SECTION I

NEUROSCIENCE
A BRIEF HISTORY OF NEUROSCIENCE

The field of knowledge described in this book is neuroscience, the multidisciplinary sciences that analyze the nervous system to understand the biological basis for behavior. Modern studies of the nervous system have been ongoing since the middle of the nineteenth century. Neuroanatomists studied the brain’s shape, its cellular structure, and its circuitry; neurochemists studied the brain’s chemical composition, its lipids and proteins; neurophysiologists studied the brain’s bioelectric properties; and psychologists and neuropsychologists investigated the organization and neural substrates of behavior and cognition.

The term neuroscience was introduced in the mid-1960s, to signal the beginning of an era in which each of these disciplines would work together cooperatively, sharing a common language, common concepts, and a common goal—to understand the structure and function of the normal and abnormal brain. Neuroscience today spans a wide range of research endeavors from the molecular biology of nerve cells (i.e., the genes encoding the proteins needed for nervous system function) to the biological basis of normal and disordered behavior, emotion, and cognition (i.e., the mental properties by which individuals interact with each other and with their environments). For a more complete, but concise, history of the neurosciences see Kandel and Squire (2000).

Neuroscience is currently one of the most rapidly growing areas of science. Indeed, the brain is sometimes referred to as the last frontier of biology. In 1971, 1100 scientists convened at the first annual meeting of the Society for Neuroscience. In 2006, 25,785 scientists participated at the society’s 36th annual meeting at which 14,268 research presentations were made.

THE TERMINOLOGY OF NERVOUS SYSTEMS IS HIERARCHICAL, DISTRIBUTED, DESCRIPTIVE, AND HISTORICALLY BASED

Beginning students of neuroscience justifiably could find themselves confused. Nervous systems of many organisms have their cell assemblies and macroscopically visible components named by multiple overlapping and often synonymous terms. With a necessarily gracious view to the past, this confusing terminology could be viewed as the intellectual cost of focused discourse with predecessors in the enterprise. The nervous systems of invertebrate organisms often are designated for their spatially directed collections of neurons responsible for local control of operations, such as the thoracic or abdominal ganglia, which receive sensations and direct motoric responses for specific body segments, all under the general control of a cephalic ganglion whose role includes sensing the external environment.

In vertebrates, the components of the nervous system were named for both their appearance and their location. As noted by Swanson, and expanded upon in Chapter 2 of this volume, the names of the major parts of the brain were based on creative interpretations of early dissectors of the brain, attributing names to brain segments based on their appearance in the freshly dissected state: hippocampus (shaped like...
the sea horse) or amygdala (shaped like the almond), cerebrum (the main brain), and cerebellum (a small brain).

**NEURONS AND GLIA ARE CELLULAR BUILDING BLOCKS OF THE NERVOUS SYSTEM**

This book lays out our current understanding in each of the important domains that together define the full scope of modern neuroscience. The structure and function of the brain and spinal cord are most appropriately understood from the perspective of their highly specialized cells: the neurons, the interconnected, highly differentiated, bioelectrically driven, cellular units of the nervous system; and their more numerous support cells, the glia. Given the importance of these cellular building blocks in all that follows, a brief overview of their properties may be helpful.

**Neurons Are Heterogeneously Shaped, Highly Active Secretory Cells**

Neurons are classified in many different ways, according to function (sensory, motor, or interneuron), location (cortical, spinal, etc.), the identity of the transmitter they synthesize and release (glutamatergic, cholinergic, etc.), and their shape (pyramidal, granule, mitral, etc.). Microscopic analysis focuses on their general shape and, in particular, the number of extensions from the cell body. Most neurons have one axon, often branched, to transmit signals to interconnected target neurons. Other processes, termed dendrites, extend from the nerve cell body (also termed the perikaryon—the cytoplasm surrounding the nucleus of the neuron) to receive synaptic contacts from other neurons; dendrites may branch in extremely complex patterns, and may possess multiple short protrusions called dendritic spines. Neurons exhibit the cytological characteristics of highly active secretory cells with large nuclei; large amounts of smooth and rough endoplasmic reticulum; and frequent clusters of specialized smooth endoplasmic reticulum (Golgi apparatus), in which secretory products of the cell are packaged into membrane-bound organelles for transport out of the cell body proper to the axon or dendrites. Neurons and their cellular extensions are rich in microtubules—elongated tubules approximately 24 nm in diameter. Microtubules support the elongated axons and dendrites and assist in the reciprocal transport of essential macromolecules and organelles between the cell body and the distant axon or dendrites.

**Neurons Communicate Chemically through Specialized Contact Zones**

The sites of interneuronal communication in the central nervous system (CNS) are termed synapses in the CNS and junctions in somatic, motor, and autonomic nervous systems. Paramembranous deposits of specific proteins essential for transmitter release, response, and catabolism characterize synapses and junctions morphologically. These specialized sites are presumed to be the active zone for transmitter release and response. Paramembranous proteins constitute a specialized junctional adherence zone, termed the synaptolemma. Like peripheral junctions, central synapses also are denoted by accumulations of tiny (500 to 1500 Å) organelles, termed synaptic vesicles. The proteins of these vesicles have been shown to have specific roles in transmitter storage; vesicle docking onto presynaptic membranes, voltage- and Ca$^{2+}$-dependent secretion, and the recycling and restorage of previously released transmitter molecules.

**Synaptic Relationships Fall into Several Structural Categories**

Synaptic arrangements in the CNS fall into a wide variety of morphological and functional forms that are specific for the neurons involved. The most common arrangement, typical of hierarchical pathways, is either the axodendritic or the axosomatic synapse, in which the axons of the cell of origin make their functional contact with the dendrites or cell body of the target neuron, respectively. A second category of synaptic arrangement is more rare—forms of functional contact between adjacent cell bodies (somasomatic) and overlapping dendrites (dendrodendritic). Within the spinal cord and some other fields of neuropil (relatively acellular areas of synaptic connections), serial axoaxonic synapses are relatively frequent. Here, the axon of an interneuron ends on the terminal of a long-distance neuron as that terminal contacts a dendrite, or on the segment of the axon that is immediately distal to the soma, termed the initial segment, where action potentials arise. Many presynaptic axons contain local collections of typical synaptic vesicles with no opposed specialized synaptolemma. These are termed boutons en passant. The release of a transmitter may not always occur at such sites.

**Synaptic Relationships Also Belong to Diverse Functional Categories**

As with their structural representations, the qualities of synaptic transmission can also be functionally
THE OPERATIVE PROCESSES OF NERVOUS SYSTEMS ARE ALSO HIERARCHICAL

As research progressed, it became clear that neuronal functions could best be fitted into nervous system function by considering their operations at four fundamental hierarchical levels: molecular, cellular, systems, and behavioral. These levels rest on the fundamental principle that neurons communicate chemically, by the activity-dependent secretion of neurotransmitters, at specialized points of contact named synapses.

At the molecular level of operations, the emphasis is on the interaction of molecules—typically proteins that regulate transcription of genes, their translation into proteins, and their posttranslational processing. Proteins that mediate the intracellular processes of transmitter synthesis, storage, and release, or the intracellular consequences of intercellular synaptic signaling are essential neuronal molecular functions. Such transductive molecular mechanisms include the neurotransmitters’ receptors, as well as the auxiliary molecules that allow these receptors to influence the short-term biology of responsive neurons (through regulation of ion channels) and their longer-term regulation (through alterations in gene expression). Completion of the human, chimpanzee, rat, and mouse genomes can be viewed as an extensive inventory of these molecular elements, more than half of which are thought to be either highly enriched in the brain or even exclusively expressed there.

At the cellular level of neuroscience, the emphasis is on interactions between neurons through their synaptic transactions and between neurons and glia. Much current cellular level research focuses on the biochemical systems within specific cells that mediate such phenomena as pacemakers for the generation of circadian rhythms or that can account for activity-dependent adaptation. Research at the cellular level strives to determine which specific neurons and which of their most proximate synaptic connections may mediate a behavior or the behavioral effects of a given experimental perturbation.

At the systems level, emphasis is on the spatially distributed sensors and effectors that integrate the body’s response to environmental challenges. There are sensory systems, which include specialized senses for hearing, seeing, feeling, tasting, and balancing the body. Similarly, there are motor systems for trunk, limb, and fine finger motions and internal regulatory systems for visceral regulation (e.g., control of body temperature, cardiovascular function, appetite, salt and water balance). These systems operate through relatively sequential linkages, and interruption of any link can destroy the function of the system.

Systems level research also includes research into cellular systems that innervate the widely distributed neuronal elements of the sensory, motor, or visceral systems, such as the pontine neurons with highly branched axons that innervate diencephalic, cortical, and spinal neurons. Among the best studied of these divergent systems are the monoaminergic neurons, which have been linked to the regulation of many behavioral outputs of the brain, ranging from feeding, drinking, thermoregulation, and sexual behavior. Monoaminergic neurons also have been linked to such higher functions as pleasure, reinforcement, attention, motivation, memory, and learning. Dysfunctions of these systems have been hypothesized as the basis for some psychiatric and neurological diseases, supported by evidence that medications aimed at presumed monoamine regulation provide useful therapy.

At the behavioral level of neuroscience research, emphasis is on the interactions between individuals and their collective environment. Research at the behavioral level centers on the integrative phenomena that link populations of neurons (often operationally or empirically defined) into extended specialized circuits, ensembles, or more pervasively distributed
“systems” that integrate the physiological expression of a learned, reflexive, or spontaneously generated behavioral response. Behavioral research also includes the operations of higher mental activity, such as memory, learning, speech, abstract reasoning, and consciousness. Conceptually, “animal models” of human psychiatric diseases are based on the assumption that scientists can appropriately infer from observations of behavior and physiology (heart rate, respiration, locomotion, etc.) that the states experienced by animals are equivalent to the emotional states experienced by humans expressing these same sorts of physiological changes.

As the neuroscientific bases for some elemental behaviors have become better understood, new aspects of neuroscience applied to problems of daily life have begun to emerge. Methods for the noninvasive detection of activity in certain small brain regions have improved such that it is now possible to link these changes in activity with discrete forms of mental activity. These advances have given rise to the concept that it is possible to understand where in the brain the decision-making process occurs, or to identify the kinds of information necessary to decide whether to act or not. The detailed quantitative data that now exist on the details of neuronal structure, function, and behavior have driven the development of computational neurosciences. This new branch of neuroscience research seeks to predict the performance of neurons, neuronal properties, and neural networks based on their discernible quantitative properties.

Some Principles of Brain Organization and Function

The central nervous system is most commonly divided into major structural units, consisting of the major physical subdivisions of the brain. Thus, mammalian neuroscientists divide the central nervous system into the brain and spinal cord and further divide the brain into regions readily seen by the simplest of dissections. Based on research that has demonstrated that these large spatial elements derive from independent structures in the developing brain, these subdivisions are well accepted. Mammalian brain thusly is divided into hindbrain, midbrain, and forebrain, each of which has multiple highly specialized regions within it. In deference to the major differences in body structure, invertebrate nervous systems most often are organized by body segment (cephalic, thoracic, abdominal) and by anterior–posterior placement.

Neurons within the vertebrate CNS operate either within layered structures (such as the olfactory bulb, cerebral cortex, hippocampal formation, and cerebellum) or in clustered groupings (the defined collections of central neurons, which aggregate into “nuclei” in the central nervous system and into “ganglia” in the peripheral nervous system, and in invertebrate nervous systems). The specific connections between neurons within or across the macro-divisions of the brain are essential to the brain’s functions. It is through their patterns of neuronal circuitry that individual neurons form functional ensembles to regulate the flow of information within and between the regions of the brain.

CELLULAR ORGANIZATION OF THE BRAIN

Present understanding of the cellular organization of the CNS can be viewed simplistically according to three main patterns of neuronal connectivity.

Three Basic Patterns of Neuronal Circuitry Exist

Long hierarchical neuronal connections typically are found in the primary sensory and motor pathways. Here the transmission of information is highly sequential, and interconnected neurons are related to each other in a hierarchical fashion. Primary receptors (in the retina, inner ear, olfactory epithelium, tongue, or skin) transmit first to primary sensory fields, then to secondary relay cells, and finally to the primary sensory fields of the cerebral cortex. For motor output systems, the reverse sequence exists with impulses descending hierarchically from the motor cortex to the spinal motoneuron. It is at the level of the motor and sensory systems that beginning scholars of the nervous system will begin to appreciate the complexities of neuronal circuitry by which widely separated neurons communicate selectively. This hierarchical scheme of organization provides for a precise flow of information, but such organization suffers the disadvantage that destruction of any link incapacitates the entire system.

Local circuit neurons establish their connections mainly within their immediate vicinity. Such local circuit neurons frequently are small and may have relatively few processes. Interneurons expand or constrain the flow of information within their small spatial domain and may do so without generating action potentials, given their short axons.

Single-source divergent circuitry is utilized by certain neurons of the hypothalamus, pons, and medulla. From their clustered anatomical location, these neurons extend multiple branched and divergent connections...
to many target cells, almost all of which lie outside the brain region in which the neurons of origin are located. Neurons with divergent circuitry could be considered more as interregional interneurons rather than as sequential elements within any known hierarchical system. For example, different neurons of the noradrenergic nucleus, the locus coeruleus (named for its blue pigmented color in primate brains) project from the pons to either the cerebellum, spinal cord, hypothalamus, or several cortical zones to modulate synaptic operations within those regions.

**Glia Are Supportive Cells to Neurons**

Neurons are not the only cells in the CNS. According to most estimates, neurons are outnumbered, perhaps by an order of magnitude, by the various non-neuronal supportive cellular elements. Nonneuronal cells include macroglia, microglia, and cells of the brain’s blood vessels, cells of the choroid plexus that secrete the cerebrospinal fluid, and meninges, sheets of connective tissue that cover the surface of the brain and comprise the cerebrospinal fluid-containing envelope that protects the brain within the skull.

Macroglia are the most abundant supportive cells; some are categorized as astrocytes (nonneuronal cells interposed between the vasculature and the neurons, often surrounding individual compartments of synaptic complexes). Astrocytes play a variety of metabolic support roles, including furnishing energy intermediates and providing for the supplementary removal of excessive extracellular neurotransmitter secretions (see Chapter 13). A second prominent category of macroglia is the myelin-producing cells, the oligodendroglia. Myelin, made up of multiple layers of their compacted membranes, insulates segments of long axons bioelectrically and accelerates action potential conduction velocity. Microglia are relatively uncharacterized supportive cells believed to be of mesodermal origin and related to the macrophage/monocyte lineage. Some microglia reside quiescently within the brain. During periods of intracerebral inflammation (e.g., infection, certain degenerative diseases, or traumatic injury), circulating macrophages and other white blood cells are recruited into the brain by endothelial signals to remove necrotic tissue or to defend against the microbial infection.

The blood–brain barrier is an important permeability barrier to selected molecules between the bloodstream and the CNS. Evidence of a barrier is provided by the greatly diminished rate of access of most lipophobic chemicals between plasma and brain; specific energy-dependent transporter systems permit selected access. Diffusional barriers retard the movement of substances from brain to blood as well as from blood to brain. The brain clears metabolites of transmitters into the cerebrospinal fluid by excretion through the acid transport system of the choroid plexus. The blood–brain barrier is much less prominent in the hypothalamus and in several small, specialized organs (termed circumventricular organs; see Chapters 34 and 39) lining the third and fourth ventricles of the brain: the median eminence, area postrema, pineal gland, subformical organ, and subcommissural organ. The peripheral nervous system (e.g., sensory and autonomic nerves and ganglia) has no such diffusional barrier.

**The Central Nervous System Can Initiate Limited Responses to Damage**

Because neurons of the CNS are terminally differentiated cells, they cannot undergo proliferative responses to damage, as can cells of skin, muscle, bone, and blood vessels. Nevertheless, previously unrecognized neural stem cells can undergo regulated proliferation and provide a natural means for selected neuronal replacement in some regions of the nervous system. As a result, neurons have evolved other adaptive mechanisms to provide for the maintenance of function following injury. These adaptive mechanisms range from activity dependent regulation of gene expression, to modification of synaptic structure, function, and can include actual localized axonal sprouting and new synapse creation. These adaptive mechanisms endow the brain with considerable capacity for structural and functional modification well into adulthood. This plasticity is not only considered to be activity dependent, but also to be reversible with disuse. Plasticity is pronounced within the sensory systems (see Chapter 23), and is quite prominent in the motor systems as well. The molecular mechanisms employed in memory and learning may rely upon very similar processes as those involved in structural and functional plasticity.
How does a simple epithelium differentiate into specialized collections of cells and ultimately into distinct brain structures? How do neurons grow processes that find appropriate targets some distance away? How do nascent neuronal activity and embryonic experience shape activity?

Sensory systems and motor systems (Sections IV and V) encompass how the nervous system receives information from the external world and how movements and actions are produced (e.g., eye movements and limb movements). These questions range from the molecular level (how are odorants, photons, and sounds transduced into informative patterns of neural activity?) to the systems and behavioral level (which brain structures control eye movements and what are the computations required by each structure?).

An evolutionarily old function of the nervous system is to regulate respiration, heart rate, sleep and waking cycles, food and water intake, and hormones to maintain internal homeostasis and to permit daily and longer reproductive cycles. In this area of regulatory systems (Section VI), we explore how organisms remain in balance with their environment, ensuring that they obtain the energy resources needed to survive and reproduce. At the level of cells and molecules, the study of regulatory systems concerns the receptors and signaling pathways by which particular hormones or neurotransmitters prepare the organism to sleep, to cope with acute stress, or to seek food or reproduce. At the level of brain systems, we ask such questions as what occurs in brain circuitry to produce thirst or to create a self-destructive problem such as drug abuse?

In recent years, the disciplines of psychology and biology have increasingly found common ground, and this convergence of psychology and biology defines the modern topics of behavioral and cognitive neuroscience (Section VII). These topics concern the so-called higher mental functions: perception, attention, language, memory, thinking, and the ability to navigate in space. Work on these problems traditionally has drawn on the techniques of neuroanatomy, neurophysiology, neuropharmacology, and behavioral analysis. More recently, behavioral and cognitive neuroscience has benefited from several new approaches: the use of computers to perform detailed formal analyses of how brain systems operate and how cognition is organized; noninvasive neuroimaging techniques, such as positron emission tomography and functional magnetic resonance imaging, to obtain pictures of the living human brain in action; and molecular biological methods, such as single gene knockouts in mice, which can relate genes to brain systems and to behavior.

**1. FUNDAMENTALS OF NEUROSCIENCE**

**THIS BOOK IS INTENDED FOR A BROAD RANGE OF SCHOLARS OF THE NEUROSCIENCES**

This textbook is for anyone interested in neuroscience. In preparing it we have focused primarily on graduate students just entering the field, understanding that some of you will have majored in biology, some in psychology, some in mathematics or engineering, and even some like me, in German literature. It is hoped that through the text, the explanatory boxes, and, in some cases, the supplementary readings, you will find the book to be both understandable and enlightening. In many cases, advanced undergraduate students will find this book useful as well.

Medical students may find that they need additional clinical correlations that are not provided here. However, it is hoped that most medical scholars at least will be able to use our textbook in conjunction with more clinically oriented material. Finally, to those who have completed their formal education, it is hoped that this text can provide you with some useful information and challenging perspectives, whether you are active neuroscientists wishing to learn about areas of the field other than your own or individuals who wish to enter neuroscience from a different area of inquiry. We invite all of you to join us in the adventure of studying the nervous system.

**CLINICAL ISSUES IN THE NEUROSCIENCES**

Many fields of clinical medicine are directly concerned with the brain. The branches of medicine tied most closely to neuroscience are neurology (the study of the diseases of the brain), neurosurgery (the study of the surgical treatment of neurological disease), and psychiatry (the study of behavioral, emotional, and mental diseases). Other fields of medicine also make important contributions, including radiology (the use of radiation for such purposes as imaging the brain—initially with X rays and, more recently, with positron emitters and magnetic waves) and pathology (the study of pathological tissue). To make connections to the many facets of medicine that are relevant to neuroscience, this book includes discussion of a limited number of clinical conditions in the context of basic knowledge in neuroscience.
THE SPIRIT OF EXPLORATION CONTINUES

Less than a decade into the twenty-first century, the Hubble space telescope continues to transmit information about the uncharted regions of the universe and clues to the origin of the cosmos. This same spirit of adventure also is being directed to the most complex structure that exists in the universe—the human brain. The complexity of the human brain is enormous, describable only in astronomical terms. For example, the number of neurons in the human brain (about \(10^{12}\) or 1000 billion) is approximately equal to the number of stars in our Milky Way galaxy. Whereas the possibility of understanding such a complex device is certainly daunting, it is nevertheless true that an enormous amount has already been learned. The promise and excitement of research on the nervous system have captured the attention of thousands of students and working scientists. What is at stake is not only the possibility of discovering how the brain works. It is estimated that diseases of the brain, including both neurological and psychiatric illnesses, affect as many as 50 million individuals annually in the United States alone, at an estimated societal cost of hundreds of billions of dollars in clinical care and lost productivity. The prevention, treatment, and cure of these diseases will ultimately be found through neuroscience research. Moreover, many of the issues currently challenging societies globally—instability within the family, illiteracy, poverty, and violence, as well as improved individualized programs of education—could be illuminated by a better understanding of the brain.

THE GENOMIC INVENTORY IS A GIANT STEP FORWARD

Possibly the single largest event in the history of biomedical research was publicly proclaimed in June 2000 and was presented in published form in February 2001: the initial inventory of the human genome. By using advanced versions of the powerful methods of molecular biology, several large scientific teams have been able to take apart all of an individual’s human DNA in very refined ways, amplify the amounts of the pieces, determine the order of the nucleic acid bases in each of the fragments, and then put those fragments back together again across the 23 pairs of human chromosomes.

Having determined the sequences of the nucleic acids, it was possible to train computers to read the sequence information and spot the specific signals that identify the beginning and ending of sequences likely to encode proteins. Furthermore, the computer systems could then sort those proteins by similarity of sequences (motifs) within their amino acid building blocks. After sorting, the computers could next assign the genes and gene products to families of similar proteins whose functions had already been established. In this way, scientists were rapidly able to predict approximately how many proteins could be encoded by the genome (all of the genes an individual has). Whole genome data are now available for humans, for some non-human primates, for rats, and for mice.

Scientifically, this state of information has been termed a “draft” because it is based on a very dense, but not quite complete, sample of the whole genome. What has been determined still contains a very large number of interruptions and gaps. Some of the smaller genes, whose beginning and ending are most certain, could be thought of as parts in a reassembled Greek urn, held in place by bits of blank clay until further excavation is done. However, having even this draft has provided some important realities.

Similar routines allowed these genomic scholars to determine how many of those mammalian genes were like genes we have already recognized in the smaller genomes of other organisms mapped out previously (yeast, worm (Caenorhabditis elegans), and fruitfly (Drosophila melanogaster)) and how many other gene forms may not have been encountered previously. Based on current estimates, it would appear that despite the very large number of nucleotides in the human and other mammalian genomes, about 30 times the length of the worms and more like 15 times the fruitfly, mammals may have only twice as many genes—perhaps some 30,000 to 40,000 altogether. Compared to other completed genomes, the human genome has greatly increased its representation of genes related to nervous system function, tissue-specific developmental mechanisms, and immune function and blood coagulation. Importantly for diseases of the nervous system that are characterized by the premature death of neurons, there appears to have been a major expansion in the numbers of genes related to initiating the process of intentional cell death, or apoptosis. Although still controversial, genes regulating primate brain size have been reported, but links to intellectual capacity remain unproven.

Two major future vistas can be imagined. To create organisms as complex as humans from relatively so few genes probably means that the richness of the required proteins is based on their modifications, either during transcription of the gene or after translation of the intermediate messenger RNA into the
protein. These essential aspects of certain proteins account for a small number of brain diseases that can be linked to mutations in a single gene, such as Huntington’s Disease (see Chapter 31). Second, though compiling this draft inventory represents a stunning technical achievement, there remains the enormously daunting task of determining, for example, where in the brain’s circuits specific genes normally are expressed, and how that expression pattern may be altered by the demands of illness or an unfriendly environment. That task, at present, is one for which there are as yet no tools equivalently as powerful as those used to acquire the flood of sequence data with which we are now faced. This stage has been referred to as the end of “naïve reductionism.”

In the fall of 2005, a six-nation consortium of molecular biologists announced the next phase of genomic research. The new focus will be toward refining the initial inventories to compare whole genomes of healthy and affected individuals for a variety of complex genetic illnesses (the HapMap project). Complex genetic diseases, such as diabetes mellitus, hypertension, asthma, depression, schizophrenia, and alcoholism, arise through the interactions of multiple short gene mutations that can increase or decrease one’s vulnerability to a specific disease depending on individual life experiences. Ultimately, as the speeds of genome sequencing improve still further and the cost is reduced, it may be possible to predict what diseases will be more likely to affect a given person, and predict the lifestyle changes that person could undertake to improve his or her opportunities to remain healthy.

In order to benefit from the enormously rich potential mother lode of genetic information, next we must determine where these genes are expressed, what functions they can control, and what sorts of controls other gene products can exert over them. In the nervous system, where cell–cell interaction is the main operating system in relating molecular events to functional behavioral events, discovering the still-murky properties of activity-dependent gene expression will require enormous investment.

**NEUROSCIENCE TODAY: A COMMUNAL ENDEAVOR**

As scientists, we draw from the work of those who came before us, using other scientists’ work as a foundation for our own. We build on and extend previous observations and, it is hoped, contribute something to those who will come after us. The information presented in this book is the culmination of hundreds of years of research. To help acquaint you with some of this work, we have described many of the key experiments of neuroscience throughout the book. We also have listed some of the classic papers of neuroscience and related fields at the end of each chapter, and invite you to read some of them for yourselves.

The pursuit of science has not always been a communal endeavor. Initially, research was conducted in relative isolation. The scientific “community” that existed at the time consisted of intellectuals who shared the same general interests, terminology, and paradigms. For the most part, scientists were reluctant to collaborate or share their ideas broadly, because an adequate system for establishing priority for discoveries did not exist. However, with the emergence of scientific journals in 1665, scientists began disseminating their results and ideas more broadly because the publication record could be used as proof of priority. Science then began to progress much more rapidly, as each layer of new information provided a higher foundation on which new studies could be built.

Gradually, an interactive community of scientists evolved, providing many of the benefits that contemporary scientists enjoy: Working as part of a community allows for greater specialization and efficiency of effort. This not only allows scientists to study a topic in greater depth but also enables teams of researchers to attack problems from multidisciplinary perspectives. The rapid feedback and support provided by the community help scientists refine their ideas and maintain their motivation. It is this interdependence across space and time that gives science much of its power.

With interdependence, however, comes vulnerability. In science, as in most communities, codes of acceptable conduct have evolved in an attempt to protect the rights of individuals while maximizing the benefits they receive. Some of these guidelines are concerned with the manner in which research is conducted, and other guidelines refer to the conduct of scientists and their interactions within the scientific community. Let us begin by examining how new knowledge is created.

**THE CREATION OF KNOWLEDGE**

Over the years, a generally accepted procedure for conducting research has evolved. This process involves examining the existing literature, identifying an important question, and formulating a research plan. Often, new experimental pathways are launched when one
scientist reads with skepticism the observations and interpretations of another and decides to test their validity. Sometimes, especially at the beginning of a new series of experiments, the research plan is purely “descriptive,” for example, determining the structure of a protein or the distribution of a neurotransmitter in brain. Descriptive initial research is essential to the subsequent inductive phase of experimentation, the movement from observations to theory, seasoned with wisdom and curiosity. Descriptive experiments are valuable both because of the questions that they attempt to answer and because of the questions that their results allow us to ask. Information obtained from descriptive experiments provides a base of knowledge on which a scientist may draw to develop hypotheses about cause and effect in the phenomenon under investigation. For example, once we identify the distribution of a particular transmitter within the brain or the course of a pathway of connections through descriptive work, we may then be able to develop a theory about what function that transmitter or pathway serves.

Once a hypothesis has been developed, the researcher then has the task of designing and performing experiments that are likely to disprove that hypothesis if it is incorrect. This is referred to as the deductive phase of experimentation, the movement from theory to observation. Through this paradigm the neuroscientist seeks to narrow down the vast range of alternative explanations for a given phenomenon. Only after attempting to disprove the hypothesis as thoroughly as possible may scientists be adequately assured that their hypothesis is a plausible explanation for the phenomenon under investigation.

A key point in this argument is that data may only lend support to a hypothesis rather than provide absolute proof of its validity. In part, this is because the constraints of time, money, and technology allow a scientist to test a particular hypothesis only under a limited set of conditions. Variability and random chance may also contribute to the experimental results. Consequently, at the end of an experiment, scientists generally report only that there is a statistical probability that the effect measured was due to intervention rather than to chance or variability.

Given that one can never prove a hypothesis, how do “facts” arise? At the conclusion of their experiments, the researchers’ first task is to report their findings to the scientific community. The dissemination of research findings often begins with an informal presentation at a laboratory or departmental meeting, eventually followed by presentation at a scientific meeting that permits the rapid exchange of information more broadly. One or more research articles published in peer-reviewed journals ultimately follow the verbal communications. Such publications are not simply a means to allow the authors to advance as professionals (although they are important in that respect as well). Publication is an essential component of the advancement of science. As we have already stated, science depends on sharing information, replicating and thereby validating experiments, and then moving forward to solve the next problem. Indeed, a scientific experiment, no matter how spectacular the results, is not completed until the results are published. More likely, publication of “spectacular” results will provoke a skeptical scientist into doing an even more telling experiment, and knowledge will evolve.

responsibile conduct

Although individuals or small groups may perform experiments, new knowledge is ultimately the product of the larger community. Inherent in such a system is the need to be able to trust the work of other scientists—to trust their integrity in conducting and reporting research. Thus, it is not surprising that much emphasis is placed on the responsible conduct of research.

Research ethics encompasses a broad spectrum of behaviors. Where one draws the line between sloppy science and unethical conduct is a source of much debate within the scientific community. Some acts are considered to be so egregious that despite personal differences in defining what constitutes ethical behavior, the community generally recognizes certain research practices as behaviors that are unethical. These unambiguously improper activities consist of fabrication, falsification, and plagiarism: Fabrication refers to making up data, falsification is defined as altering data, and plagiarism consists of using another person’s ideas, words, or data without attribution. Each of these acts significantly harms the scientific community.

Fabrication and falsification in a research paper taint the published literature by undermining its integrity. Not only is the information contained in such papers misleading in itself, but other scientists may unwittingly use that information as the foundation for new research. If, when reported, these subsequent studies cite the previous, fraudulent publication, the literature is further corrupted. Thus, through a domino-like effect one paper may have a broad negative impact on the scientific literature. Moreover, when fraud is discovered, a retraction of the paper
provides only a limited solution, as there is no guarantee that individuals who read the original article will see the retraction. Given the impact that just one fraudulent paper may have, it is not surprising that the integrity of published literature is a primary ethical concern for scientists.

Plagiarism is also a major ethical infraction. Scientific publications provide a mechanism for establishing priority for a discovery. As such, they form the currency by which scientists earn academic positions, gain research grants to support their research, attract students, and receive promotions. Plagiarism denies the original author of credit for his or her work. This hurts everyone: The creative scientist is robbed of credit, the scientific community is hurt by the disincentive to share ideas and research results, and the individual who has plagiarized—like the person who has fabricated or falsified data—may well find his or her career ruined.

In addition to the serious improprieties just described, which are in fact extremely rare, a variety of much more frequently committed “misdemeanors” in the conduct of research can also affect the scientific community. Like fabrication, falsification, and plagiarism, some of these actions are considered to be unethical because they violate a fundamental value, such as honesty. For example, most active scientists believe that honorary authorship—listing as an author someone who did not make an intellectual contribution to the work—is unethical because it misrepresents the origin of the research. In contrast, other unethical behaviors violate standards that the scientific community has adopted. For example, although it is generally understood that material submitted to a peer-reviewed journal as part of a research manuscript has never been published previously and is not under consideration by another journal, instances of retraction for dual publications can be found on occasion.

**Scientific Misconduct Has Been Formally Defined by U.S. Governmental Agencies**

The serious misdeeds of fabrication, falsification, and plagiarism generally are recognized throughout the scientific community. These were broadly recognized by federal regulations in 1999 as a uniform standard of scientific misconduct by all agencies funding research. What constitutes a misdemeanor is less clear, however, because variations in the definitions of accepted practices are common. There are several sources of this variation. Because responsible conduct is based in part on conventions adopted by a field, it follows that there are differences among disciplines with regard to what is considered to be appropriate behavior. For example, students in neuroscience usually coauthor papers with their advisor, who typically works closely with them on their research. In contrast, students in the humanities often publish papers on their own even if their advisor has made a substantial intellectual contribution to the work reported. Within a discipline, the definition of acceptable practices may also vary from country to country. Because of animal use regulations, neuroscientists in the United Kingdom do relatively little experimental work with animals on the important topic of stress, whereas in the United States this topic is seen as an appropriate area of study so long as guidelines are followed to ensure that discomfort to the animals is minimized.

The definition of responsible conduct may change over time. For example, some protocols that were once performed on human and animal subjects may no longer be considered ethical. Indeed, ethics evolve alongside knowledge. We may not currently be able to know all of the risks involved in a procedure, but as new risks are identified (or previously identified risks refuted), we must be willing to reconsider the facts and adjust our policies as necessary. In sum, what is considered to be ethical behavior may not always be obvious, and therefore we must actively examine what is expected of us as scientists.

Having determined what is acceptable practice, we then must be vigilant. Each day neuroscientists are faced with a number of decisions having ethical implications, most of them at the level of misdemeanors: Should a data point be excluded because the apparatus might have malfunctioned? Have all the appropriate references been cited and are all the authors appropriate? Might the graphic representation of data mislead the viewer? Are research funds being used efficiently? Although individually these decisions may not significantly affect the practice of science, cumulatively they can exert a great effect.

In addition to being concerned about the integrity of the published literature, we must be concerned with our public image. Despite concerns over the level of federal funding for research, neuroscientists are among the privileged few who have much of their work funded by taxpayer dollars. Highly publicized scandals damage the public image of our profession and hurt all of us who are dependent on continued public support for our work. They also reduce the public credibility of science and thereby lessen the impact that we can expect our findings to have. Thus, for our own good and that of our colleagues, the scientific community, and the public at large, we must strive to act with integrity.
You are about to embark on a tour of fundamental neuroscience. Enjoy the descriptions of the current state of knowledge, read the summaries of some of the classic experiments on which that information is based, and consult the references that the authors have drawn on to prepare their chapters. Think also about the ethical dimensions of the science you are studying—your success as a professional and the future of our field depend on it.

References


Floyd E. Bloom