

Chapter 3

Neuroscience Primer

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This chapter describes the major anatomical components of the nervous system, some of the basic processes underlying neural growth, development, and communication, and the response of the nervous system to injury. A grasp of these basic concepts of neuroscience is helpful to understanding neural grafting. Additional information is available from a number of sources (1,3,4).

ORGANIZATION OF THE NERVOUS SYSTEM

The nervous system can be divided into two parts: the central nervous system (CNS) and the peripheral nervous system (PNS) (figure 3-1). The CNS is made up of the brain and spinal cord. The PNS is composed of all the nerves, nerve cells, and specialized sensory receptors that lie outside the CNS. Sensory information about the outside world is brought into the CNS via the nerves and sensory receptors in the PNS; activation and regulation of activity in muscles, glands, and organs are conveyed by the motor, or outflow, component of the PNS. Most information processing, decisionmaking, and coordination of activities is under the control of the CNS.

Cellular Components

There are two major classes of cells in the nervous system: neurons, or nerve cells, and glia, or glial cells.

Neurons

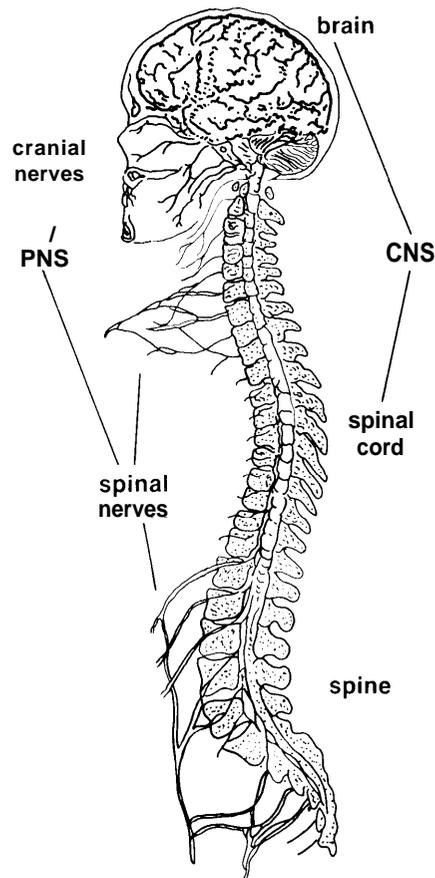
All information processing in the nervous system is done by networks of neurons that communicate with each other. Neurons consist of a cell body with long extensions, much like branches of a tree, called dendrites. Also projecting out of the cell body is a single fiber called the axon, which can extend for great distances (figure 3-2). All nerves in the body are actually the bundled axons of many neurons conveying information to and from the CNS. The end of the axon is also branched.

Glial Cells

Glial cells support neurons by carrying on important chemical and physiological reactions and producing a variety of substances that are needed for

normal neurological functioning. There are a number of different types of glial cells in the PNS and CNS--astrocytes, microglia, Schwann cells, and oligodendrocytes (figure 3-3). Schwann cells (in the PNS) and oligodendrocytes (in the CNS) produce myelin, a fatty insulating material that forms a sheath around axons and speeds the conduction of electrical impulses. Both of these types of cells play a crucial role in nerve cell regeneration: Schwann cells support regrowth of peripheral nerves, while recent evidence suggests that oligodendrocytes inhibit the regrowth of damaged axons in the CNS. The other glial cells help regulate the biochemical environment within the nervous system, provide

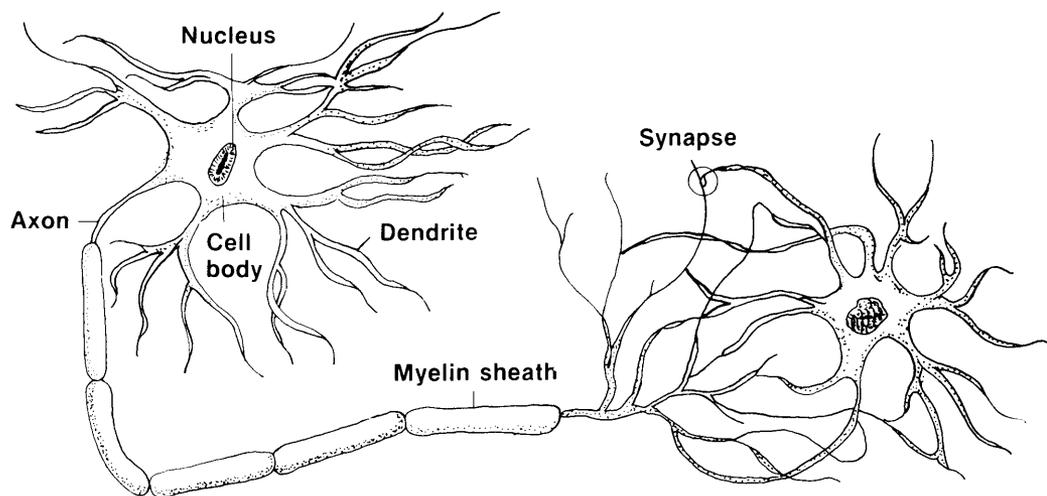
Figure 3-1-Components of the Nervous System



The nervous system is composed of the central (CNS) and peripheral nervous systems (PNS).

SOURCE: C. Romero-Sierra, *Neuroanatomy, A Conceptual Approach* (New York, NY: Churchill Livingstone, 1986).

Figure 3-2—The Neuron



Two neurons in synaptic contact.
SOURCE: R. Restak, *The Brain* (New York, NY: Bantam Books, 1984).

structural support for the neurons, and supply certain substances that are essential for the nervous system to work properly.

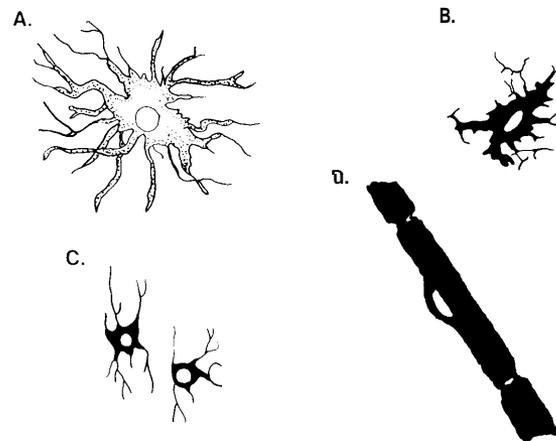
Central Nervous System

The Brain

One useful way of visualizing the brain is as a mushroom. The cap of the mushroom is the cerebral cortex, and the stem of the mushroom is the rest of the brain, which is made up of hundreds of nuclei (figure 3-4). A nucleus is a group of cells that share the same anatomical region and, to varying degrees, the same function. Information is conveyed throughout the brain and spinal cord along the axons extending from nuclei. For any given function, such as vision, a number of nuclei and areas of the cerebral cortex must act together in a coordinated and synchronized manner so that information can be accurately analyzed.

The anatomy of the brain and the intricacy of the connections among nuclei are exceedingly complex. Information from every area of the nervous system about many different functions is constantly being combined, compared, contrasted, and coordinated. The brain determines the relevance of each bit of information, fits it in with all other information available, and decides what actions should or should not be taken to regulate bodily functions and to

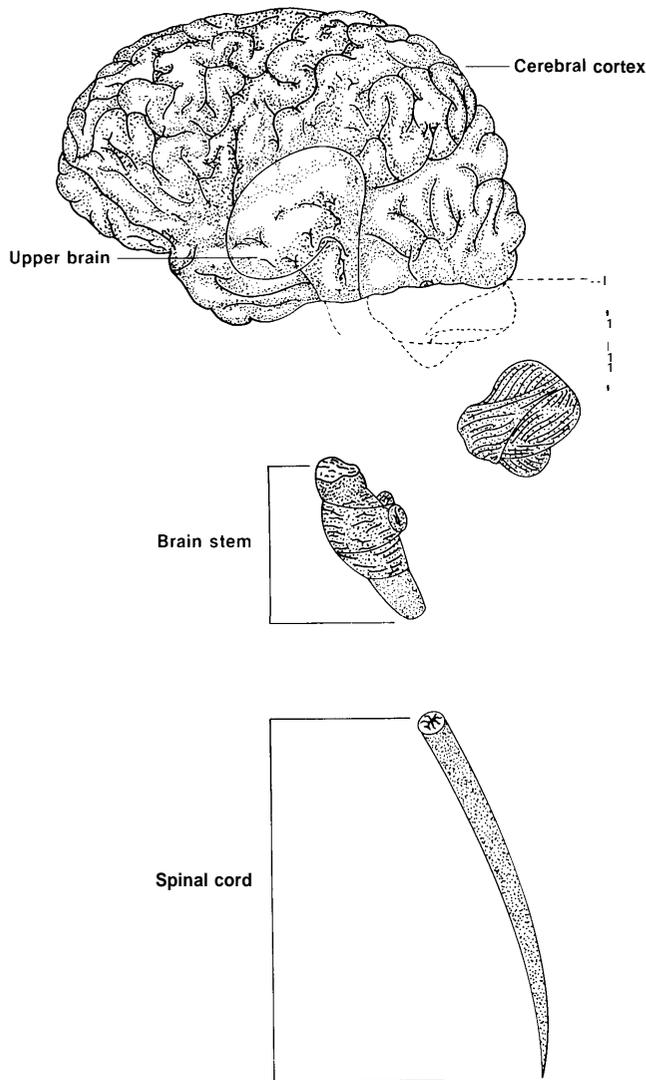
Figure 3-3-Glial Cells



Types of glial cells include: A) astrocytes, B) microglia, C) oligodendrocytes, D) Schwann cells (surrounding an axon).
SOURCE: Adapted from J.A. Kiernan, *Introduction to Human Neuroscience* (Philadelphia, PA: J.B. Lippincott, 1987).

permit successful interaction with the external environment. The result is everything that makes up life and existence as human beings perceive it—from the maintenance of heart rate to falling in love; from finding food to contemplating the nature of the universe. All of these arise from the biological events that make up the activity of the human brain.

Figure 3-4—The Central Nervous System



The brain (cerebral cortex, upper brain, brain stem) and the spinal cord.

SOURCE: Adapted from R. Restak, *The Mind* (New York, NY: Bantam Books, 1988).

The bottom of the stem of the mushroom is the brain stem, which regulates essential bodily functions. Heart rate, blood pressure, and respiratory activity are all controlled by nuclei in the brain stem. Higher up the stem of the mushroom is the upper brain, containing other structures, such as the hypothalamus and the thalamus. Each of these is a collection of nuclei with specific functions. The

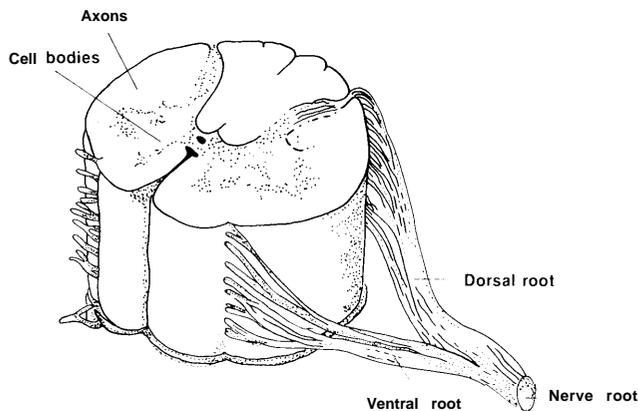
thalamic nuclei are primarily involved in analyzing and relaying sensory and motor information. Some hypothalamic nuclei control behaviors such as eating, drinking, and sexual activity; others help with regulating the activity of the endocrine system. Still further up the stem of the mushroom are the basal ganglia, nuclei that help mediate movement. Also in this area are some of the nuclei of the limbic system, which is involved in emotional behaviors, and the hippocampus, a limbic nucleus that is also one of the nuclei crucial to learning and memory. These are only a sampling of the many nuclei located in the stem of the mushroom.

Overlying the stem is the cerebral cortex, the evolutionary newest part of the brain and its most advanced decisionmaking portion. The cerebral cortex consists of layers of neurons and their axons, which communicate with each other and with other regions of the brain. Roughly divided into four lobes on each side, the cerebral cortex receives sensory information and analyzes, deciphers, and puts it into context based on previous experience. Combining new input with experience, the cerebral cortex decides what actions should be taken and institutes those actions by activating the proper motor and endocrine networks. It is at the level of the cerebral cortex that differences among species become most notable. Warm-blooded animals have a more highly developed cerebral cortex than cold-blooded animals. The cortex is most fully developed in humans, with highly developed frontal lobes and specialized areas to subservise the development and use of language. The frontal lobes are thought to be the seat of higher order thinking, which gives humans the ability to engage in abstract thought and to develop philosophical concepts of morality, self, and place in the universe.

The Spinal Cord

Extending downward from the base of the stem of the mushroom is the spinal cord. The spinal cord is composed of a central core of cells surrounded by pathways of axons. Leaving and entering the spinal cord are the nerves that bring sensory information into the CNS and convey motor and other activating information out into the periphery (figure 3-5). The spinal cord is divided into 31 segments that are demarcated by collections of nerves called nerve roots. The spinal segments and their nerve roots serve the organs of the body and corresponding regions of muscles and skin in the limbs and along

Figure 3-5-The Spinal Cord



The spinal cord is made up of a central core of cell bodies, surrounded by axons. The nerve roots convey information into (dorsal root) and out of (ventral root) the spinal cord.

SOURCE: Adapted from A.C. Guyton, *Basic Neuroscience: Anatomy and Physiology* (Philadelphia, PA: W.B. Saunders, 1987).

the trunk of the body. There is communication among segments and between the segments and the brain. Some basic functions, such as motor reflexes, are organized and directed from within the spinal cord. The spinal cord also contains a column of specialized cells that help control the autonomic functions of the body (see later discussion of the autonomic nervous system). All the areas within the spinal cord that control bodily activities are modulated by the brain.

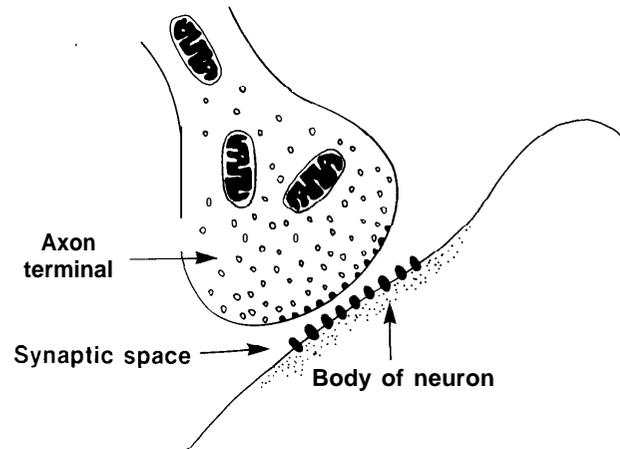
Peripheral Nervous System

The PNS is made up of all the sensory nerves coming into, and motor nerves leaving, the spinal cord via the nerve roots. These include the nerves of the autonomic nervous system. In addition, the PNS includes some sensory and motor nerves that enter and exit from the brain stem.

Autonomic Nervous System

The autonomic nervous system is made up of the portions of the CNS and PNS that are concerned with the control of visceral functions. These functions include heart rate, blood pressure, digestion, and reflexive sexual activities. Within the CNS, the neurons of the autonomic nervous system are in the brain stem and the spinal cord; in the PNS, the neurons occur in specialized groups, known as ganglia. The ganglia are found in columns on either

Figure 3-6-The Synapse



The anatomy of a synapse.

SOURCE: Adapted from A.C. Guyton, *Basic Neuroscience: Anatomy and Physiology* (Philadelphia, PA: W.B. Saunders, 1987).

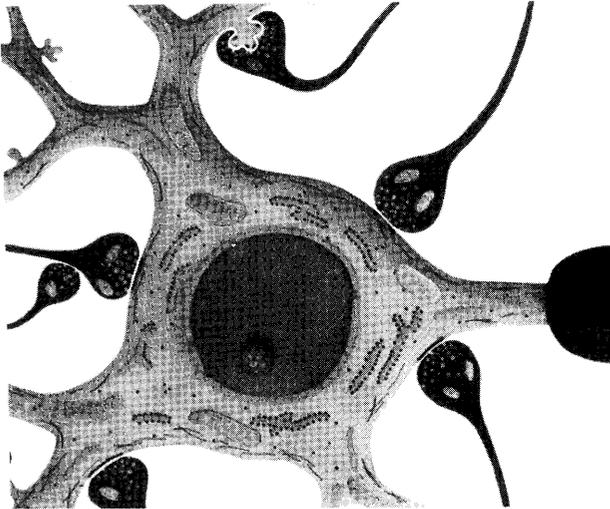
side of the spinal cord or in close association with the organs they serve (2).

NEURAL COMMUNICATION

Information in the nervous system is conveyed by chains of neurons. It usually travels through a neuron in one direction—through the dendrites, through the cell body, and along the axon. The end of the axon of one neuron interacts with the next neuron in the chain. Information in the nervous system is coded as an electrical-chemical message that is sent from one neuron to the next. The point where the axon of one neuron connects with a dendrite or cell body of another neuron is called a synapse (figure 3-6). The two neurons never actually touch each other; instead, there is a small space between them called the synaptic space. Because the end of the axon and the dendrites of a neuron are branched, the axon of any one neuron can form synapses with thousands of other neurons and thus can send messages to and receive messages from thousands of other neurons (figure 3-7).

When a neuron generates a nerve impulse, or “fires,” an electrical message is sent along the axon toward the synapse. When the electrical message gets to the synapse, it causes the release of a chemical, called a neurotransmitter, from the axon into the synaptic space. The neurotransmitter acts as a messenger, moving across the synaptic space and binding to the membrane of the next neuron. The

Figure 3-7-A Neuron and Its Synapses



The terminals of many axons can make synapses with the dendrites or cell body of one neuron.

SOURCE: R. Restak, *The Mind* (New York, NY: Bantam Books, 1988).

binding of the neurotransmitter to the membrane then initiates, facilitates, or hinders an electrical message in that neuron. The time it takes for this process to occur, from the initiation of a message in one neuron to the release and binding of the neurotransmitter and the initiation of a message in the next neuron, is measured in thousandths of a second.

There are many different kinds of neurotransmitters. Whether and when a neuron will release a neurotransmitter is determined by the combined action of all its synapses, with their excitatory and inhibitory neurotransmitters, at any one time.

GROWTH AND DEVELOPMENT

In humans, the first signs of the developing nervous system appear in the third week of embryonic development (figure 3-8). The cells destined to form the brain and other parts of the nervous system then go through a period of proliferation, during which time they multiply. At the same time, the cells migrate to their proper positions in the developing brain. Following this period of proliferation and migration, the cells stop dividing and differentiate into the various types of neurons and glial cells that make up the nervous system. At this time, the number of neurons becomes fixed; for the rest of the person's life, no new neurons are thought to be

produced. Most glial cells, on the other hand, maintain the capacity to replicate.

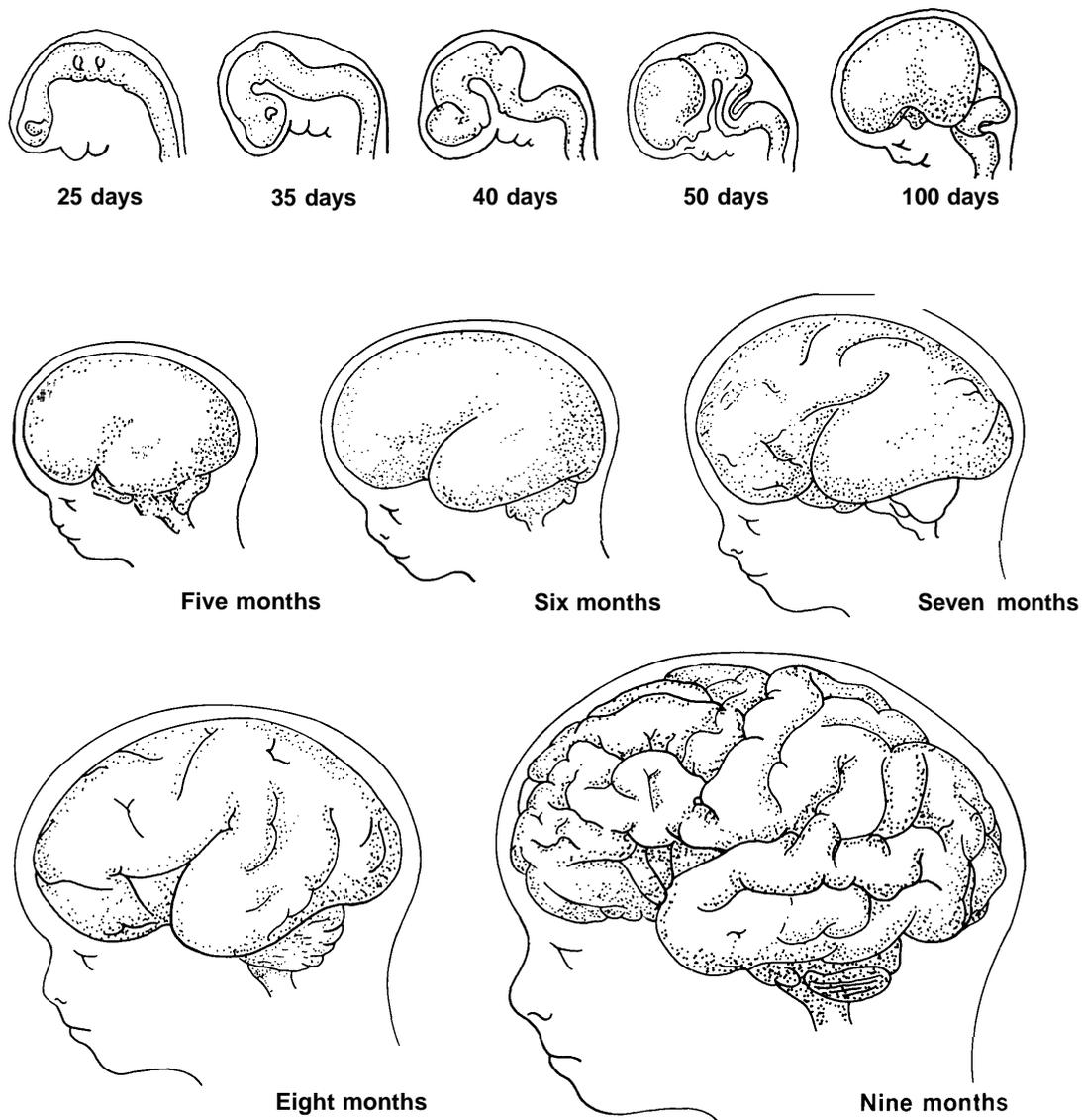
The mechanisms by which neurons migrate to the proper location and axons find their way to the proper target site and form synapses are not fully understood. The process of axonal growth is thought to include an initial, genetically predetermined map of axonal pathways. The growing axons are guided to their final destinations by chemicals called *neurotrophic* (nourishing) and *neurotropic* (guiding) factors (see box 3-A). Neurotrophic factors promote axonal growth and neuronal survival, and neurotropic factors provide a surface, or substrate, for the axon to grow along to its target. These factors act as signposts to guide the growing axons and provide chemical addresses for them to reach. Which chemical address, or target site, an axon will search for is believed to be genetically programmed within each neuron.

Once the cells are in position, differentiation occurs: the dendrites and axons of the neurons begin to grow and establish the proper synaptic contacts. In the case of some axons this can mean elongation over considerable distances, while in other cases all of the synaptic contacts of a neuron can occur within a few millimeters of the cell. The ultimate wiring of the brain, made up of billions of synapses and connections, is extremely complex. Although in humans most axons reach their target sites before birth, the final configuration of the synaptic contacts is not completed until well after birth.

There are many more neurons in the developing nervous system than there are in the mature nervous system. It has been estimated that about half of the cells initially generated die. Death is caused by competition between the growing neurons for available synaptic sites and a matching of the number of neurons to the needs of the developing nervous system. This process results in the survival of those neurons that have grown properly. There are about 200 billion neurons in the mature human brain.

Although the general pattern of synapses established once an axon reaches its target is both genetically predetermined and under the control of chemical factors, the final, precise synaptic pattern of an axon can also be shaped by other factors. These include the amount and kind of activity that occur in the pathway in response to outside stimulation. This flexibility in synapse formation in response to

Figure 3-8-The Development of the Human Brain



The human brain shown in its developmental sequence, starting at 25 days and progressing through birth.
SOURCE: R. Restak, *The Brain* (New York, NY: Bantam Books, 1984).

environmental stimuli is maintained throughout life and may play a role in learning and memory.

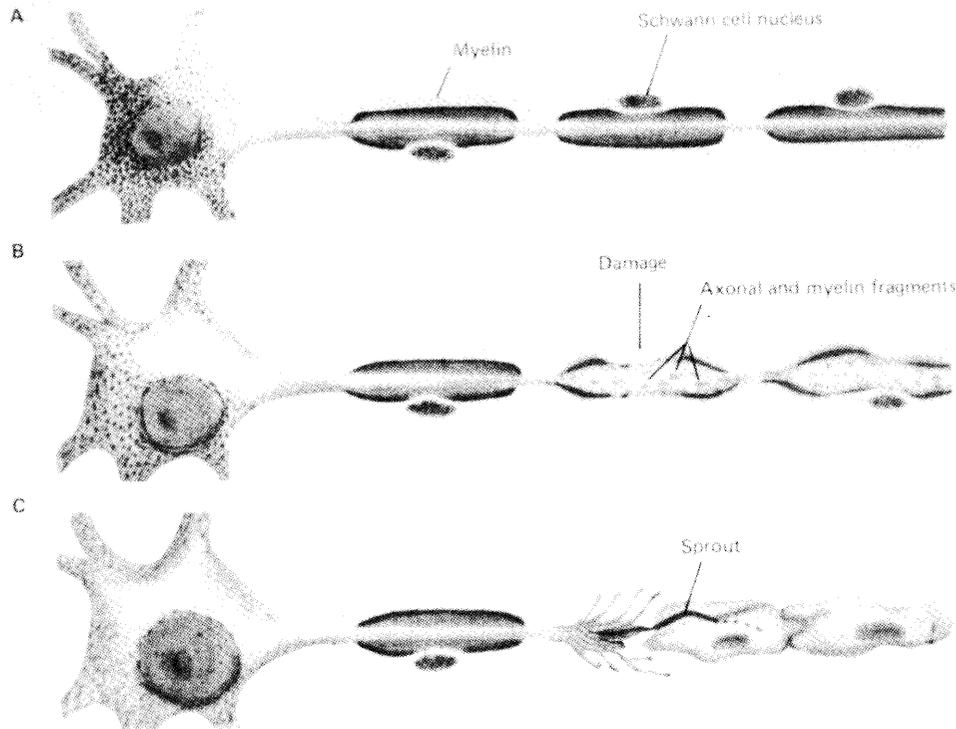
RESPONSE TO INJURY

The CNS and PNS respond differently to injury. When a peripheral nerve is damaged, the axons of the damaged neurons can regrow; but when damage occurs in the CNS, axonal regrowth is limited. Research on animals has shown that this difference is due not to differences in peripheral and

central neurons (in fact, many peripheral nerves arise from cell bodies in the CNS), but to variations in the environment surrounding the axons in the CNS and PNS.

The key element in axon regrowth in the PNS is the presence of Schwann cells and the growth factors they secrete. Schwann cells normally surround each axon, supplying its fatty myelin sheath. When a peripheral nerve is damaged and dies, the bundled axons die and leave behind the Schwann cells that

Figure 3-9—The Response of a Neuron in the Peripheral Nervous System to Injury



A) The normal neuron and part of the axon; B) the axon is injured and the section away from the cell body dies; C) the end of the injured axon begins to grow into the remaining Schwann cells.

SOURCE: Reprinted by permission from "Reactions of Neurons to Injury," *Principles of Neuroscience*, 2d ed., E.R. Kandel and J.H. Schwartz (eds.) (New York, NY: Elsevier Science Publishers, 1985), p. 191.

had surrounded them. When the nerve regenerates, its axons grow within the column of remaining Schwann cells to the sense organ or muscle to which they were originally connected (figure 3-9). Schwann cells release neurotrophic and neurotropic factors that promote elongation and provide a pathway for the regenerating axons.

When the CNS is damaged, there is some regrowth that is limited to a small area around the wound. A process called synaptic sprouting occurs, whereby fibers from nearby, undamaged axons form new branches and make new synapses to replace some of the lost ones. However, unlike Schwann cells, the myelin-producing oligodendrocytes of the CNS do not promote regrowth of the damaged axons. In fact, recent studies have shown that

oligodendrocytes actively block regeneration. Furthermore, following an injury, another type of glial cell, the astrocyte, forms a scar at the site of the wound and blocks regrowth. Why there are mechanisms in the CNS that actively block healing is not known. It is thought that once all the wiring of the brain is established, the growth-promoting mechanisms that were present during development are no longer needed, and these inhibitory mechanisms take over to prevent any further growth that could short-circuit the completed brain. By learning more about the differences in the environments that allow regeneration in the PNS and block it in the CNS, scientists may ultimately be able to control the processes involved and enable CNS damage to be repaired.

Box 3-A—Neurotrophic and Neurotropic Factors

During the last few years, neuroscientist have learned that the development, maintenance of function, and response to injury of neurons are influenced by chemicals called neurotrophic and neurotropic factors. These substances are produced by some neurons and glial cells and can affect the nervous system in two ways. Some are secreted by a cell into the spaces between cells in the nervous system; they can then be absorbed by neurons to initiate an intracellular process, such as growth of an axon. Other factors can act externally to guide the growing axon along a particular path to its region of synaptic contact. A chemical that stimulates growth or development is called a neurotrophic agent, while one that helps guide a growing neuron is called a neurotropic agent.

Only a few substances have been positively identified as neurotrophic or neurotropic factors. Of them, nerve growth factor (NGF) has been the most extensively studied. NGF is a protein that is known to promote growth in specific areas of the peripheral nervous system and to play a role in the development of vertebrate sensory systems. What role NGF plays in the central nervous system (CNS) is not well understood. It seems that NGF has a selective effect on certain populations of cells in the brain that use acetylcholine as their neurotransmitter. NGF promotes growth and development of these cells in the fetal brain and, when extra amounts are administered in experimental conditions, can promote growth and prevent cell death following an injury in the adult brain. It has also been shown that NGF can facilitate the incorporation of some neural grafts. The observation that NGF seems to exert this effect only on certain cells in the brain suggests that there maybe different neurotrophic factors for different groups of brain cells. Thus far, other substances that have been identified as having possible neurotrophic or neurotropic effects include ciliary neurotrophic factor, brain-derived neurotrophic factor, neurotrophin-3, glia-derived nexin, fibroblast growth factors, insulin and insulin-like growth factors, epidermal growth factor, S100 protein, and laminin. What role these play in CNS regeneration is unclear at this point.

Neurotrophic and neurotropic factors are known to be present in the developing CNS and to play an important role in the formation of neuronal circuitry. Much less is known about their role in the mature CNS. When an injury occurs in the brain, there is an increase in neurotrophic activity at the site of the wound. This activity seems to promote the limited amount of healing and cell survival that is seen following some injuries. It is also thought that some of these factors are important for maintaining normal function and structural integrity in the adult brain. It has been observed that some neurons die in the absence of neurotrophic factors. It is possible that some of the factors associated with growth and development are either no longer present or are somehow inactivated within the adult CNS. Introducing missing factors or stimulating deactivated ones in the CNS by implanting tissues that produce neurotrophic and neurotropic factors may reestablish the environment needed for growth.

SOURCE: Office of Technology Assessment, 1990.

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