cycles of artificial selection, breeding "high" and "low" flies from each successive generation as parents for the next generation. These experiments resulted in the isolation of distinct "high" and "low" geotactic lines that have been propagated for decades, and still exist today.

Other pioneering behavioral genetic experiments were reported in 1971 by Seymour Benzer and his students at the California Institute of Technology on **circadian activity** of *Drosophila* (see also Chapter 11). Flies, like other animals, show periods of activity and inactivity that are governed by an endogenous clock **entrained** to the daily light–dark cycle. Using a photoelectric monitoring device, Benzer monitored activity of flies during the day and night. Normal wild-type flies showed a 24-hour circadian rhythm. Benzer identified mutants that had altered circadian rhythms. He found three such mutants: one was arrhythmic, displaying random periods of rest and activity; one had a significantly shorter circadian period of only 19 hours; and the third mutant had an unusually long circadian rhythm of 28 hours (Figure 1.33). All of these mutants were out of synch with the daily light–dark cycle. In addition to their locomotor behavior, their rhythms of eclosion (emergence from the pupal case) were similarly disrupted. Flies eclose usually in the early morning hours, the time of day when they are most active. Benzer found that all three mutations were located in a single gene. They mapped it to the *X*-chromosome, and named it "*period (per)*." This gene was subsequently found to be a transcriptional regulator, and only one of many components that make up the biological clock. The experiments by Benzer were critical to developing the field of **chronobiology**, i.e. the study of biological clocks. They were also important, because circadian variation in gene expression impacts the experimental

**Box 1.2   Model organisms**

Throughout the history of the biological sciences a number of animals have found widespread use as laboratory models, because they are easy to rear in large numbers in the laboratory and sophisticated genetic techniques could be developed that allow scientists to address questions more easily in these laboratory species under controlled genetic and environmental conditions than in wild animals in their natural habitats. Fruit flies (*Drosophila*), rats, mice, and the nematode *Caenorhabditis elegans* are the most frequently used **model organisms** in behavioral genetics. However, questions are often raised as to what extent findings in laboratory animals that have been propagated in captivity under artificial conditions for many generations reflect reality in nature. Whereas this is a legitimate concern, many questions can only be addressed under controlled conditions, and the advantages offered by the resources and techniques available for studies on these organisms are substantial and outweigh their possible disadvantages. With the ever-increasing number of sequenced genomes, the number of "model organisms" is likely to expand. Honeybees (*Apis mellifera*) are now recognized as a model for studies on the genetic architecture of social behavior (sociogenomics), whereas songbirds are becoming an increasingly valued model for studies of genetic control of neural plasticity during song learning (a model for acquisition of language) and pair-bond formation. Sequenced genomes and extensive databases have become available for both species. In the decades ahead there will likely be an upsurge in comparative genomics approaches, which will be accompanied by extended comparisons between behaviors in laboratory strains and natural populations. Thus, the definition of what exactly is a "model system" is likely to become more blurred, as technologies become available to study the genetic underpinnings of behaviors in more species at the whole-genome level. Such developments will be especially welcome for understanding the evolution of analogous behaviors in related species.

design of behavioral experiments. The manifestations of behaviors may be affected by the time of day at which measurements are taken. The most extreme example is, perhaps, courtship and mating in *Drosophila*, which occurs only during specific times of the circadian day, with a major activity peak in the morning and a smaller peak of activity in the late afternoon.

The studies of Benzer and Hirsch are often viewed as contrasting approaches to the study of behavior, with Benzer as the proponent of the "one-gene-at-a-time" approach, and Hirsch the protagonist of the "multiple genes ensemble" approach. In reality, however, both approaches are complementary, rather than mutually exclusive. The "Hirschian" strategy, however, has recently gained especially strong support as whole-genome analyses are becoming increasingly more sophisticated. Genes identified in such an approach can then be studied intensively individually in a "Benzerian" approach.

Behavioral studies in mice have benefited greatly from a major breakthrough in the late 1980s when Mario Capecchi, Sir Martin Evans, and Oliver Smithies developed methods for deleting genes in mice through **homologous recombination**, a discovery that earned them the 2007 Nobel Prize. Such "knock-out" mice proved to be powerful tools for clarifying the functions of specific genes on physiology and behavior. **Transgenic** mouse technologies were further expanded to allow introduction of foreign genes at defined locations in the genome ("knock-in" mice), and by constructing strains in with the expression of transgenes could be targeted to certain cells or tissues, and could even be controlled temporally. These methods will be discussed in greater detail in Chapter 9.

Although transgenic mice have generated many new insights, this "one-gene-at-a-time" approach led to the notion that each gene contributes a specific function, a conceptual framework that began to erode when whole-genomic approaches and transcriptional profiling studies revealed that there is extensive functional **pleiotropy**
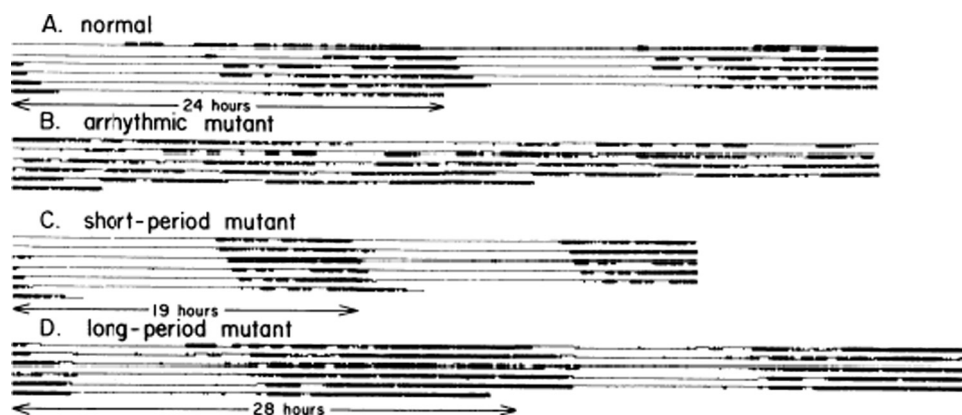


**FIGURE 1.33**   Locomotor activity recorded for normal flies and arrhythmic period mutants and short- and long-period mutants. (From Konopka and Benzer, (1971). *Proc. Natl. Acad. Sci. USA.*)

(that is, a gene can contribute to the manifestation of multiple phenotypes) with wide-ranging genetic interactions. It is becoming increasingly clear that, with few exceptions, behaviors are emergent properties of complex genetic networks, rather than the result of linear genetic pathways that are composed of genes with single dedicated functions.

The availability of whole-genome sequences of an increasing number of species, including *Homo sapiens*, chimpanzee, rat, mouse, zebrafish, zebra finch, *Drosophila*, honeybee, and the nematode *C. elegans*, to name but a few, together with advanced neurobiological techniques, will in the future enable powerful comparative genomic approaches that will allow us not only to define the genetic architecture of behaviors and understand the relation of genetic networks with neural function, but also to gain insights into the evolutionary processes that have occurred to shape the behavioral phenotypes which we observe today.

## SUMMARY

Experimental approaches with predictive value for the study of animal behaviors were first performed by the pioneers of experimental psychology, such as Pavlov, Thorndike, and Skinner, and the early behavioral ecologists, Lorenz, von Frisch, and Tinbergen. A thorough understanding of the genetic basis of behaviors, like most of the foundations of modern biology, rests on Darwin's concept of natural selection, which envisions that the best-adapted individuals in a population will have a more favorable chance to survive and contribute to the next generation. Following the rediscovery of Mendel's rules of inheritance at the turn of the twentieth century, it was recognized that genes provide the physical targets for natural selection during evolution. The modern evolutionary synthesis reformulated Darwin's concept, by viewing evolution as a change of allele frequencies within a gene pool. Whereas the incidence of phenotypes that are determined by a single segregating gene can be readily predicted according to Mendel's rules, complex (or "quantitative") traits that arise from multiple segregating genes that are influenced by the environment require more complex statistical analyses. Such analyses, including analysis of variance and likelihood distributions, were pioneered by Roland Fisher building on earlier work by Francis Galton and his protégé Karl Pearson, who had laid the statistical groundwork for regression and correlation analyses. Fisher, Haldane, Wright, and others studied gene flow in populations and laid the foundation for population genetics. The second half of the twentieth century saw the rise of molecular genetics, with Watson and Crick's discovery of the structure of DNA, elucidation of the genetic code, formulation of the central dogma, and the flow of genetic information from DNA to RNA to protein. These discoveries coincided with major advances in the neurosciences as Huxley, Hodgkin, and Katz explored the mechanisms for neural signal propagation and synaptic transmission. The early experimental psychologists and behavioral ecologists paid little attention to contemporary advances in genetics and neuroscience, but were able to provide independent insights into fundamental aspects of behavior, including instinctive behaviors, such as imprinting and social communication. Tinbergen framed the study of behavior as a series of questions that could be answered through scientific studies, which asked how behaviors are elicited and modified through learning and interactions with the environment, and how they develop and evolve. Some of the first experiments in behavioral genetics were done by Benzer and Hirsch on circadian behavior and geotaxis, respectively, using the fruit fly *Drosophila melanogaster*, developed earlier as a favorable genetic model organism by Thomas Hunt Morgan. Advances in genetics (especially the availability of whole-genome sequences and the development of methods for gene targeting), and the neurosciences around the turn of the twenty-first century are facilitating the integration of the disciplines of behavioral genetics, neuroscience, ecology, and ethology into the modern science of behavioral biology. One of the central goals of behavioral genetics is to explore how regulation of gene expression enables the nervous system to drive and modify appropriate behaviors, and how changes in allele frequencies cause behaviors to evolve.

## STUDY QUESTIONS

1. How does classical conditioning described by Pavlov differ from operant conditioning described by Skinner?
2. What contributions did Lorenz and von Frisch make to understanding social behavior?
3. What contribution did Tinbergen make to define the modern field of ethology?
4. Describe the conceptual difference between the evolutionary theories of Lamarck and Darwin.
5. Explain why Mendel was able to derive his fundamental rules for inheritance, whereas Galton fell short of making the same discoveries.
6. What is eugenics? Why did it appear a reasonable concept in the early days of the history of genetics, and why has it fallen into disrepute?
7. What is the fundamental contribution of the modern evolutionary synthesis as formulated by Dobzhansky?
8. What is Haldane's rule?
9. What was the early evidence that DNA represents the genetic material?
10. What critical pieces of information enabled Watson and Crick to develop their model for the structure of DNA?
11. What is the central dogma?
12. What were some of the major contributions made to behavioral genetics by Thomas Hunt Morgan?
13. Describe the contributions of S. Benzer and J. Hirsch to behavioral genetics.

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