Development and Growth of the Nervous System

Individuals are as old as their neurons in the sense that almost all neurons are generated by early postnatal life and are not generally replaced by new ones during a lifetime. The genetically driven development of the complex circuitry of the nervous system continues throughout life, tempered and honed by a combination of constraints readjustments and responses to the influences and demands from both the internal and external environments.

The cardiovascular system and the nervous system are the first organ systems to function during embryonic life. In humans, the heart begins to beat late in the third week after fertilization. Before the heart begins to beat, the nervous system commences to differentiate and change in shape. Growth in size occurs after the heart commences to pulsate and blood slowly circulates to bring oxygen and essential nutrients to the developing nervous system. During the second month, when stimuli are applied to the upper lip of the embryo, there is an avoidance reflex withdrawal of the head. A mother might feel life as early as the 12th prenatal week.

From a relatively few primordial cells present several weeks after fertilization of the ovum, the nervous system undergoes a remarkable change to attain its complex and intricate organization. Once a neuroblast leaves the ventricular layer of the neural tube, not only is it committed to differentiate into a neuron but also it will never divide again. To generate the estimated 100–200 billion neurons in the mature brain requires a calculated production of more than 2500 neurons per minute during the entire prenatal period. The brain of a 1-year-old child has as many neurons as it will ever have. Throughout life, cells are continuously lost at an estimated rate of 200,000 per day in humans. The estimate is based on the observation of the 5 to 10% loss of brain tissue with age. Assuming that there is a 7% loss of neurons over a life-span of 100 years and with
100 billion neurons at 1 year of age, 200,000 neurons will be lost per day. Because the brain has so many neurons, most individuals get through life without losing so many that they become mentally disabled.

The central goal of developmental neurobiology is to gain an understanding of the interactions and resolution of the forces of “nature” versus “nurture”. Nature is the cell’s intrinsic potential contained in the genetic pool to mastermind the neuroblast to attain the full repertoire of cellular processes and features of the mature neurons. Nurture refers to the extrinsic epigenetic extracellular factors, both tropic and trophic, that shape the development of the neuron and continue to operate even on the mature neuron.

Differentiation and growth continue postnatally, attaining the organized complexity of the entire nervous system. It continues throughout life as the nervous system is remodeled through plasticity. The totality of events occurring during the development of the brain is not the exclusive property of rigid genetic codes. For example, the human brain probably contains more than one trillion synapses, and there simply is not enough genes, to account for this complexity.

The normal development of a neuron and its subsequent integration into neuronal circuits result from activities at both (1) the genetic level and (2) the epigenetic level. The former (genetic) comprises (a) transcription or the transfer of information from DNA molecules into RNA molecules and (b) translation or the transfer of information from the RNA molecules into polypeptides. The latter (epigenetic) includes many environmental and extracellular factors that can modify, regulate, or channel subsequent development. Epigenesis involves neurotropic and neurotrophic molecules that have critical roles in the structural changes occurring during ontogeny of the nervous system. Tropic (having affinity for and turning toward) factors are molecules to which, for example, growth cones are attracted (see contract guidance in Neuronal Navigation and Development). Trophic (relating to nutrition for survival) factors are molecules secreted by their targets (target-derived neurotrophic factors) and are essential for the differentiation, growth, and survival of neurons. Neurons in part depend on one another for trophic factors, which affect their signaling efficiency and even their survival.

The neurotrophic concept states that during development, neurons are critically dependent for their survival on these target-derived factors. The presence of limited amounts of these factors ensures that only a select proportion of neurons survives and do not succumb to naturally occurring cell death (see Apoptosis or Naturally Occurring Neuronal Death) and, thus, the appropriate innervation density of the target is attained. The scenario during development can be categorized as a competitive, yet regulated “battleground” among many influences:

1. The genetic impetus is to produce, during early development, an oversupply of neurons, axons, and dendrites (including their terminal branches) and synapses.
2. The growth of the axons to their target is usually attained by a specific route; however, alternate routes are possible.
3. The projections of the axons from several sources to a specific target neuron or structure (e.g., muscle) is generally diffuse and intermingled in the vicinity of their definitive target.
4. Competition occurs among the oversupply of axonal terminals for appropriate targets (neuron or synapses) with the elimination of supernumerary neurons, axons, and synaptic terminals.

Experimental evidence indicates that developmental changes continue to occur even in old age. Dendrites and axons of neurons of the cerebral cortex of old rats (equivalent in human terms of roughly 75 years) respond to an enriched environment by forming new axon terminals and synaptic connections. Investigations reveal that the structure and chemistry of the brain can be affected by experiences
throughout life, indicating that there is more flexibility and plasticity in neuronal connectivity in old age than previously thought. Thus, the debate over nature or nurture with regard to the brain and behavior is essentially over. Although many details remain to be resolved, both are involved.

**ORIGIN OF THE NERVOUS SYSTEM**

When the human embryo is but 1.5 mm long (18 days old), the ectoderm (outer germ layer) differentiates and thickens along the future midline of the back to form the neural plate (see Fig. 6.1). With the transfer of certain chemical substances from the underlying mesoderm, the induction of this ectoderm occurs so it is now irreversibly committed to form neural tissue. The neural plate is exposed to the surface and to the amniotic fluid; it is continuous laterally with the future skin. Certain portions of the ectoderm differentiate and thicken in the head region to form placodes, which are progenitors of the organs of special sense such as the eyes (optic placode), ears (otic placode), and nose (nasal placode). In fact, the neural plate is a giant placode. The neural plate elongates, and its lateral edges are raised to form the neural folds or keyhole stage (see Fig. 6.1). The anterior end of the neural plate enlarges and will develop into the brain. The lateral edges, or lips, continue to rise and grow medially until they meet and unite in the midline, to form the neural tube. This midline union commences in the cervical region and progresses both cephalically and caudally until, in 25 days, the entire plate is converted into the neural tube (see Fig. 6.1). The tube becomes detached from the skin and sinks beneath the surface (see Fig. 6.2). The cavity of the neural tube persists in the adult as the ventricular system of the brain and the central canal of the spinal cord.

The cephalic end of the neural tube differentiates and enlarges into three dilations called

![Figure 6.1: Dorsal aspect of human embryo: (A) Primitive-streak plate stage of a 16-day presomite embryo; (B) two-somite keyhole stage of an approximately 20-day embryo (note the first somites, neural fold, and neural groove); (C) seven-somite stage of an approximately 22-day embryo; (D) 10-somite neural tube stage of an approximately 23-day embryo.](image-url)
Figure 6.2: Development of the spinal cord, neural crest, somite, and spinal nerve (transverse sections) in a human embryo of the following ages: (A) approximately 19 days; (B) approximately 20 days; (C) approximately 26 days; (D) after 1 month. The alar plate gives rise to sensory (afferent) neurons and the basal plate gives rise to motor (efferent) neurons. The sulcus limitans is the boundary between alar and basal plates.
the “primary brain vesicles.” Rostrally to caudally, the three divisions are the prosen- cephalon or forebrain, the mesencephalon or midbrain, and the rhombencephalon or hindbrain. A bilateral column of cells differentiates from the neural ectoderm at the original junction of the skin ectoderm and the rolled edges of the neural plate. These two columns of cells become the neural crests (see Fig. 6.2).

The neural tube is the primordial structure for the central nervous system (CNS) (brain and spinal cord), including all neurons in the CNS, oligodendroglia, and astroglia. The neural crest gives rise to a number of neural and non-neural derivatives. The neural derivatives include (1) neurons in all the sensory, autonomic, and enteric ganglia, (2) cells of the pia mater and arachnoid and the sclera and choroid coats of the eye, (3) neurolemma (Schwann) cells and satellite cells of the ganglia, (4) adrenal medullary cells, and (5) receptor cells of the carotid body. Some neurons of sensory ganglia of cranial nerves V, VII, IX, and X are derived from cells of the otic placode.

Several mesodermally derived elements are associated with the nervous system, including the meninges. Those that secondarily invade the CNS include the blood vessels and microglial cells.

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**ESTABLISHING PATTERNS AND REGIONS OF THE BRAIN AND SPINAL CORD**

The ectoderm of the presomite stage is induced by trophic factors derived from the underlying mesoderm and notochord to differentiate into neuroectoderm and the neural plate that will develop into the CNS. Molecular genetic studies indicate that the development of the early CNS progresses within a program in which genomic transcription factors are involved with neural induction. Furthermore, these studies are revealing the role of genes in establishing the patterns and regions within the nervous system (Hatten, 1999) that activate the genesis of the anterior–posterior axis pattern (AP axis, rostrocaudal axis) of the CNS. During early development, there is an induction pathway linked to a program of transcription factors that establishes the neuroectoderm and its neuroregulation, or leads to the differentiation of the neural tube and the CNS. The transcription factor program is a determinant resulting in the dominant AP axis pattern of forebrain, midbrain-cerebellum, hindbrain and spinal cord. The dorsal-ventral axis pattern is established as the expression of other transcription factors. The dorsalization of specific neural cells types occurs following their induction by locally acting peptide growth factors, whereas the ventralization of other cell types following their induction is by signal regulatory sonic hedgehog factors.

**Spinal Cord**

The spinal cord comprises 31 segments arranged in an AP axis. The development of the neural tube into these spinal segments is determined by the AP axis and the influences of the AP sequences of mesodermal somites (see Fig. 6.1). Thus, the basic AP-axis segmentation is derived from an immediate source, namely the dermatome. In turn, each somite and its associated spinal cord segment is integrated into a structural and functional unit consisting of a spinal nerve together with its dorsal and ventral roots, the combination of neural crest and dorsal root ganglion, its sensory dermatomal distribution, and its motor neurons and myotome (see Figs. 7.1–7.3 and 8.1).

**Regional Patterning of the Neural Tube and the Brain**

The regionalization of the neural tube into the brain is a gene expression patterning resulting in an AP-axis segmentation. However, other multiple gene expression patterns can modify the basic pattern (Rubenstein, 1998). Thus some genes may encode protein factors that regulate the transcription of other downstream genes that, in turn, control cellular differentiation.

1. In the hindbrain and spinal cord, HOX genes (a subset of homeobox genes) appear to
control the identity of cells in the hindbrain as well as the overlapping segmental patterns of the spinal cord and spinal ganglia. The spatial order of the gene expression patterns in the neural tissue is reflected in an orderly distribution of the genes on specific chromosomes. This segmentation is noted in the roots of the spinal nerves (see Fig. 7.1) and in the brainstem (see Fig. 22.1).

2. Evidence of this basic axial gene is expressed patterns in the neural plate and early- to mid-gestational developing prosencephalon (forebrain) Thus, gene expression patterns of the forebrain reflect the simpler AP-axial sequences of the neural plate. The complexity of forebrain reorganization apparently results from multiple distinct pattern ing mechanisms. This indicates that there are several forebrain (prosencephalic) gene expression patterns.

**DIFFERENTIATION OF NEURONS AND GLIAL CELLS**

The embryonic neural tube eventually comprises four concentric zones: ventricular, subventricular, intermediate (mantle), and marginal (see Fig. 6.3). The adult nervous system is derived from these basic zones, none of which corresponds precisely to any adult components.

The ventricular zone consists of dividing cells. The nucleus of each ventricular cell migrates to the luminal end of the cell (adjacent to the central canal), rounds up, and undergoes a mitotic division; after dividing, the nuclei of the daughter cells migrate to the apical portions of their respective cells, where the replication of its deoxyribonucleoproteins occurs. Thus, the ventricular zone is known as the lamina of the to-and-fro nuclear movement. The mitotic and nuclear migration cycle lasts from 5 to 24 hours. Ventricular cells are the progenitors of neurons and macroglia (astroglia and oligodendroglia) of the CNS.

The precursor cells of glial cells can be distinguished from those of neurons by the presence of glial fibrillary acidic protein (GFAP) in dividing glial precursor cells of the ventricular zone. The first glial cells to be formed appear at about the same time as the first neurons. As previously stated, most, but not all, neurons in humans are generated during prenatal life. In

**Figure 6.3.** The four zones of the embryonic CNS (neural tube). The ventricular cells (stem cells) are derived from neuroectodermal cells of the neural plate. The ventricular stem cells divide into new stem cells that remain within the ventricular zone and others that migrate into the subventricular zone. Within the subventricular zone, the stem cells differentiate either into glioblasts, neuroblasts, or ependymal cells. Some glioblasts differentiate into radial glia cells that extend from the ventricular zone and as a glial fiber to the pial surface of the neural tube. The arrows within the stem (ventricular) cells indicate the direction in which the nucleus migrates to and fro during a mitotic cycle. Arrows outside the cells indicate the direction of the migration of neuroblasts and glioblasts (progenitors of astrocytes and oligodendroglia). The neuroblasts are guided in their migration by the radial glial fibers.
contrast, the precursors of the glial cells retain some capacity for proliferation throughout life.

The subventricular zone in time differentiates from the ventricular zone. It is composed of small cells that proliferate by mitosis but do not exhibit the to-and-fro nuclear movements during the mitotic cycles. This zone persists only a few days in the spinal cord, but many months and even years in the cerebrum. It generates certain classes of neurons and macroglia of the CNS. It gives rise to (1) the rhombic lips located on the lateral margins of the medulla and (2) the ganglionic eminence located in the floor of each lateral ventricle. The rhombic lips generate certain brainstem and cerebellar neurons, including the billions of interneurons of the cerebellar cortex (Chap. 18). The ganglionic eminence generates many of the small neurons of the basal ganglia (Chap. 23) and of some other deep structures of the cerebrum.

After these newly differentiated neurons have apparently lost their capacity to synthesize DNA, the mitotic cycle ceases and the cells are triggered to migrate from both the ventricular and subventricular zones into the intermediate zone or even farther to form the cortical plates (see below). Never again will these postmitotic cells divide. Those cells that migrate into the rhombic lips and ganglionic eminences, as noted earlier, retain their capacity to undergo mitosis. As a rule, the large neurons differentiate before the small neurons. The large neurons are primarily those whose axons extend long distances, and small neurons (local circuit neurons) are those whose fibers are confined to the region immediately surrounding the cell body.

The intermediate (mantle) zone evolves into the gray matter of the CNS, with its complex neural organization. The neurons that migrate and collect to form the cortical plates differentiate into neurons of the cerebral cortex and cerebellar cortex. Most cerebellar cortical neurons are derived from the rhombic lips.

The marginal zone is the cell-sparse layer with no primary cells of its own. Eventually, it is invaded by axons, both myelinated and unmyelinated, and macroglia to form much of the white matter.

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### NEURAL STEM CELLS

Stem cells are “persistent embryonic” cells present even in adults. They have the several potentials of being able to (1) replicate themselves as self-renewal precursors, (2) proliferate large numbers of progeny by neurogenesis, and (3) retain multilineage potential over an extended time. The inner cell mass of the blastocyst consists of embryonic stem cells, which are totipotent stem cells with the capability, under proper conditions, to develop into almost any cell type. The germinative zones of the neural tube and the neural crest are comprised of neural stem cells, called multipotent stem cells (derivative, progenitor or persistent stem cells (see Fig. 6.3).

Multipotent neural stem cells (NSC) are progenitor cells of the nervous system with the capability of developing into neurons and neuroglia (oligodendrocytes and astrocytes) of the CNS and into neurons, Schwann cells and satellite cells of the peripheral nervous system (PNS). Note that microglial are mesodermal derivatives. Some NSCs persist and exhibit activity throughout life. A stem cell is characterized by the combination of both its morphological fate and its functional role. Although NSCs have a high capability for self-renewal in the developing and immature nervous system, they remain quiescent and divide much less frequently in the mature nervous system, but they can resume activity on demand. Thus, NSCs exhibit an impressive power of renewal.

In consort with general biological phenomena, the numbers and activity of the NSCs and their progeny are homeostatically regulated. In adults, persistent neurogenesis of new progenitor neurons from NSCs occurs in the olfactory neuroepithelium (olfactory mucosa), olfactory bulb, dentate gyrus of the hippocampus, and in the prefrontal, posterior parietal, and inferior temporal gyri of the cerebral cortex (Chapter 25). Other locations where NSCs in the adult give rise to derivative cells remain to be uncovered; their capabilities have been questioned and, at best, are markedly reduced. Typically,
many potential NSCs remain quiescent and unrecognized unless activated to supply a need. The fate of the genetic potential of the multipotential NSCs to become neurons or glial cells is expressed in a sequential progression of restriction stages: (1) differentiation into neuroblasts or glioblasts, followed by (2) differentiation into committed neuronal or glial progenitor cells, and, ultimately in adults, into specific neurons or glia.

The precise roles of a variety of molecular factors that regulate and influence the development and ultimate fate of each NSC are incompletely understood. The following are some of the types of molecular factors involved in the potential resident NSCs expression of their genetic potential in the sequence of differentiation and restriction stages leading to their fates as committed functional stem cells: (1) transformation (growth) factors that modulate during the restriction stages as each cell passes through its development; (2) signal factors that act as guideposts during each cell’s migration to its destination; and (3) induction factors that are involved in the modifications associated with interactions and adjustments to the specific environment of the NSCs.

**Stem Cell Therapies**

The developmental potentials of NSCs can have significance in regenerative and reparative (cell replacement) therapies. Transplantation of NSCs as donor cells from embryonic and fetal sources into the brain and spinal cord is being evaluated for roles in regenerative therapy and reparative therapy for several neurologic disorders such as Parkinson’s disease, Huntington’s disease and Alzheimer’s disease, as well as for traumatic injuries resulting in, for example, paraplegia. The symptoms of parkinsonism are associated with the degeneration of dopaminergic neurons in the basal ganglia (Chap. 24). Neurons obtained from selected sites of aborted fetuses were grafted into the basal ganglia of patients with Parkinson’s disease (Bjorklund, in Barinaga, 2000). In many cases, the transplanted fetal tissues (containing either stem or fetal cells) significantly relieved some of the symptoms, including slowness of movement and rigidity. This indicates that survival of transplanted fetal cells into the brain does occur and they have the capacity to express relevant functional activity.

**THE NEURON: EARLY DEVELOPMENT THROUGH MATURITY**

**Neuronal Navigation and Docking During Early Development**

The stages involved in the creation of the neuronal network of the brain and spinal cord and its integration with the peripheral nerves during prenatal development are precise and apparently predetermined to a considerable degree. The first two stages are pathway selection and target selection. In humans, they are instrumental in establishing the basic groundwork of the neuronal networks and pathway systems during prenatal life. The third, the activity-dependent and experience-dependent stage, continues throughout life.

Evidence is available that identifies some of the factors involved in assembling, integrating, and maintaining the 100 billion neurons of the human nervous system. Because there are more neurons than genes, each neuron cannot possibly have its own gene to regulate the navigational system controlling (1) pathway selection or cell migration from the ventricular layer of the neural tube and (2) target selection or the guidance of the growth of axons at their tips (growth cones) as their endings “hone in” to make synaptic connections with their target neurons. The development of the nervous system from the neural plate and neural crest stage to the mature nervous system is synchronized by genetic influences and epigenetic factors. In essence, each neuroblast differentiates into a neuron with its axon terminals, which must migrate to and dock in its designated site, and be there at the right time to be integrated into a prescribed circuitry.

At the time a neuroblast commences to migrate from the ventricular zone of the neural
plate, it becomes a postmitotic cell that is (1) incapable of dividing and (2) is branded to become a neuron. The kinetics of cell migration commences as each neuroblast (and glioblast) leaves the ventricular zone at a definite time to navigate to its port of call in the brain and spinal cord. The differentiation of each immature neuron, and the specific path it takes to reach its destination, is determined (1) by the activation of specific sets of genes combined (2) with a variety of epigenetic external signals from other cells in the environment. Initially, the neuroblasts of the brain contact the fibers of the radial glial cells. These are specialized cells, each with a process extending to the ventricular surface and another to the pial surface. The neuroblasts migrate along the scaffolds of these glial fibers by contact (mechanical) guidance (see Fig. 6.3). However, many neuroblasts migrate without the guidance of the glial fibers. Both of these migratory patterns are apparently accomplished with the aid of tropic molecular cues or markers, which attract the migrating neuroblast or its growing tip. This establishes the basic structural matrix of the brain and spinal cord. In addition, there are neurotrophic factors, which are chemical substances released by the targets of neurons. Such factors trigger chemical changes in the neurons that are critical for the survival, differentiation, and growth of neurons. Nerve growth factor (NGF) is the prototypical target-derived neurotrophic factor (family of proteins called neurotrophins) (Chap. 2). Other putative neurotrophins have been proposed. The view that there is a single target-derived neurotrophic factor for each neuron is being modified; more than one factor can presumably influence the development and survival of some neurons. In addition, some neurotrophic factors can be derived from sources other than the target. Once the immature neuron arrives at its destination, the outgrowth of its axon begins. The terminal tip of the elongating axon is the growth cone characterized by the presence of finger-like projections (filopodia) or flattened extensions called lamellipodia (see Fig. 6.4). The growth cones act as mobile sentinels. Powered by actin microfilaments, the cones actively explore and probe the tissue environment. Filopodia protrude randomly from the leading edge of the growth cone. Those that extend in the “intended” new direction of growth become stabilized, whereas the others are retracted. Stabilization involves the concentration of actin in the filopodia and a local consolidation of the microtubules in the growth cone. This establishes the new direction in which the axis cylinder continues to elongate. Receptor molecules on the cone’s plasma membrane, acting as sensors, are responsive to the diffusible molecules in the vicinity. Chemotrophic factors furnish guidance cues leading to the precision of pathfinding as the axon elongates and sprouts collateral branches. Some guidance cues can be inhibitory and, thus, modulate random collateral sprouting of branches and prevent aberrant growth. The glycoproteins laminin and fibronectin are growth factors present in the extracellular matrix of both the developing PNS and CNS. The cone responds to molecular cues (chemoaffinity) and guidepost cells, which trigger radical turns (even right angle) in the trajectory of an axon and also define the location of branching sites for the development of collateral branches (see Fig. 6.4). It has been established that growth cones follow cues and markers that are encoded by the cells with which they are in direct contact or that diffuse from target cells. However, the molecular nature of these cues remains elusive.

One of the primary goals of developmental neurobiology is to identify the chemical signals involved with the accurate guidance of growing axons as they establish the basic circuitry of the nervous system. Directing axons to their mark during development is presently conceived to involve, in part, diffusible chemotropic (neurotropic) factors secreted by cells along the designated pathways and target cells. These factors apparently affect the biochemical and functional properties of the receptor sites on the axonal growth cones. This is an expression of epigenesis, in which chemotropic factors contribute to the patterns associated with axon
Figure 6.4: (A) Growth cone. The growth cone is a specialized sensory motor structure at the growing terminal of an axon (neurite). (A) Each growth cone is a structure comprised of a central core domain (C) and a peripheral domain (P) from which extends the leading edge of fingerlike protuberances called filopodia at the base of which are weblike veils called lamellipodia; these are shaped by actin filaments (one of the protein filaments of the cytoskeleton). Neurotubules are abundant in the organelle-rich central domain and the actin filaments predominate as tight bundles in the filapodia and as dense interwoven networks in the lamellipodia. (B) Directional responses of cones mediated by diffusing guidance molecules from a distant producer site, expressed as attractive or repellent, are called (1) chemo-attractive (Ch-A) or (2) chemo-repellent (Ch-R) responses. Directional growth responses of the growth cones mediated by direct contact with membrane-bound guidance molecules, expressed as either attractive or repellent, are called (3) contact-dependent (Co-D) or (4) contact-repellent responses (Co-R).
pathfinding and axon fasciculation (Jessel and Sanes, 2000).

Early differentiation of the nervous system is regulated by a series of chemical inductive signals, some derived from mesoderm. The mesodermal notochord conveys local signals that induce the formation of the floor-plate of the neural tube (see Fig. 6.2). In turn, the cells of the floor-plate secrete diffusible proteins (axon-guidance factors) called netrin-1 and netrin-2, named for the Sanskrit word for “one who guides” (Kennedy et al., 1994). The axons originating dorsally in the neural tube near the roof-plate grow ventrally to the region near the floor-plate (see Fig. 6.5). Netrins possess commissural outgrowth-promoting activity signals that cause the growing axons to decussate (cross over) as commissural axons to the contralateral side. The floor-plate apparently releases these factors even when the human embryo is as young as 1 mo old. Thus, they have a role in the act of designating the sites of the decussation of various fiber systems in the spinal cord and brainstem. Examples include the spinothalamic fibers in the anterior white commissure (see Fig. 9.2) and the internal

Figure 6.5: (A) In the neural tube, the cell bodies of commissural interneurons are located dorsally. The growth cones of their axons migrate toward the ventral midline in response to cues from attractant guidance molecules of the midline floor-plate. (B) In the hindbrain, the cell bodies of the commissural axons of the trochlear (IV) cranial nerve are located ventral to the central canal near the floor-plate before crossing the midline (decussating) dorsal to the floor-plate (see Fig. 13.14). The growth cones of their axons nerve migrate dorsally toward the midline as a presumed response to the repellent cues of guidance molecules of the floor-plate. (C) The decussation of the growth cones of axons of interneurons or of ascending tract fibers (e.g., spinothalamic) results from the attractant axon-guidance factor netrin (circles) released by cells in the floor-plate. During the crossing of the floor-plate, the netrin receptors of the axon’s growth cones are suddenly silenced by a guidance molecule called “slit” (triangles) that activates the “slit” receptor of the growth cone. By the “hierarchical organization of guidance molecules,” the activated “slit” receptor silences the netrin receptor to the attractant response netrin, but not the growth-stimulatory response to the netrin receptor (see text). This growth cone is able to continue its growth, decussation, and pathfinding migration as a postdecussated ascending fiber in the growth-permissive microenvironment with its molecular guidance factors within the developing CNS.
arcuate fibers from the dorsal column nuclei that decussate in the medulla to form the medial lemniscus (see Fig. 10.3).

The glycoproteins, called neural cell adhesion molecules (NCAMs), contribute to the general adhesive properties of neurons that are important as identity sites enabling one neuron to recognize another. An NCAM molecule on one neuron can bind to a counterpart NCAM molecule on another neuron during development of specific populations of neurons. However, NCAM molecules might not have a role in promoting axonal growth. Rather, NCAMs are requisite for anchoring the growth cone to a surface, but not for the directed migration and guidance. The axons and dendrites grow out in a predetermined manner during normal development, with axonal outgrowth preceding dendritic outgrowth. Axons utilizing growth cones as sensors can be conceived as navigating through an epigenetic landscape that guides their growth through reactions to a variety of chemical factors and physical substrates.

In summary, there are presumed to be a variety of (1) outgrowth-promoting protein molecules that stimulate the increase in numbers and lengths of axons—these include such chemotropic factors as laminin and nitrins—and (2) outgrowth-suppressing molecules that have the opposite effect. These chemotropic factors combine to influence the directed migration and guidance of the growing axons to their targets. The NCAMs have an anchoring role to bind the axon to a surface.

The goal of each axon is to make functional synaptic connections with such targets as other neurons (dendrites, cell bodies, and axons) and effectors (muscles and glands). Complex interactions between the nerve terminal and the postsynaptic cell are critical for the initially immature synapse to become stabilized and functionally effective. The growth cone matures into the presynaptic nerve terminal by honing its capability to store and release transmitter spontaneously into a mature terminal with a coordinated response to action potentials. The postsynaptic cell requires some of this differentiation. In turn, the postsynaptic cell is modified by influences from the presynaptic membrane, which regulates the number and distribution of transmitter receptors and other molecules of the postsynaptic membrane.

The interaction of the axon terminal (growth cone) with the plasma membrane of a myotube (immature striated muscle fiber) at a neuromuscular junction (motor end plate) illustrates the influence of the presynaptic terminal on the postsynaptic membrane. Prior to the arrival of the motor nerve terminal, the acetylcholine (ACh) receptors are uniformly distributed over the surface of a muscle fiber. Following the arrival of the future synaptic site, the axon terminal induces the accumulation of a new cluster of ACh receptors on the muscle membrane at the point of ACh release. Some receptors are redistributed as they diffuse within the membrane and become immobilized in the cluster. Others are synthesized anew and inserted within the cluster. Thus, the presynaptic ending controls the synthesis and distribution of receptors on the postsynaptic membrane. A diffusible protein, called acetylcholine receptor-inducing activity (ARIA), has a role in this transformation. Following the clustering of the receptor sites at the motor end plate, the receptors outside of the vicinity of the end plate disappear.

In summary, the precision of the molecularly guided navigation during these two stages is coupled by giving rise to the basic neuronal connections specified by recognition molecules. Thus, the basic connectivity of complex circuitry of the nervous system is established in the sensory systems such as the posterior column–medial lemniscal pathways (Chap. 10), the motor systems such as the corticobulbar and corticospinal pathways (Chap. 11), and other integrating circuits such as those associated with the basal ganglia (Chap. 24). These are presumed to have developed independently of activity or experience.

Oligodendrocytes develop relatively late, always after the growth of the axon in the CNS. This timing is essential because these glia cells
exert inhibitory influences on axonal growth and regeneration. This results from the action of membrane-bound inhibitors of mature oligodendrocytes and CNS myelin.

**Activity-Dependent and Experience-Dependent Stage**

This stage is involved with refining the coarser features of the circuitry by fine-tuning the patterns of connectivity of the pathway systems through activity and experience. The impetus to accomplish this is through activity and by the experience gained by responding and adjusting to both external and internal environmental stimuli. Many of these connections continue to be capable of modification throughout life. The activity-dependent and experience-dependent plasticity of the ocular dominance columns of the visual cortex is expressed in anatomical and physiological changes during the critical period that results in amblyopia (Chap. 19). Activity- and experience-induced changes in the nervous system are phenomena responding to and associated with the continuous honing of the skills in proficient athletes and musicians. Structural plasticity, axonal sprouting, and the changes in number of dendritic spines can be enhanced (or suppressed) in appropriate neurons through an increase (or decrease) in activity. Engaged exposure to sensory stimulation (e.g., touch or visual) during development can lead to significant increases in the number of dendritic spines and synapses in neocortical neurons of the primary sensory areas (Chap. 25). Even the cortical map of the primary sensory cortex can be modified by activity and experience (Chap. 25). The ability of axons to regenerate in the adult is an expression of the neuron’s retention of an embryonic potential throughout life (Chap. 2). A physiological expression of motor learning and skills by the activity of inhibitory synapses is noted in the “importance of inhibition” (Chap. 3). Changes at the molecular level that are associated with memory presumably involve the second-messenger system and modulatory glutamate transmitters acting through NMDA receptors on postsynaptic neurons (Chap. 15).

**DEVELOPMENT OF THE CEREBELLM**

The development of the cerebellum presents a dramatic example of the migration of germinal cells (neuroblasts and glioblasts) from two sources navigating along different routes to finally mesh into the intricate circuitry that characterizes the cortex and deep nuclei of the cerebellum (see Figs. 6.6 and 18.3). Only a few aspects of these precisely timed and integrated sequences will be outlined.

The two sources are (1) the ventricular zone of the neural (cerebellar) plate and (2) the rhombic lip of the dorsolateral lower pons. The routes are (1) direct migration from the ventricular zone to the primordial cerebellum (cerebellar plate) and (2) migration from the rhombic lip to the outer surface (external granular layer) of the cerebellar plate.

The neuroblasts of the ventricular zone migrate into the cerebellar plate to form two strata: Neuroblasts of the deep stratum differentiate into the neurons of the deep cerebellar nuclei (dentate, emboliform, globose and fastigial nuclei), whereas those of the superficial stratum differentiate into the Purkinje cells and Golgi cells (neurons of the cerebellar cortex). Neuroblasts from the rhombic lip migrate over the surface of the cerebellar plate to form the external granular layer. This layer gives rise to the granule cells, basket cells, and stellate cells (neurons of the cerebellar cortex). Glial cells are derived from the same sites as the neurons.

The results of these migrations from dual sources to the right places and arrivals at the right times lead to the formation of the complex integrated circuitry involving the neurons of the cerebellum (see Fig. 6.6).

The Purkinje cells form their dendritic trees within the molecular layer. At the same time, the granule cells migrate from the external granular layer through the molecular layer to the granular layer (deep to the cell bodies of the
Purkinje cells). These cells are guided (contact guidance) along the processes of radial glial cells (Bergmann glial cells). Neurotrophic factors and interactions among the differentiating Purkinje cells and granule cells contribute to the events within the molecular layer. Among these are the formation and orientation of the parallel fibers of the granule cells and the complete differentiation of the dendritic trees of the Purkinje cells, as well as the specific connections of these neurons with each other and with other neurons. To these can be added the sequence involving the differentiation, growth, and synaptic connections of the Golgi cells, stellate cells, and basket cells and of the climbing fibers and mossy fibers.

**NEURAL PLASTICITY**

Neural plasticity is the expression of the capability of the nervous system to modify its morphologic components and their functional roles. As a concept, plasticity involves certain changes occurring in both differentiating and mature neurons, synapses, and networks. Broadly defined, neural plasticity is the potential of both the developing and mature nervous system to change the neural phenotype based on altered patterns of circuits, connections, or activity. Plasticity is operative as a factor in the ability of an organism to alter its behavior in response to novel stimuli from the internal and external environments.

Plasticity is reflected in a neuron’s ability to change (1) innately (genetic), (2) in response to stimuli from the environment (epigenetic), and (3) in response to influences from neurotrophic factors. These plasticities are variously specified as developmental, chemical, neurotrophic, neuronal, synaptic (strength), and others (regenerative, adaptive, short or long term, experience-dependent, representational [e.g. body parts], and behaviorally induced).
Developmental Plasticity

Plasticity is active during ontogeny as neuroanatomical and neurophysiological changes as neurons integrate and mature as components of circuits, pathways, and processing complexes (e.g., nuclei and cortices of the sensory and motor systems). Plasticity continues throughout life. For example, neural changes occur within the mature cerebral cortex, whose input and output pathways are dynamically altered in response to a continuous stream of inputs from sensory, behavioral, and experiential activities. Some plasticity is expressed as a means of enhancing and focusing the precision of a neuron’s output along with modifications of the neural circuitry, including by pruning surplus collateral branches by microglial phagocytosis.

Chemical Plasticity

The dynamics of the chemistry of the brain has a role in plasticity. For example, the brain is continuously turning over its biochemical constituents that might be involved in coping with changing demands. Radioactive isotope studies reveal the rapidity of biochemical turnover. On the basis of half-life, free amino acids in the brain are incorporated into proteins within 30 minutes. Depending on the particular chemical substance, the rate ranges from a “fast turnover” of a few hours to a “slow turnover” measured in days. In the case of myelin, the half-life of one of its constituents, lecithin, is about 15 days. Proteins, considered to be rather stable, also turn over to a significant degree. A rat replaces about 25% of its brain protein every 30 days, so that by 6 months, only about 1–2% of the original protein remains.

Neurotrophic-Derived Plasticity

During early development, prior to innervating the sweat glands, postganglionic sympathetic neurons are adrenergic (release norepinephrine). Following innervation of the sweat glands by these postganglionic neurons, an interaction occurs with target-derived (i.e., sweat gland) neurotrophic factor that triggers the conversion of these adrenergic neurons to cholinergic ones. This illustrates that neurons are not irrevocably genetically programmed to produce one transmitter. Rather, the choice of transmitter synthesized and released by a neuron can be acquired at a late developmental stage and can be changed to another transmitter by a neuron’s environment (MacAllister et al., 1999).

The differentiation of neurons during development can be dependent on and influenced by multiple neurotrophic factors. This applies to neuroblasts, which presumably have an unrestricted progenitor potential. Such an embryonic neuroblast (stem cell) is present in the inner layer of the optic cup. Evidence indicates that such a specific neuroblast is prompted by diffusible factors to differentiate into any of the cells of the adult retina, namely rods, cones, bipolar, horizontal, amacrine, retinal ganglion neurons, and also glial (Muller’s) cells (Chap. 19). Those developing cells that can differentiate into only one mature neuronal type are called highly restricted progenitor cells.

Neuronal Plasticity

Neurons possess the capability of generating new branches (axonal and dendritic sprouting), to form new synapses (synaptic replacement), to modify synapses (synaptic change), and, thereby, to modify neuronal circuits. These features of neuronal plasticity are lifelong expressions. The broad concept of learning and memory, including a vast array of coordinated learned movements (e.g., dexterous movements exhibited in music, athletic, and ordinary activities), involve synaptic plasticity. These adaptations occur at all levels, including sensory inputs, processing centers (nuclei), pathways, cortical areas, and motor outputs.

Synaptic Plasticity

Electrical synapses do not exhibit plasticity. They are involved with the rapid and essentially stereotyped responses that are the hallmark of electrical transmission. Because these synapses are not readily modified and changed in effectiveness, they maintain a stable functional
structure that continuously communicates bidirectionally via ionic currents and gap-junction channels.

In contrast, chemical synapses (those releasing neurotransmitters) exhibit both short-term and long-term plasticity. They mediate both excitatory and inhibitory activities and, in addition, can produce more subtle and complex behavioral activities than the stereotyped responses of electrical synapses. Because these synapses can undergo short or lasting changes in effectiveness, chemical synapses have an order of plasticity that is significant in such manifestations as from how we move, perceive, and feel to such phenomena as learning memory and other higher functions of the nervous system (learning and memory applies to non-cognitive motor skills as well as to cognition).

Synaptic plasticity is expressed as the "strengthening or weakening of synapses," which can be of short or long duration. Short-term or transient changes (e.g., minutes to hours) in the influx or accumulation of calcium ions within the presynaptic terminal can affect the amount of transmitter released. The free-calcium-ion concentration in the presynaptic terminal can be the basis for a number of mechanisms that convey plasticity to chemical synapses. Short-term memory is associated with transient synaptic plasticity changes and long-term memory with permanent changes. An emerging view of synaptic plasticity suggests that local neurotrophic action and synapticlly associated protein synthesis promotes synaptic remodeling. Evidence indicates that the addition of synapses (increase in synapses per neuron) as well as changes in synaptic structure occur during learning and memory.

Synaptic Plasticity and Dendritic Spines

Several features make dendrites, especially those with spines, basic to an understanding of learning and memory. These features are as follows: (1) About 90% of all synapses are with dendrites; (2) plasticity changes result in strengthening or weakening the synapses; (3) spines are characterized as multifunctional integrative units; in vivo imaging has demonstrated that spines can form, collapse, and reform and also change in size and shape rapidly in response to a diverse array of stimuli and thereby exhibit activated-dependent plasticity (Chap. 3).

A generalization is emerging that the more recently phylogenetically evolved parts of the brain, those concerned with higher neural functioning, are more flexible or plastic than the older parts of the brain. This plasticity is reflected in the ability of certain parts of the brain to reorganize itself after damage and to recover function. Stated in cellular terms, neurons in some newer parts of the brain are more capable of extending new branches and forming new synapses than neurons in other parts of the brain (Dowling, 1993). The capacity for functional plasticity is maintained throughout old age.

The biological expression of each person's individuality is based on a distinctive genetic constitution combined with unique epigenetic modifications involving a degree of plasticity.

INTRANEURONAL TRANSPORT OF SIGNALS

Anterograde and retrograde transport convey macromolecules, including neurotrophic factors, that are involved in such roles as general maintenance of the neuron, axonal growth during development, axonal remodeling as an expression of plasticity, and regeneration of injured neurons (Chap. 2). These transport systems are essential for coordinating the complex functional interrelations between the cell body and the entire axon and dendrites, especially because macromolecules are synthesized in the cell body. Some macromolecules are thought to convey signals (signal peptides); that is, they act as messengers with roles in influencing various aspects of the neuronal processes. Newly synthesized macromolecules by each neuron are delivered from the cell body, via the anterograde transport pathway in the axon, to sites where these proteins are utilized by the neuron throughout its life history, from early development through maturity.
Indications are that neurons utilize the retrograde transport pathway to convey signal peptides generated by events (e.g., axon injury) in the axon to the cell body and nucleus of the neuron. Means of conveying information from the sites of axonal growth, reorganization, and injury are essential because axons have a limited capacity for synthesizing macromolecules. Retrograde communication can influence activity, for example, in the gene transcription essential for supplying macromolecules required for axonal repair, regeneration, and plasticity, and even learning (Ambron et al., 1995). This rapid retrograde transport is a system by which the needs of each axon are continuously communicated to the biosynthetic centers of the neuron. Another role of signals is to inform the cell body of the neuropeptide transmitter stores in the axon terminals and to adjust the activity of the biosynthetic centers of the cell body to maintain adequate supplies of transmitters in the terminals (Chap. 3).

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**RECI PROCAL SCHWANN CELL–AXON INTERACTIONS**

From the early stages of development through old age, reciprocal Schwann cell–axon interactions occur with profound effects by one on the other. The vehicles for these activities are signal molecules (information carriers) that are (1) generated by Schwann cells to and act on neurons or (2) generated by neurons and their axons to act on Schwann cells. Among these signal molecules are neurotrophic factors involved with growth and survival. Neurons and Schwann cells are critically dependent on signaling mechanisms of immense and subtle complexity. Although less well documented, significant glial cell–axon interactions are also presumed to occur.

The Schwann cells influence the differentiation and growth of axons. Their released soluble factors have roles in guiding the growing axon, promoting its maintenance, and ensuring its survival. The ensheathment and myelination of both unmyelinated and myelinated axons are specially regulated by contact with axons. This relationship is essential for the conduction of the nerve impulse. The Schwann cells play a critical role in several aspects of axonal regeneration in the PNS. The ability of these cells to promote the regenerative efforts of the CNS (Chap. 2) has stimulated interest in using Schwann cells as autographs for CNS repair.

The neuron through its axons exerts, through chemical factors, influences that can (1) stimulate differentiation of Schwann cells, (2) induce and repress the proliferation of Schwann cells, and (3) modify the migration and growth of Schwann cells. By these means, the appropriate placement in functionally relevant numbers of Schwann cells is reached during development, maintenance and regeneration.

The relation of Schwann cells and axons is not stereotypic, as demonstrated in several variants form the typical nerve with each fiber ensheathed by its own Schwann cells. In unmyelinated fibers, the usual pattern of ensheathment is for the Schwann cell to harbor a number of nerve fibers within individual channels continuous with the Schwann cell surface (see Fig. 2.8A). A variant occurs in the olfactory nerve, where clusters of groups of fine fibers are enclosed in troughs communally within the Schwann cell (see Fig. 2.8B). Another is in the enteric plexus of the gut (autonomic nervous system; Chap. 20, Fig. 20.4), where enteric glia cells (equivalent of Schwann cells) ensheathe both the cell bodies and their processes.

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**APOPTOSIS OR NATURALLY OCCURRING NEURONAL DEATH**

The life cycle of neurons consists of mitosis, differentiation, migration, maturation, and death. During development, massive numbers of neurons are lost as a result of a process called apoptosis (programmed cell death, physiological cell death [PCD]). Apoptosis is conserved throughout evolution, occurring in such forms as nematode worms, with which important insights were derived. The purpose of
apoptosis is the removal of surplus or damaged cells. It is essential for development and tissue homeostasis, and when dysregulated, it can result in cancer, neurodegenerative disease, or autoimmunity.

**Control of Survival or Death of Neurons**

During ontogeny, at least half of all neurons do not survive; they die via programmed cell death. The morphologic features of apoptosis are cell shrinkage, condensation and clumping of nuclear (DNA) chromatin, cellular fragmentation into discrete granular masses, and phagocytosis of cellular remnants by macrophages. This contrasts with necrotic cell death following traumatic injury in which there is early dilatation of the nucleus with scattering of chromatin against the nuclear membrane, rapid hydrolysis of the cell membrane, and dilatation and fragmenting of cytoplasmic organelles.

The nervous system sculpts excess neurons in order to maintain a precisely regulated homeostasis for the steady-state preservation of neuronal organization and optimal functioning of the nervous system during development. This neuronal suicide is accomplished by activating intrinsic biochemical and molecular mechanisms. Astrocytes, oligodendroglia, and Schwann cells also undergo programmed cell death. Apoptosis is essential in eliminating superfluous neurons and injured neurons associated with disease-related deterioration or neuronal damage resulting from toxic exposure, low oxygen, or traumatic injury. The debris is removed by the macrophages that act as scavengers of the immune system’s cleanup crew. This suggests that neurons are initially overproduced and then are required to compete for the just normal amount of available target-derived neurotrophins. Consequently, some neurons succumb by apoptosis.

The differentiation and survival of neurons and glia require *trophic support*, which appears to be dependent and promoted by the critical action of multiple protein neurotrophic factors produced by target cells. Nerve growth factor (NGF), the first described, is one of many that have been divided into several classes: (1) neurotrophin class (NGF, neurotrophin 3, neurotrophin 4/5, brain-derived neurotrophic factor); (2) interleukin 6 class (e.g., ciliary neurotrophic factor); (3) transforming growth factor α class (e.g., glial-derived neurotrophic growth factor); (4) fibroblast growth factor class; and (5) hepatocyte growth factor class. Genes encode neurotrophic factors and their receptors on target cells.

Apoptosis is orchestrated and tightly regulated by interconnected biochemical pathways involving protein factors that act either as “death” activators or as “death” inhibitors. The potential role of apoptosis during development includes the reorganization of neuronal branches, including synaptic connections, in addition to removal of unnecessary neurons. Early cell death is a possible destiny for any neuron, but this fate can be circumvented by avoiding apoptotic signals or by receiving appropriate survival signals from *neurotrophins*. Apoptosis has been characterized as a *default pathway* for all cells, and only by receiving the appropriate survival signals can neurons or glia escape. Genes encode several components of the biochemical machinery of *apoptosis*. This cell death in the mammalian nervous system is activated by intracellular and extracellular apoptotic signals that control biochemical pathways involving families of caspaces. In the living cell, caspaces exist as inactive proteolytic enzymes (zymogens), and when activated, they can cleave substrate proteins by a proteolytic program that mediates apoptosis.

Originally, neurotrophic factors were believed, as noted by their name, to promote the survival of neurons by stimulating their metabolism in beneficial ways. However, gene-targeted studies have demonstrated that the survival of neurons also is dependent on neurotrophins, which act to suppress an *endogenous cell death program*. This is accomplished by a biochemical linkage between a neurotrophic factor that inhibits the signaling cascade activating caspaces. Elimination of neurotrophins and their receptors leads to neuronal death by loss of trophic support.
From Genes to Survival or Apoptotic Death

Genes encode the neurotrophic factors and their receptors to initiate the molecular basis for trophic support by the neurotrophins. The genetically mediated neurotrophins are integral to the assemblies of neurons that are dependent on the cell-to-cell interactions and, more specifically, by the neuron-to-target-cell interactions, for neuron survival during development. As such, the neurotrophins are regulators of development, maintenance, and function of the nervous system. The “survival genes” are dependent on neurotrophins to protect neurons from apoptotic death by inhibiting the activation of the caspace-generated biochemical cascades. The “death genes” promote the programs that activate the families of proteases called caspas, which are central to the death cell role. Activation of caspase enzymes leads to the proteolytic activity of substrate proteins within the neuron, leading to apoptosis.

During ontogeny, by limiting the quantity of neurotrophins to an appropriate amount, the neurotrophin can function in a survival mode to ensure a match between the viable number of surviving neurons and the requirement for appropriate target innervation to meet the functional demands of the neuron.

Some basic elements relevant to the caspace biochemical pathways associated with activation or inhibition of apoptosis are outlined. The caspas comprise over a dozen members (caspases are derived from pro-caspases). They cleave numerous types of protein, producing many products essential to neuronal viability. A number of stimuli can trigger apoptosis by activating caspas to act as the “executioners” of neuronal death apoptosis. Neurotrophins suppress endogenous death programs. The binding of neurotrophins to tyrosine kinase receptors is considered to trigger the activation of a biochemical pathway leading to the phosphorylation of protein substrates that inhibit caspase activity to thereby avoid apoptosis. Neurotrophin deprivation triggers caspase activation and a fate by apoptosis. Possibly this deprivation permits cleavage of pro-caspase, resulting in apoptosis. Insufficient neurotrophins allows for the dominance of the “death genes.”

In addition, neurotrophins fine-tune and regulate axon growth, dendritic pruning, and patterning of the innervation with other neurons and effectors (i.e., muscle cells) and the expression of proteins in normal neuronal function (neurotransmitters, channels, neurotubules, and others). In the mature nervous system, neurotrophins are thought to have some control over synapse function and neuronal plasticity. Simultaneously, they modulate neuronal survival.

Apoptosis in Neurodegenerative Diseases

Degeneration occurring in Alzheimer’s disease, Huntington’s disease, and amyotrophic lateral sclerosis might be associated with apoptosis. These diseases have the following in common: (1) There is a familial form with Mendelian inheritance patterns, (2) there is selective degeneration of particular neuronal types, and (3) all are associated with cellular or extracellular degeneration aggregates.

AGING OF THE BRAIN

The number of neurons tends to decrease with age, for as neurons die, they are not replaced by new neurons. The consequences of a slight loss are not necessarily noticeable because the remaining neurons can functionally compensate for a small decrease in numbers.

The brain is said to decrease gradually in weight over the years, losing as much as 10% between the ages of 20 and 90 years. This is presumably related to the loss and atrophy of neurons and glia and to the decrease of extracellular spaces. The loss of cells varies from region to region, with the brainstem exhibiting only a slight decline and the cerebral cortex undergoing the greatest loss. Some evidence indicates that the decrease in weight and the degree of cortical atrophy in healthy old individuals who have no neuropathological condition in the brain is relatively slight. Within the cerebral cortex, the loss of neurons is greatest
in the neocortex of the frontal pole, precentral gyrus, cingulate gyrus, and primary visual cortex.

Neurons undergo senescence. Aging of neurons is evidenced by a change in size (either decrease or increase), by the accumulation of pigment, or by a decrease in amount of Nissl substance. In humans, the quantity of ribonucleoproteins in the alpha motoneurons of the spinal cord increases significantly from birth to 40 years of age, plateaus from 40 to 60 years, and decreases thereafter. In elderly people, the decrease in the weight of the brain, increase in the size of the ventricles, and calcification in the meninges are all signs of an aging nervous system.

An indication of the degree of the aging process after the prime of life is obtained by comparing several parameters in the 30-year-old age group with those in the 75-year-old group. In the older group, the reduction in brain weight is about 10%; in the blood flow to the brain, about 20%; in the number of nerve fibers in large nerves, about one-third; in the number of taste buds, about two-thirds; and in the velocity of nerve conduction, about 10%. The last correlates with the observation that the rate and magnitude of reflex responses to stimulation decrease with age.

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**SPINAL CORD AND PERIPHERAL NERVOUS SYSTEM**

Up to about the third fetal month, the spinal cord extends throughout the entire length of the developing vertebral column. At this time, the dorsal (sensory) roots and the ventral (motor) roots of the spinal nerves extend laterally at right angles from the spinal cord. The roots unite in the intervertebral foramina to form spinal nerves. The roots and spinal nerves are products of outgrowths from the spinal cord and neural crests (see Fig. 6.2). Because the growth in length of the bony vertebral column exceeds that of the spinal cord during fetal and early postnatal life, the spinal cord after the third fetal month becomes relatively shorter than the vertebral column. This is accompanied by an elongation of the roots of the spinal nerves between the spinal cord and the intervertebral foramina.

At birth, the caudal end of the spinal cord is located at the level of the L3 vertebra, and at adolescence, as in the adult, the caudal end is at the level approximately between the L1 and L2 vertebrae. As a result of this disparity in growth, the lumbar, sacral, and coccygeal roots become directed caudally at an acute angle to the spinal cord. The subarachnoid space below the first lumbar vertebra in the adult is occupied by dorsal and ventral roots of spinal nerves (cauda equina) and by the filum terminale, not by the spinal cord (see Fig. 7.1).

Adjacent to the neural tube are 31 pairs of somites. These are embryonic structures that differentiate into muscles, skeleton (including the vertebral column), and connective tissues (see Figs. 6.1 and 6.2). The somites are segmental (metameric) structures arranged in sequence from the first cervical through the coccygeal levels. By segmental is meant a repeating unit of similar composition.

Each pair of nerves develops in association with each pair of somites. The apparent segmentation of the spinal cord is dependent on the development of the paired segmental spinal nerves. The bilateral neural crest also becomes segmented into paired units, one pair for every future sensory (dorsal root) ganglion of each spinal nerve.

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**BRAIN**

**Prenatal Development**

Early in the second fetal month, the “three-vesicle brain” differentiates into a “five-vesicle brain” (see Fig. 6.7). The prosencephalic vesicle is subdivided into the telencephalon, or endbrain, and the diencephalon, or between (twixt) brain. The mesencephalic vesicle remains as the midbrain; the rhombencephalic vesicle is subdivided into the metencephalon, or afterbrain, and the myelencephalon, or spinal brain.
The development of the “contorted” brain from the tubelike structure is the result of the complex integration of several processes: (1) three bends known as flexures, (2) differential enlargement of the different regions, (3) growth of portions of the cerebral hemispheres over the diencephalon, midbrain, and cerebellum, and (4) the formation of sulci and gyri in the cerebral and cerebellar cortices (see Figs. 6.7 to 6.9). The flexures are the mesencephalic (midbrain) flexure (forming an acute angle on the anterior surface of the brain), the pontine flexure (forming an acute angle on the posterior surface), and the cervical flexure at the lower medulla (forming an acute angle on the anterior surface). The posterolateral margin of the rhombencephalon is the rhombic lip, which develops into the cerebellum. The differential enlargement is most pronounced in the cerebral and cerebellar hemispheres. The telencephalon during development surrounds most of the diencephalon; there is an intussusception (telescoping) of the diencephalon into the telencephalon (see Figs. 6.7 to 6.9).

At the end of the third fetal month the main outlines of the form of the brain are recognizable and the external surface of the cerebrum is still smooth. Fissuration commences in the fourth fetal month with the appearance of the lateral sulcus of the cerebrum and posterolateral sulcus of the cerebellum separating the nodulus and attached flocculi from the vermis of the posterior lobe (see Fig. 18.1). The central sulcus, calcarine sulcus, and parietooccipital
sulcus are indicated by the fifth fetal month; all of the main gyri and sulci of the cerebral cortex are present by the seventh fetal month. The external structure of the cerebral hemisphere of the 8-month fetus is characterized by the prominence of the precentral and postcentral gyri, by a wide-open lateral sulcus exposing the insula, and by the presence of all primary and secondary sulci and a few tertiary sulci. The occipital lobe overrides the cerebellum. During the last month of fetal life, the frontal and temporal lobes are stubby, the insula is still exposed to the surface, and the occipital poles are blunt. The cortical gyri are broad and plump,

**Figure 6.8:** Human brain (lateral view): (A) 4-month fetus; (B) 6-month fetus; (C) 8-month fetus; (D) newborn infant. (Adapted from Corliss.)
and the fissures are shallow. The patterns of the primary and secondary sulci are simple.

The cerebrum of the full-term neonate is more fully developed in the regions posterior to the central sulcus than in the anterior regions. The frontal pole and the temporal pole are relatively short, and the insula is almost completely covered by the adjacent lobes. The number of tertiary sulci is still small. The pia mater is not completely adherent to the brain and does not dip into all the sulci. The superficial blood vessels are straight. The brain has a gelatinous consistency. The cortex is poorly demarcated from the white matter. By the end of infancy, at 2 years of age, the relative size and proportions of the brain and its subdivisions are essentially similar to those of the adult brain. The brain is firmer. The gray cortex is demarcated from the subcortical white matter, which is now myelinated. The superficial cortical blood vessels are predominately tucked into the fissures and sulci. After the end of the second year, the tertiary sulci dominate the topographic pattern of the cerebral surface. These sulci are variable from brain to brain and thereby put the stamp of individuality on each brain. Tertiary sulcation can continue throughout life.

**Postnatal Growth**

The large brain in the newborn infant exceeds 10% of the entire body weight; in the
adul, the brain constitutes only approximately 2% of the total body weight. The postnatal growth of the brain is rapid, especially during the first 2 years after birth. The brain weighs about 350 g in the full-term infant and about 1000 g at the end of the first year. The rate of growth slows down after this, and by puberty, the brain weighs about 1250 g in girls and 1375 g in boys. It appears that the brain of a girl grows more rapidly than that of a boy up to the third year, but the brains of boys grow more rapidly after that. This brain size is reflected in the growth of the cranial skeleton. In contrast to the adult, the young child has a large cranium in relation to the face. Head circumference is a measure of the growth of the brain. The head circumference is 34 cm at birth, 46 cm at the end of the first year, 48 cm at the end of the second year, 52 cm at 10 years, and only slightly larger at puberty and in the adult.

CRITICAL PERIODS: EFFECTS OF GENETIC AND ENVIRONMENTAL FACTORS ON DEVELOPMENT

Of all the malformations and congenital defects in human beings, ranging from minor observable variations from the norm to lethal abnormalities, as many as one-half are estimated to involve the nervous system. Although the entire nervous system develops as an integrated organ system, its various parts and subparts maturate at different rates and tempos. During ontogeny, each structure passes through one or more critical period, during which it is sensitive to various influences. These periods are generally times of rapid biochemical differentiation. At such a period, the proper influences have a significant role in advancing normal development. When normal influences are wanting or when abnormal influences are exerted at these critical times, subsequent normal development is often impaired. When the impaired development results in anatomic abnormalities that are present at birth, they are called congenital malformations. These abnormalities are usually caused by genetic factors (chromosomal abnormalities or mutant genes) and environmental factors.

Genetic Factors

Many cases of congenital mental deficiency and retardation are the result of trisomy of autosomes (three chromosomes instead of the usual pair). Down syndrome (mongolism) is a genetic condition in which there are three copies of chromosome 21.

Another genetic disease, phenylketonuria (PKU), is a clinical syndrome of marked mental retardation associated with irritability and abnormal electroencephalogram (EEG) patterns. This condition is the result of an inherited inborn error of phenylalanine metabolism (transmitted by an autosomal recessive gene) that results in an excessive accumulation of the amino acid phenylalanine and its metabolites. The basic defect is a deficiency of the enzyme phenylalanine hydroxylase in the liver; it is essential for the conversion of phenylalanine to tyrosine. Treatment consists of placing PKU patients on a low-phenylalanine diet commencing in the first year of life; it must be done at this time because the brain damage caused by this condition is the result of the accumulation of excess phenylalanine, which reaches its peak between the second and third years of life.

Nutrition

Malnutrition and undernutrition during fetal life, infancy, and childhood have an effect on the developing nervous system. Certain nutritional deficiencies, especially those occurring at the critical early rapid period of maturation, can result in permanent damage. In humans, the critical period extends from the second trimester of pregnancy through most of the first year after birth. During this interval, many neurons and macroglia are being replicated and much of the brain growth is taking place. Evidence indicates that under severe protein malnutrition, the rates of proliferation of new neurons and glial cells are reduced. This reduction occurs during fetal life because even the fetus is not protected from maternal malnutrition. The developing brain is vulnerable during
the remainder of this critical period of postnatal life; the formation of glial cells is impaired, and myelination is inefficient. Severe malnutrition during this period in human infants is known as marasmus. If the child is fed a nutritionally adequate diet after this period, the damage is not completely repaired, even though normal appearance can be achieved in some subjects. Those who appear to be healthy have brains, that could be damaged by the protein deficiency. The functional abnormalities in children reared on nutritionally inadequate diets could consist of transient apathy, lethargy, or hyperirritability, together with a lesser intellectual development as measured by a decrease of some 10–20% of mental capacity.

Prolonged protein deficiency in children from 1 to 2 years of age can result in kwashiorkor. In this condition, the number of neurons is not reduced, because the deficiency occurs after the full complement of neurons is formed; however, the complete differentiation and connectivity of cortical cells could be impaired. If, after being subjected to prolonged, severe malnutrition, children with kwashiorkor are fed a normal diet, their IQ test scores still remain below those of other children in the same population, including siblings who were not subjected to severe malnutrition.

The timing of nutritional deprivation is a critical factor in determining whether or not subsequent recovery from the effects of such deficiencies is possible. In contrast to brains of fetuses and young children, the brains of adolescents and adults are more resistant to permanent effects of malnutrition. The young and mature adult victims of starvation during World War II did not show any loss of intelligence after their nutritional rehabilitation.

The effects of malnutrition assume gigantic proportions in the world today. Roughly 60% of the world’s preschool population (over 500 million children) are exposed to varying degrees of undernutrition. These children live primarily in underdeveloped lands on diets low in proteins and calories. Malnutrition is contributory to the early death of many of them. Survivors grow up in poverty and become adults with physical and mental handicaps. Thus, these poverty (nongenetic) conditions are perpetuated through their children—to be passed down from one generation to the next.

**Hormones**

The mental retardation associated with cretinism in humans is the result of a thyroid hormone deficiency at a critical period during the late stages of in utero development (estimated to begin at the seventh fetal month). The cerebral cortex of cretinoid individuals is poorly developed. There is a reduction in the number and size of neuronal cell bodies, as well as hypoplasia of both their axons and dendrites. Mental retardation of the cretinoid human child can be prevented or effectively remedied if adequate doses of thyroid hormones are given during the first year of life.

**Amblyopia (Lazy Eye)**

Amblyopia, or lazy eye, is a condition of reduced visual acuity caused by inadequate stimulation of the macula of one eye by formed objects between the second and fourth years of age. It results in a defect in the image viewed by the macula of the affected eye. The slightly cross-eyed child favors one eye over the other to avoid seeing double (diplopia). In response to the altered balance of visual output from the two eyes, long-lasting anatomical and physiological changes occur in the ocular dominance columns of the visual cortex (Chap. 19). An inadequate input to the visual cortex from the macula of the abnormal eye was insufficient during the critical period to nurture the maturation of the experience-dependent synaptic plasticity in the ocular dominance columns. This failure during the critical period results in a permanent amblyopia. Ocular dominance plasticity is one of the best examples of synaptic plasticity in the neocortex.

The concept of critical period during childhood is the basis for the suggestion that young children should be exposed to rich visual experiences, even more than they can handle intelligently. This should help to ensure the optimal maturation of the child’s visual pathways.
Spina Bifida

Spina bifida is one of the more common defects that occur at spinal cord levels. The term is used to cover a wide range of closure defects, usually located in the lower lumbar region (see Fig. 6.10). The most extreme version occurs when the neural plate in the lumbar region remains as a plate exposed to the outside. An infant with this defect has bladder and bowel incontinence, sensory loss, and motor paralysis of the lower extremities. In less severe cases, the meninges or the meninges along with the spinal cord, though displaced backward, are still covered by the skin. In a minor form, only the bony neural arches might be defective and functional impairment is absent.

SUGGESTED READINGS


Bagri A, Marin O, Plump AS, et al. Slit proteins prevent midline crossing and determine the dorsoventral position of major axonal pathways


