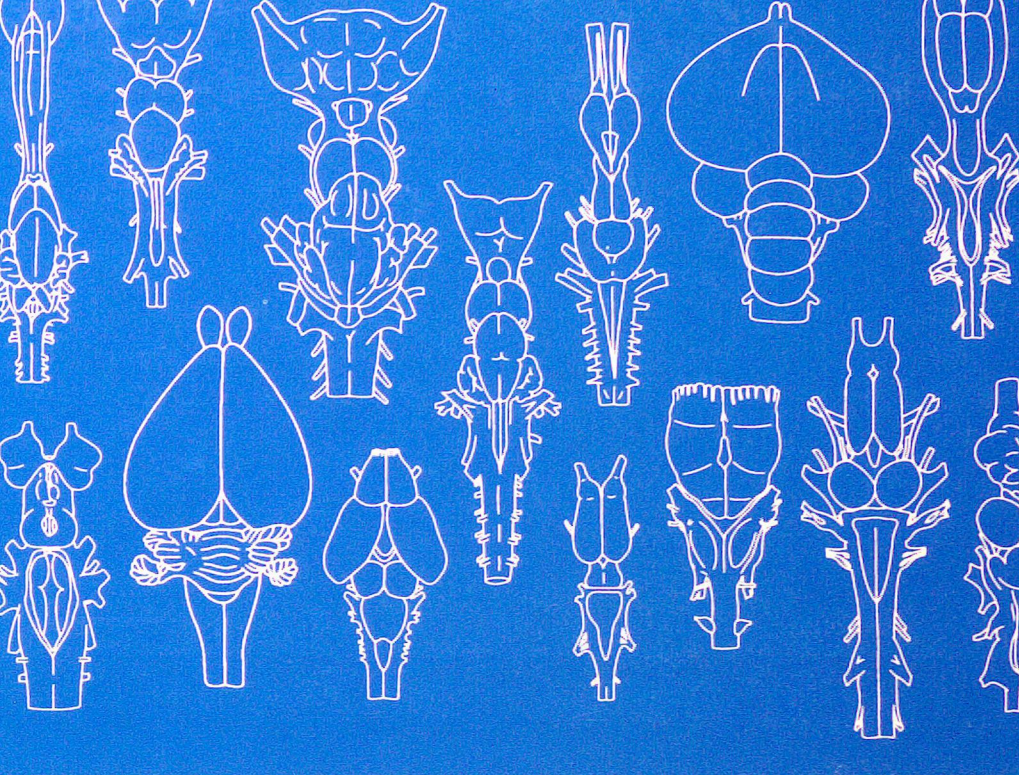

SECOND EDITION

COMPARATIVE VERTEBRATE NEUROANATOMY

Evolution and Adaptation

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3

The Vertebrate Central Nervous System

INTRODUCTION

One of the principal evolutionary events that preceded the sequences of brain and head evolution in vertebrates was a novel embryological event: the development of the mouth as a distinct body opening that is separate from the original gut opening, at or near which the anus eventually forms. Animals that possess this characteristic are known as **deuterostomes**, which means "second mouth." Deuterostomes comprise two major groups—the Ambulacraria, which includes echinoderms (starfishes, sea urchins, and many related genera) and hemichordates (pterobranchs and acorn worms), and the Chordata. The extant members of the latter group are the tunicates (sea squirts), cephalochordates (*Branchiostoma*, previously called *Amphioxus*), and vertebrates (hagfishes, lampreys, and jawed vertebrates). Some of the key evolutionary changes in deuterostome and chordate evolution have affected events that occur relatively early in embryological development. Because a basic understanding of embryological development is of great value for understanding brain structure across adult species, we will begin this chapter with a brief overview of this process in vertebrates.

DEVELOPMENT OF THE BRAIN

Following the fertilization of a deuterostome egg, development proceeds with repeated cleavages of the cells (Fig. 3-1). The pattern of cleavage is variable among the different groups of deuterostomes but in all groups results in the formation of a **blastula** [Fig. 3-2(A)], a sphere of cells around a central cavity, the **blastocoel**. The blastula is already polarized at this stage, with an **animal hemisphere** and a **vegetal hemisphere**. Some differences also exist among deuterostomes in particular features of the course of development following the blastula stage, but a general pattern of development is consistent among all deuterostomes.

In vertebrates, the process of gastrulation (Fig. 3-2) follows the blastula stage, with continued cell proliferation and the specification and arrangement of various groups of cells relative to the parts of the body that they will eventually form. The developing **gastrula** initially consists of two cell layers: an outer layer of cells, the **ectoderm**, which is derived from the animal hemisphere of the blastula and from which the skin and nervous system will form, and an inner layer, which consists initially of **endoderm**. The endoderm is derived from the vegetal hemisphere of the blastula and surrounds the cavity, called the **archenteron**, which will become the lumen of the gut. The archenteron expands during gastrulation, obliterating the blastocoel. The opening of the gut cavity is the **blastopore**. As gastrulation proceeds, the roof of the archenteron, formed by the dorsal part of the inner layer of cells, differentiates to form mesodermal tissue, which in turn gives rise to a midline structure called the **notochord**, as well as to lateral sheets of tissue that will form muscle and bone. The rest of the inner layer remains endoderm, the tissue of the gut.

During the later stages of gastrulation, the notochord and the part of the mesoderm immediately rostral to it, called the prechordal mesoderm, induce formation of the neural tube. In the absence of signals from the mesoderm, the ectoderm is prevented from achieving a neural fate by the action of **bone morphogenetic proteins** (**BMPs**). The dorsal mesoderm, including the notochord, releases several molecules, such as

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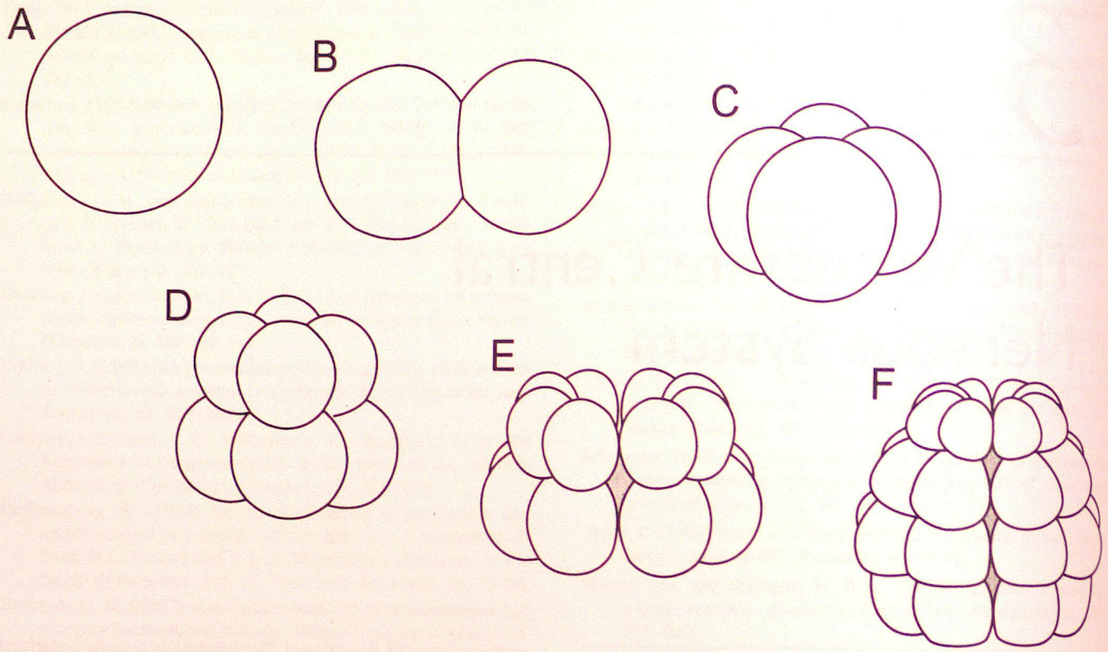

FIGURE 3-1. Earliest stages of cell division beginning with a single-celled, fertilized egg (A) with subsequent divisions up to the 32-cell stage (F), which with continued cell division will eventually form the blastula. After Liem et al. (2001). Used with permission of Thomson Learning Global Rights Group.

the proteins **chordin**, noggin, and ceberus. These molecules block the action of the BMPs in the overlying ectoderm, allowing it to thicken and form the **neural plate** [Fig. 3-2(E,F)]. A pair of **neural folds** [Fig. 3-2(F)] develops along this plate; the folds grow dorsally, meet and then fuse to form the **neural tube** (Fig. 3-3). The lumen (inner space) of this tube forms the ventricular system, while the central nervous system, composed of the brain and spinal cord, develops within the walls of the tube.

Segmental Development of the Vertebrate Brain

The vertebrate brain comprises three main divisions, which, from rostral to caudal, are the **prosencephalon** ("forward brain"), **mesencephalon** ("middle brain"), and **rhombencephalon** ("rhomb" referring to the rhomboid shape of its ventricle). The prosencephalon, or **forebrain**, has two parts: the **telencephalon** ("end brain") and the **diencephalon** ("through brain"). The mesencephalon, or **midbrain**, is a single entity, and the rhombencephalon, or **hindbrain**, has two parts: the **metencephalon** ("after brain"), which comprises the cerebellum and the rostral part of the hindbrain, and the **myelencephalon** ("marrow brain," referring to its continuity with the spinal cord), which is the more caudal part of the hindbrain.

During embryological development, the neural tube undergoes a series of flexures in the rostrocaudal direction. The rostral part of the brain flexes ventrally [Fig. 3-4(A)]. A transverse, ventral fold develops on the ventral surface of the tube in the position where the pituitary gland will form. A pair of lateral bulges in the rostral part of the forebrain forms the cerebral hemispheres of the telencephalon. A single eye stalk initially emerges from the rostral-most aspect of the hypothalamus, which is the most ventral division of the diencephalon. Under the influence of the signaling molecule **Sonic hedgehog** (**Shh**), which is released from the more ventrally lying mesoderm, the eyestalk splits in two to form the paired eyes. The epithalamus, which is the most dorsal division of the diencephalon and which includes the epiphysis [Fig. 3-4(B)], develops in the dorsal part of the diencephalon.

The midbrain lies caudal to the ventral fold in the neural tube. Paired bulges in the roof of the midbrain expand to form the **tecta** (plural of **tectum**), or roof of the midbrain, while the more ventral part of the midbrain becomes the **tegmentum** (the main body of the midbrain). The dorsal portions of both the caudal midbrain and the rostral hindbrain enlarge to form the cerebellum [Fig. 3-4(B)].

The central nervous system, despite the complexity of its structural components, is basically a hollow tube, the lumen of which is the central canal and the brain ventricles. During embryonic development, the neural tube is formed by the folding of the neural plate, as discussed above. In the rostral part of the neural tube, which will eventually become the brain, a rostrocaudal series of bulges, called **neuromeres**, then develops. The neuromeres, which are serial brain segments,

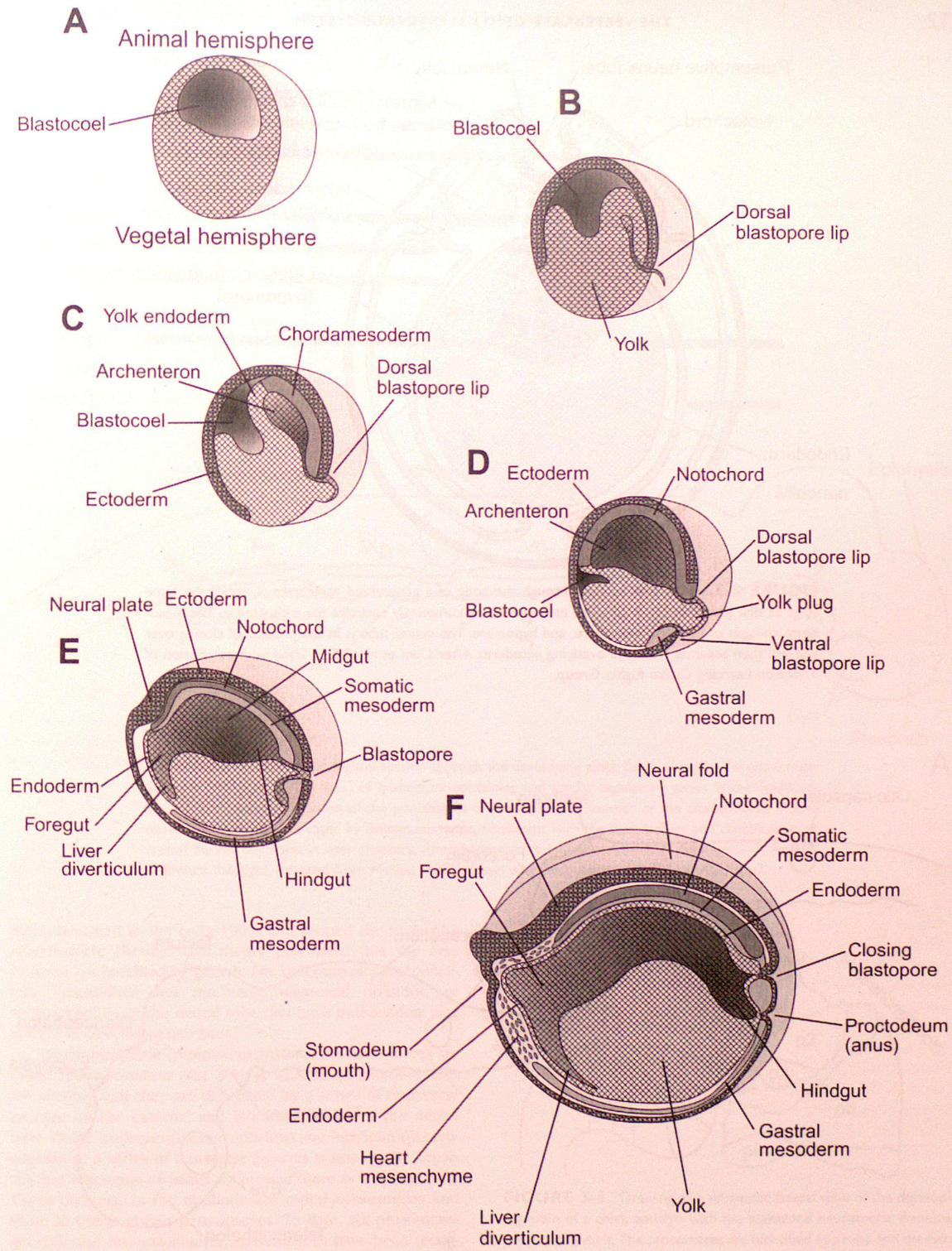

FIGURE 3-2. Drawings of sections through a blastula (A) and stages of gastrulation (B–F) to form an embryo in a frog. In B–F, rostral is toward the left. A–E are sagittal sections viewed from a slight angle, whereas F is drawn in the true sagittal plane. Modified from drawings in Rugh (1964), which were adapted from a 1949 publication by Huettner, with additional information from Liem et al. (2001) and Gilbert (1994). Used with permission of Elizabeth Rugh Downs.

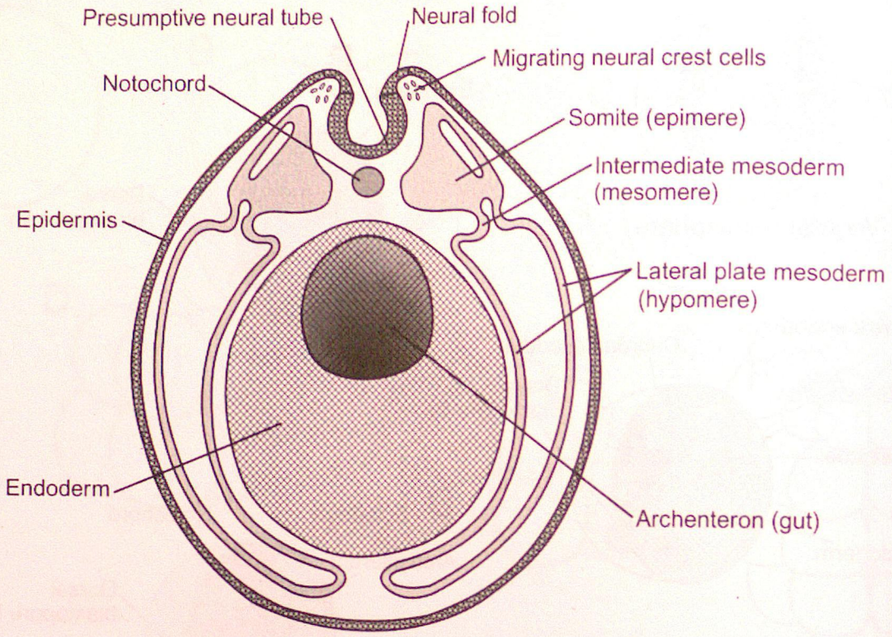

FIGURE 3-3. Transverse section through the body of a generalized vertebrate at about the same stage as that shown in Fig. 3-2(F). The endoderm now completely encircles the archenteron. The mesoderm consists of epimere, mesomere, and hypomere. The neural tube is in the process of closing over and will then separate from the overlying ectoderm. After Liem et al. (2001). Used with permission of Thomson Learning Global Rights Group.

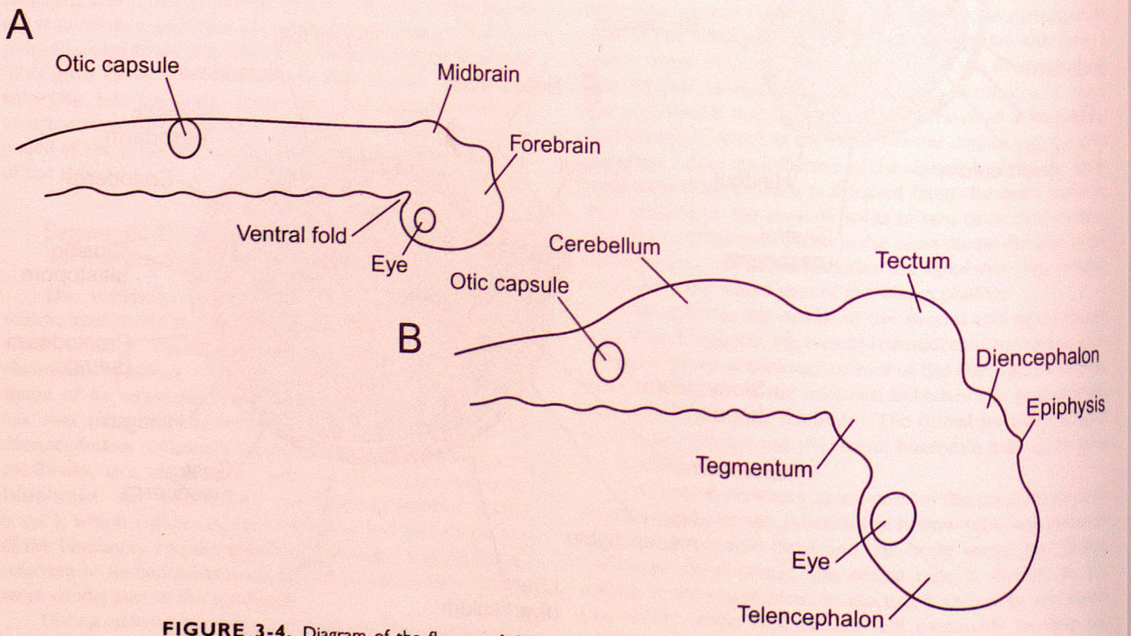

FIGURE 3-4. Diagram of the flexure of the neural tube during formation of the brain. Rostral is toward the right.

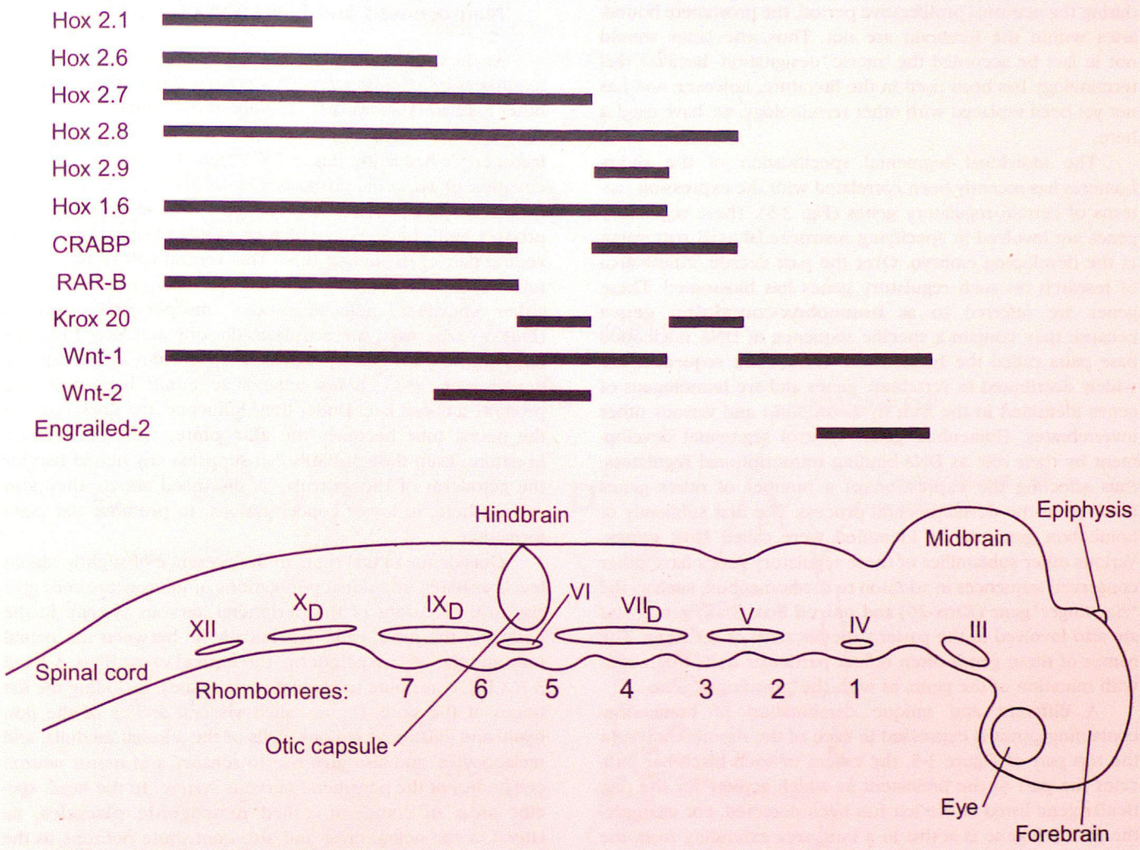

FIGURE 3-5. Schematic sagittal section through the developing chick brain, showing the expression patterns (indicated by the bars) of homeobox-containing and similar regulatory genes in the hindbrain and midbrain and the location of the populations of neurons for a number of the cranial nerve motor nuclei. The latter are indicated by Roman numerals, consistent with the terminology and classification of cranial nerves discussed in later chapters. Rhombomeres are indicated by Arabic numbers 1–7. Rostral is toward the right. Adapted from Noden (1991). Used with permission of S. Karger AG, Basel.

were identified in the early 1900s and formed the basis of a **neuromeric theory**. This theory postulated that the neuromeres are specified by genetic fate determinants and constitute longitudinal and transverse segmental divisions, or compartments, of the neural tube that have independent and individual developmental fates.

In the hindbrain (rhombencephalon), the neuromeres are called **rhombomeres** (Fig. 3-5); at least seven rhombomeres are present, and they are delineated by a series of transverse grooves on the external and internal surfaces of the neural tube. In the midbrain (mesencephalon) and forebrain (prosencephalon), a series of transverse grooves is not readily apparent, but segmental divisions are present there as well (Fig. 3-6). These divisions in the midbrain are called **mesomeres** and those in the forebrain **prosomeres**. To date, six prosomeres (p1-p6) and two mesomeres (m1 and m2) have been recognized. It should be noted that whereas the rhombomeric boundaries are barriers to neuronal migration across them

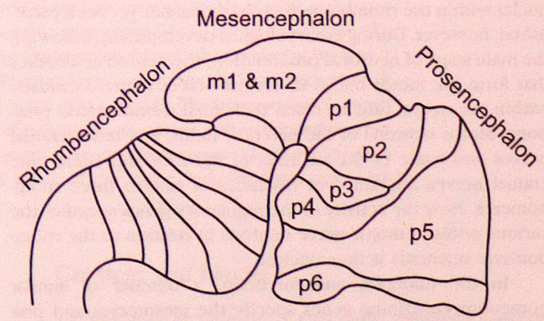

FIGURE 3-6. Drawing of a schematic lateral view of the developing brain of a chick embryo with the segmental neuromeric divisions projected onto it. The prosomeres are identified as p1–p6 and the two mesomeres as m1 and m2. Rostral is toward the right. Adapted from Puelles and Rubenstein (1993). Used with permission of Elsevier.

during the neuronal proliferative period, the prosomere boundaries within the forebrain are not. Thus, the latter should not in fact be accorded the "meric" designation. Because this terminology has been used in the literature, however, and has not yet been replaced with other terminology, we have used it here.

The individual segmental specification of the rhombomeres has recently been correlated with the expression patterns of certain regulatory genes (Fig. 3-5). These regulatory genes are involved in specifying rostrocaudal axial patterning in the developing embryo. Over the past decade, a new area of research on such regulatory genes has blossomed. These genes are referred to as **homeobox-containing genes** because they contain a specific sequence of DNA nucleotide base pairs called the **homeobox**. Homeobox sequences are widely distributed in vertebrate genes and are homologues of genes identified in the fruit fly *Drosophila* and various other invertebrates. Homeobox genes control segmental development by their role as DNA-binding transcriptional regulators, thus affecting the expression of a number of other genes involved in the developmental process. The first subfamily of homeobox genes to be identified were called **Hox genes**. Various other subfamilies of these regulatory genes have other conserved sequences in addition to the homeobox, such as the "zinc-finger" gene (*Krox-20*) and **paired box** (**Pax**) genes, and are also involved in the pattern specification of the brain. The names of these genes often reflect particular traits that occur with mutation of the gene, as with the "zinc-finger" gene.

A different and unique combination of homeobox-containing genes is expressed in each of the rhombomeres. In the top part of Figure 3-5, the extent of each black bar indicates the part of the brainstem in which activity for the particular gene listed at the left has been detected. For example, the *Hox 2.8* gene is active in a long area extending from the 2–3 rhombomere boundary caudally through the caudal-most part of the brainstem, whereas the *Krox-20* gene has two discrete areas of activity, one in rhombomere 3 and the other in rhombomere 5. The total pattern of gene activity thus forms a bar code or fingerprint-like profile that is unique for each individual rhombomere.

Whether the combined activity of these genes determines the specific identity of each rhombomere, the cranial nerve nuclei within the rhombomere, or both has not yet been established, however. During embryological development, following the main stage of neuronal proliferation, the neuron cell bodies that form the motor nuclei of cranial nerves migrate caudally within the neural tube to reach their final rhombomeric positions. Motor neurons of the seventh, ninth, and tenth cranial nerves and some of the neurons of the fifth and lateral line cranial nerves migrate over distances of one to three rhombomeres. How the activity of the regulatory genes specifies the various pools of motor nerve neurons in relation to the rhombomeric segments is thus unclear.

In the midbrain and forebrain, a number of similar homeobox-containing genes specify the mesomeres and prosomeres. These include genes referred to as the *engrailed* homologue, *En-2*, as well as *Krox-20* in the midbrain and as *Wnt-1*, *Wnt-3*, *Wnt-3A*, *Wnt-4*, *Dix-1*, *Dix-2*, *Nkx-2.2*, and so on, in the forebrain. Many of the same genes also specify brain development in invertebrates, such as *Drosophila*.

Neurogenesis and Migration of Neurons

As the neural tube differentiates rostrocaudally, it also differentiates into dorsal and ventral regions due to the actions of other regulatory genes. After closure of the neural tube [Fig. 3-7(A,B)], the underlying notochord produces the signaling factor Sonic hedgehog [Fig. 3-7(C)], which induces the differentiation of a specific group of cells in the ventral midline of the neural plate, called the **floor plate**. These cells then also produce Sonic hedgehog, which promotes a ventral fate for the ventral part of the neural tube. This ventral half of the neural tube becomes the **basal plate**, which contains motor neurons. Other signaling molecules—bone morphogenic proteins (BMPs)—arise from the ectoderm dorsally and later from the **roof plate**, which comprises cells in the dorsal part of the neural tube itself. BMPs antagonize Sonic hedgehog and promote a dorsal fate. Under their influence, the dorsal part of the neural tube becomes the **alar plate**, which is sensory in nature. Even though BMPs can suppress any neural fate for the ectoderm of the gastrula, as discussed above, they also can act here, in lower concentrations, to promote alar plate formation.

Outside the neural tube, in the presence of slightly higher levels of BMPs, additional populations of neurogenic cells give rise to the neurons of the peripheral nervous system. In the body and the head, cells that initially lie between the neural tube and the surface ectoderm, the **neural crest** [Figs. 3-3 and 3-7(A,B)], contribute to many diverse tissues, including the flat bones of the skull, the so-called visceral arches of the jaw, hyoid and gill/throat regions, cells of the adrenal medulla, and melanocytes, and also give rise to sensory and motor neuron cell bodies of the peripheral nervous system. In the head, specific areas of ectoderm, called **neurogenic placodes**, lie lateral to the neural crest and also contribute neurons to the sensory ganglia of cranial nerves. The neural derivatives of both neural crest and neurogenic placodes are considered in detail in the later chapters that cover the cranial nerves.

Within the neural tube, the central nervous system is formed by a complex process that begins with the genesis of glial cells and neurons [Fig. 3-7(D)]. Cell proliferation occurs primarily within the **ventricular zone**, which encircles the ventricular lumen. Astrocytes are produced from the earliest stages. These astrocytes are called **radial glia**, since they assume an elongated shape and span the width of the tube in a radial array from the **luminal surface** of the ventricle to the **abluminal surface** at the peripheral surface of the neural tube. As neuron cell bodies are produced, they migrate away from the region of the lumen along the shafts of the radial glia. In fact, the developing neurons produce a morphogen that maintains the radial shape of these glial cells. After neurogenesis ceases, the astrocytes can then assume the star shape for which they are named.

The degree of luminal-abluminal, or radial, migration differs markedly among different vertebrates and in different regions of the brain. The pattern of migration also varies, with nuclei and cortices being formed in different ways. In this section, we will briefly examine some of the various ways in which the neurons are assembled into structures within different regions of the brain and among different groups of vertebrates. The developmental processes involved in producing

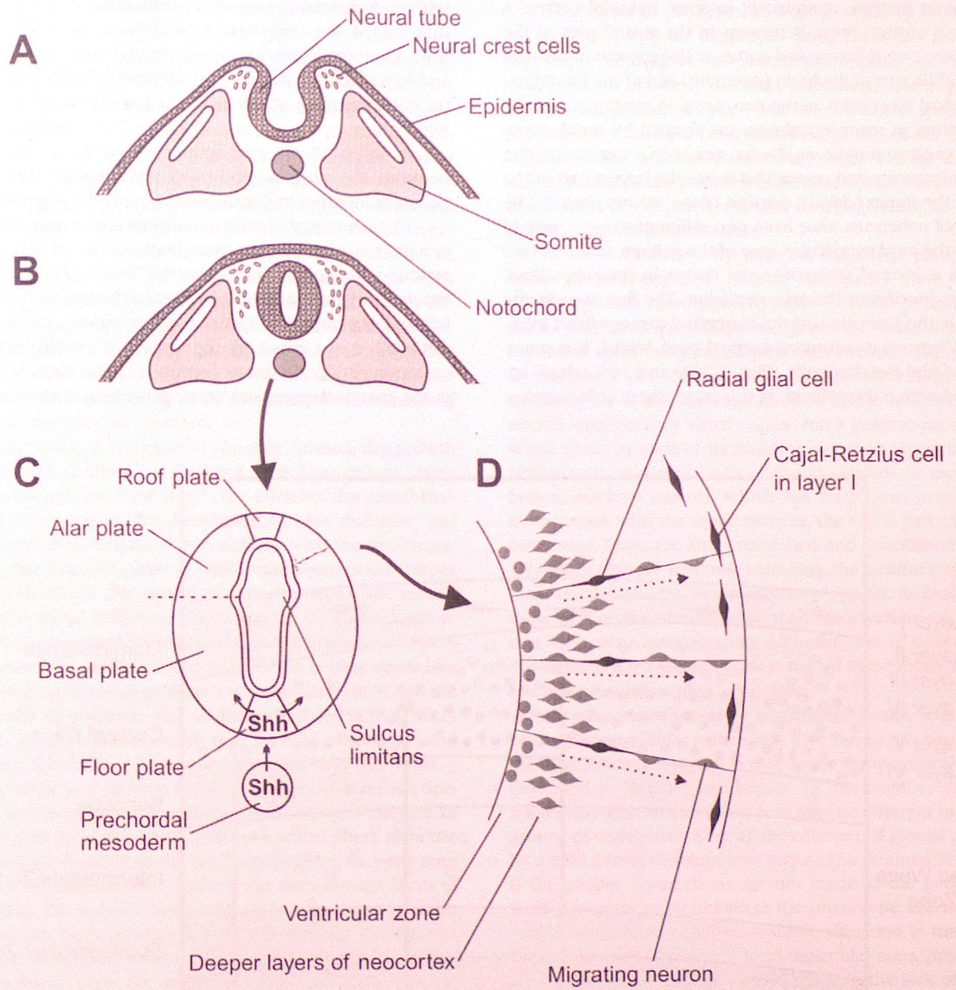

FIGURE 3-7. Drawings of the upper part of transverse sections through the developing vertebrate body (A and B), as can be compared with Fig. 3-3, to show the position of the closed neural tube (B), notochord, and neural crest cells. C: Drawing of a transverse section through the developing brain as it receives the Shh signal from the underlying prechordal mesoderm and, in turn, its own floor plate. A single radial glial cell and migrating neurons are shown in the right alar plate. The latter process is drawn in D at a higher magnification and for the special case of mammalian neocortex, with generated neurons migrating along the radial glial cells. Note that, in D, several layers that lie between the ventricular zone and the deeper layers of neocortex are omitted. The details of this region, including these layers, are shown in Fig. 3-8.

the individual neurons and their connections are complex and also subject to disruption by both local factors and more external influences. The timing of sequences in multiple groups of neurons must be properly phased for normal development to occur. The production and migration of populations of neurons to form nuclei and cortices also occurs in specifically timed sequences, since targets must be established for the growing, incoming axons to locate and reach.

Cortices and Nuclei

As discussed in Chapter 2, two basic structural patterns for populations of neurons are **cortices**, which are laminated structures that tend to be located in the more dorsal, alar plate parts of the brain, and **nuclei**, which are prevalent in both the alar and basal plates. Nuclei may consist of diffusely scattered, either loosely or more tightly packed cells or of cells aligned

in a laminar pattern, reminiscent in some cases of cortex. A number of cortical areas is present in the rostral part of the brain in some vertebrates, and cortex is also present in the roof of the middle part of the brain (midbrain) and of the hindbrain.

Cortical areas such as the neocortex in mammals and the optic tectum in many vertebrates are formed by serial migrations of generated neurons. Neocortex is an extensive region of generally six-layered cortex that forms the largest part of the pallium, the upper (dorsal) portion of the telencephalon. The neurons of neocortex arise from two different sources, one of which is the local ventricular zone of the pallium and the other of which is located external to the cortex in the subpallium, the lower portion of the telencephalon. The first step in the process is the formation of the **marginal zone**, which eventually becomes the outermost cortical layer, layer I. It is populated by **Cajal-Retzius cells** [Figs. 3-7(D) and 3-8], which are generated within the pallium. At this stage, these cells together with early-generated neuronal precursors form a single structure, called the **preplate**. Subsequently, generated neurons from the ventricular zone pass through the **subventricular** and **intermediate zones** (Fig. 3-8) and split the preplate into the definitive marginal zone and the lower layer of the preplate, which is now called the **subplate**. The **cortical plate**, in which layers VI–II of neocortex form, thus comes to lie between the marginal zone and the subplate. The subplate becomes incorporated into layer VI as its deep portion.

The neurons that arise in the ventricular zone and migrate radially into the cortical plate become the excitatory, glutamatergic components of the cortex. Within the cortical plate, the deeper-lying neurons are produced before the more superficially lying ones. This pattern of migration is called "**inside-out**" and is the result of the action of **reelin**, which is a patterning molecule that is produced by the Cajal-Retzius cells in the marginal zone, and other patterning molecules. Reelin

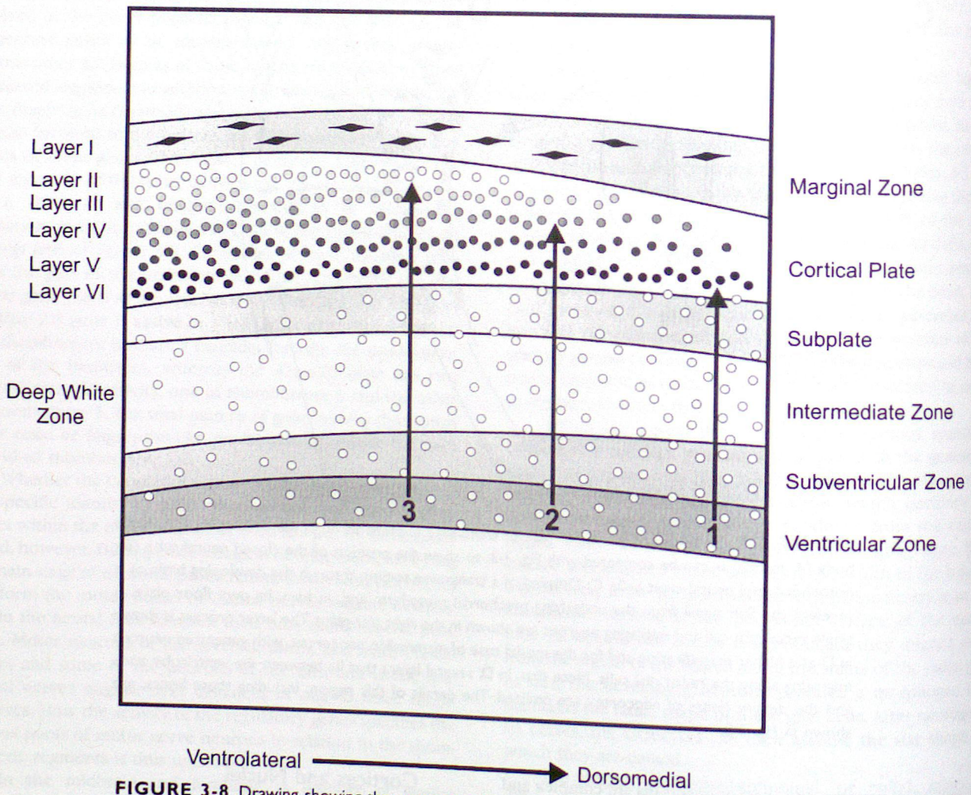

FIGURE 3-8 Drawing showing the progressive formation of neocortical layers VI–II within the cortical plate, with the neurons that form the deepest layer, layer VI, being generated earliest (arrow 1), those in the intermediate layers V–III generated subsequently and in deep to superficial order (arrow 2), and the most superficial layer, layer II, generated last (arrow 3). Cajal-Retzius cells are shown in the marginal zone, which becomes layer I. Neurons migrating radially into the cortical plate stop when they encounter the reelin signal produced by the Cajal-Retzius cells. The drawing reflects the ventrolateral (left) to dorsomedial (right) gradient of maturation of the neocortex.

inhibits the migration of the newly produced neurons. Thus, as those that will form layer VI pass through the subplate, they encounter the reelin signal and stop migrating. The layer V neurons subsequently pass through the subplate and the layer VI neurons, then encounter the reelin signal, and stop migrating. Layers IV–II are formed in a like manner. As corticogenesis comes to an end, most of the cells in layer I die off and disappear, resulting in its being an almost cell-free zone.

In addition to the neurons that arise from the ventricular zone and migrate radially to form the five main cellular layers of the neocortex, other neurons arise from the subpallium. The subpallium produces several populations of precursor neurons that migrate tangentially into the cortical plate and become the GABAergic, inhibitory neurons of the cortex. Some of these neurons migrate for substantial distances to reach the more dorsomedial cortical regions. Unlike the radial migration of the glutamatergic neurons along radial glial cells, the mechanics of tangential migration are obscure.

As the layers of the cortical plate are formed, the growth of axons and dendrites is initiated, and connections, both distant and local, are established. The nuclei of the dorsal thalamus (that lies within the diencephalon) have extensive and for the most part reciprocal connections with the neocortex. The subplate neurons, some of which contribute to the deeper part of layer VI, are the first to give rise to axons that extend toward the dorsal thalamus. They meet the ascending thalamocortical axons part of the way along, and the two sets of fibers interdigitate. The meeting and interdigitation being essential for the eventual completion of these pathways has been called the **handshake hypothesis**. The ascending and descending fibers use each other as guides, much as if you slid your right hand along your left wrist and up your left sleeve, and vice versa.

The distal end of each in-growing afferent axon is a specialized structure called a **growth cone**, which is the site of elongation of the axon. As the thalamocortical fibers from the various dorsal thalamic nuclei reach the pallium, they use cues from the subplate neurons to recognize their correct locus of termination. The axons arrive before their main target cell layer (layer IV) has been generated, but they wait for these target cells to be formed and do not grow beyond that area. However, if the subplate cells are selectively destroyed, the arriving dorsal thalamic axons do not halt in the proper position but continue growing beyond their normal area of termination and on into adjacent, unrelated areas of cortex. The subplate cells thus seem to provide a necessary signpost for the growth cones of the afferent dorsal thalamic axons.

There is a high degree of specificity in the connections of cortical structures, made possible by their geometric configuration. Different afferent axons terminate on different, specified parts—superficial to deep—of the dendritic trees of the cortical neurons. The entire area of a given cortical region is also frequently in receipt of specifically ordered projections, so that the point-to-point mapping of sensory or motor space from the external world of the animal is mapped in order onto the cortex. In-growing axons may sometimes form connections in the wrong location with reference to the map, but these axons later retract and then form connections in the place that is congruent with the map of external space. These adjustments occur as sensory information comes over the afferent axons and into the cortex.

The nuclei in the brain, as well as some of the cortices, are formed by cellular migrations along radial glia that mostly proceed in an "**outside-in**" pattern, the opposite of that in the neocortex. In this case, the more superficial, lateral groups of neurons are generated first. There are additional spatiotemporal gradients that have been identified in the dorsal thalamus. Caudal nuclei develop earlier than more rostral ones, and ventral nuclei develop earlier than more dorsal ones. Thus, different areas of the periventricular matrix give rise to different sets of nuclei at different times.

While nuclei form by different migration patterns than those of neocortex, a number of nuclei have point-to-point maps that correspond to those found in neocortex. The nuclei that have such maps are generally those that project to or have reciprocal connections with cortical, mappe[illegible] In mammals, for example, the **dorsal lateral gen[illegible] nucleus**, the dorsal thalamic nucleus that is reciproca[illegible] nected with primary visual cortex, has a point-to-point visual space in each of its multiple, separate layers of similar map is present in a midbrain nucleus of man[illegible] brates, **nucleus isthmi**, which has reciprocal, point-to-point connections with the **optic tectum**, the visual part of the midbrain roof. Maps are also established and maintained in other ascending sensory systems, including the auditory and lateral line systems and the somatosensory system. Axonal connections throughout the brain depend on a variety of guidance mechanisms to form correctly. As in the case of neocortex discussed above, the growth cone at the tip of the elongating axon is a crucial site for these processes.

As nuclei are formed by migrations of cells, some regions of the periventricular matrix may give rise to one or more specific nuclei. Such a region is called a **developmental field** (as discussed in Box 1-1 in Chapter 1). The number of distinct nuclei that arise from a given field may be different in different groups of vertebrates. Also, all the cells or cell groups produced by a field during development may not be retained in the adult if the proper connections are not made at the proper time. Such occurrences would affect the phenotype and may play a role in evolutionary change. A subtle alteration in timing or in the presence or absence of local molecular cues, produced by a mutation in the genome, could result in the lack of a particular cell group in the adult and/or the appearance of a "new" cell group with new connections. The concept of field homology applies to such situations and was discussed in Chapter 1.

Differing Patterns of Development

Within each of the major groups of vertebrates, one marked difference in brain development is present that will be discussed in detail in Chapter 4—that of wide variation in the degree of radial migration of neurons, both cortical and nuclear, away from the periventricular matrix. Those vertebrates in which relatively limited migration occurs, that we have designated as Group I, include some species from each of the four major vertebrate radiations: lampreys, some cartilaginous fishes, some ray-finned fishes, and some sarcopterygians (fleshy lobed-finned fishes and their tetrapod descendants). In contrast, hagfishes and other species in each of the three radiations of jawed vertebrates (Group II) have much more extensive migration of neurons and the formation of multiple,

BOX 3-1. What Is "Neo" About Neocortex, and What Is "Iso" About Isocortex?

The large portion of the cerebral cortex of mammals that generally exhibits six cell-and-fiber layers is variously referred to as "neocortex" or "isocortex." Neither term has the cachet of being entirely satisfactory. The former term originally was proposed in the mistaken belief that this cortex is evolutionary new, i.e. more recently evolved, than the remaining parts of the cerebral cortex, the "archicortex" (hippocampal pallium) and the "paleocortex" (olfactory cortices). The prefixes "archi" and "paleo" both mean old. These parts of the cerebral cortex generally exhibit three layers but include the so-called transitional cortices that have four to five layers.

The term "isocortex" subsequently was proposed as an alternative term to neocortex. "Iso" means "the same" or "equal." The complementary term "allocortex," meaning "different cortex," refers to the olfactory and hippocampal cortical regions, including the transitional cortices. The term isocortex has not been universally adopted and is not an accurate descriptor, however. As a global term, it grammatically begs for a comparison: the same as what? As an intraregional term, it is incorrect. All of the cortical areas that it refers to are not uniformly composed of six cell-and-fiber layers. For example, some regions are called agranular cortex because they lack the granule cells that comprise layer IV in other regions. Additionally, marked differences in cytoarchitecture (cell architecture, sometimes called cytoarchitectonics) and in myeloarchtecture (fiber architecture) occur across different regions. The German neuroanatomist Korbinian Brodmann based his identification, published in the first decade of the 20th century and now widely used, of dozens of different areas on these differences. These very differences also agrue against the use of Brodmann's own alternative term, "homogenetic cortex," for neocortex, which has never enjoyed wide acceptance.

In the sense of being evolutionarily more recent than archicortex or paleocortex, we agree that neocortex is not an accurate term. On the other hand, in terms of generally having six layers, this region of the pallium is uniquely mammalian and was a new innovation that occurred at or about the origin of mammals. In this sense of being a novel feature of mammalian brains, the term neocortex is legitimate. Also, with the declining use of the terms paleocortex and archicortex, the relative age of these cortices is a less salient issue. We used the term "isocortex" in the first edition of this book, but, for the reasons discussed here, we have decided to use "neocortex" in this second edition. It strikes us as highly ironic that a fully satisfactory, phylogenetically neutral, and accurately descriptive term for the hallmark of the mammalian brain remains elusive.

distinct layers in cortical structures as well as a greater number of discretely recognizable and larger nuclei. Two other major differences in the development of the brain among different vertebrates will be considered in this chapter. These developmental differences result in marked differences in the organization of the telencephalon.

In the initial phase of development from the closed neural tube, the telencephalon develops by a process called **evagination** in most vertebrates, including lampreys, cartilaginous fishes, amphibians, and amniotes. The central lumen of the neural tube enlarges to form the telencephalic ventricles as the telencephalon bulges outward and expands, that is, evaginates. This process is shown in Figure 3-9(A). After evagination, the part of the pallium that was originally in the most dorsomedial position (A) around the central lumen comes to lie in the most medial part of the telencephalon. This pallial area forms the hippocampal formation (the functions of which include memory and emotion) in the adult. The originally intermediate pallial area (B) becomes the dorsal pallium, which forms part or all of the major sensory, integrative, and motor pallial areas in the adult. The originally ventrolaterally-lying pallial area (C) comes to lie most laterally and gives rise to the olfactory, or lateral, pallium. A fourth pallial area, the ventral pallium, has recently been recognized in amniotes. It has been combined with the lateral pallial region in Figure 3-9 for simplicity.

In contrast, a different process takes place in the development of the telencephalon in ray-finned fishes. The areas in the basal part of the telencephalon are similarly aligned in all vertebrates, but the pallium undergoes a process called **eversion**. The part of the roof of the neural tube over the central lumen thins and elongates, and the pallial parts of the hemispheres bend outward [Fig. 3-9(B)]. After eversion, the originally most dorsomedial part of the pallium (A) comes to lie in the most lateral, or distal, position in the telencephalon. The originally intermediate part of the pallium (B) lies most dorsally, as in other vertebrates. The originally most ventrolateral pallial area (C) comes to lie in the most medial, or proximal, position in the telencephalon of the adult. Thus, in comparison with other vertebrates, the mediolateral positions of the hippocampal (A) and olfactory (C) pallial areas are reversed in the ray-finned fishes. The process of eversion reverses the topography of the pallial areas (A-B-C-D to D-C-B-A) but preserves the ordinal sequence of the regions—the topology (A-B-C-D or D-C-B-A as opposed to a disarranged sequence such as C-D-B-A). As discussed in subsequent chapters (see Chapter 25), whether this topographical reversal with preservation of topology actually occurs in the pallium of all or even some ray-finned fishes remains a matter of continuing investigation and debate.

A second major difference in telencephalic development occurs between the mammals on one hand and the nonmammalian amniotes on the other. In both mammals and sauropsids (reptiles and birds), the pallium evaginates as diagramed in Figure 3-9(A). However, how various regions of the pallium

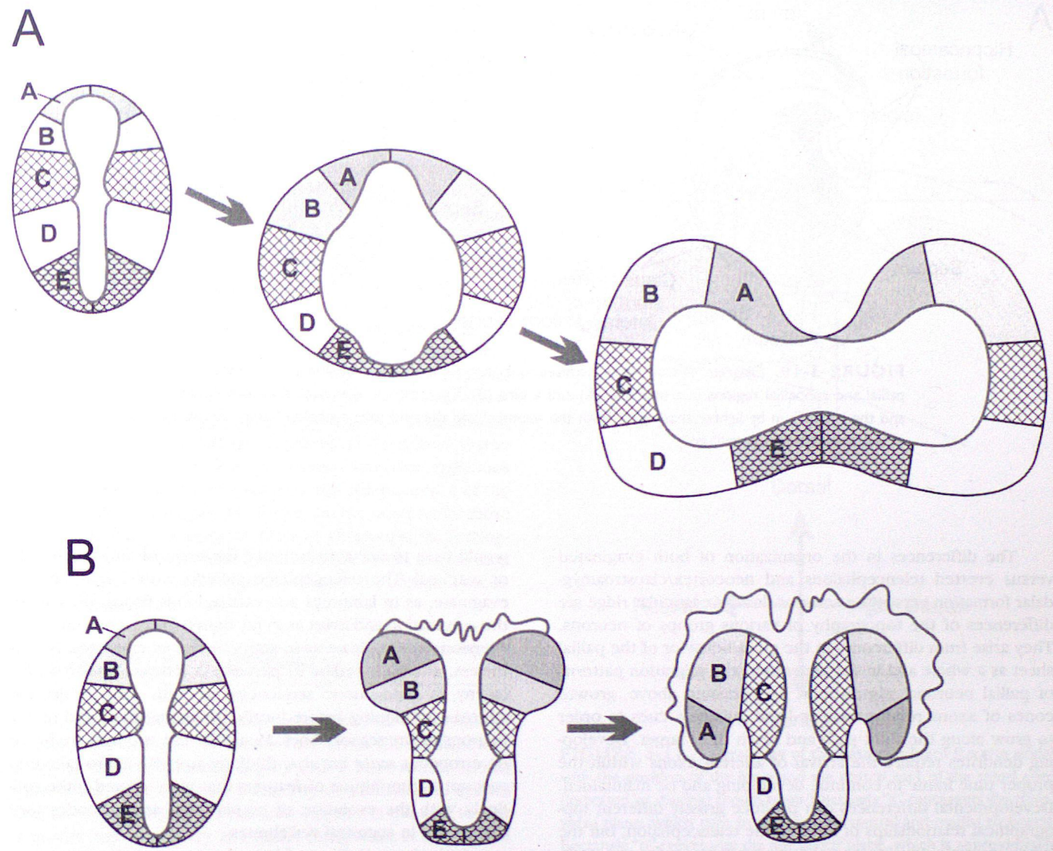

FIGURE 3-9. A: Diagram of the process of evagination in forebrain development, as occurs in most groups of vertebrates. B: Diagram of the process of eversion in forebrain development, as occurs in ray-finned fishes. In both sets of drawings, the ventricular surface is indicated by a gray line for ease of comparison between the evaginated and everted conditions. To emphasize the relative topological relationships, fewer divisions of the hemisphere are shown than actually exist. For example, the area labeled C consists of two pallial regions.

compare between them is still very much a matter of debate. In mammals [Fig. 3-10(A)], the dorsal part of the evaginated pallium forms part or all of the six-layered neocortex, while other parts form the medial (hippocampal) and lateral (olfactory) cortices. In the deeper part of the ventrolateral pallial region lies the **claustroamygdalar formation**, which is also of pallial origin. It is composed of part of a diverse nuclear group called the amygdala and associated structures. In birds [Fig. 3-10(B)] and reptiles, part of the pallium forms the dorsal cortex, a cortical area between the medial (hippocampal) and lateral (olfactory) cortices. In birds, as shown in the figure, this region is called the **Wulst**, or the **hyperpallium**. Another part of the pallium forms a region that expands inward to form a large, nuclear area called the **dorsal ventricular ridge**. The anterior part of the dorsal ventricular ridge (ADVR) was long thought to represent a huge, subpallial telencephalic area for use in stereotyped motor behaviors, but subsequent connectional and histochemical studies eliminated that hypothesis from further consideration. These studies also indicated that the ADVR is homologous (as a collection of several embryologically derived fields) to several parts of mammalian neocortex. More recent findings, particularly from embryological studies, have suggested the alternative possibility that the ADVR is homologous to part or all of the claustroamygdalar formation. A third possibility is that the ADVR is homologous as a field to both the claustroamygdalar formation and parts of neocortex. These possibilities are discussed in much more detail in later chapters.

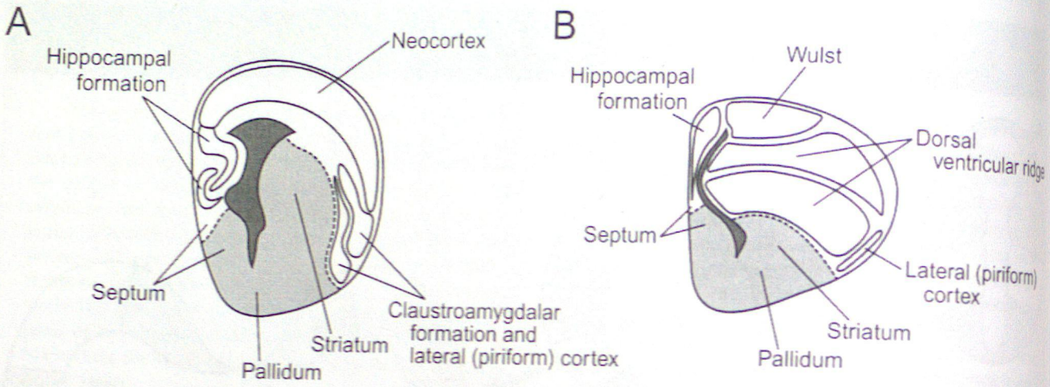

FIGURE 3-10. Diagram of transverse hemisections through the telencephalon to show the major pallial and subpallial regions in a mammal (A) and a bird (B). The ventricle is indicated by dark shading and the subpallium by lighter shading. In both the mammal and the bird telencephalon hemisections, all of the area in white is pallium.

The differences in the organization of both evaginated versus everted telencephalons and neocortex/claustroamygdalar formation versus the anterior dorsal ventricular ridge are differences of the topography of various groups of neurons. They arise from differences in the gross behavior of the pallial sheet as a whole and in the generation and migration patterns of pallial neuronal populations. As discussed above, growth cones of axons require various local guidance cues in order to grow along the right path and reach their target. Developing dendrites require the arrival of afferent axons within the proper time frame to continue developing and be maintained. Developmental differences can produce grossly different topographical relationships of areas in the telencephalon, but the other, multiple developmental factors necessary for the establishment of connections are generally unaffected and sufficient despite the alterations of topography in these cases.

Ontogeny and Recapitulation

In closing this section, there is one final aspect of brain development to consider briefly. One of the most pervasive of "old wives' tales" is the notion that ontogeny recapitulates phylogeny: in other words, that the developmental sequence is a kind of rerun of the species' evolutionary history. In the late 1800s, Haeckel promoted the idea that evolutionary change results from the addition of new ontogenetic stages to the terminal phase of the ancestor's development. Such **terminal additions** to existing sequences of development would be the basis of ontogeny recapitulating phylogeny. Terminal additions do, in fact, occur in phylogeny, but the sequence of development in vertebrate brains does not recreate adult ancestral stages of the species' evolutionary history.

From our analysis of differences in the development of the telencephalon, we can see that, for ontogeny to recapitulate phylogeny, particularly in terms of the now discredited *scala naturae* (see Chapter 1), a highly improbable series of events would have to occur to produce the brain of an adult reptile or mammal. The telencephalic pallium would first have to evaginate, as in lampreys and cartilaginous fishes, then undo the evagination and evert as in ray-finned fishes, then undo the eversion and evaginate as in amphibians and amniotes. Nevertheless, attempts persist to perceive a recapitulation of phylogeny in ontogenetic sequences, as with long projection neurons developing before locally projecting ones and motor neurons before sensory ones. Many of these attempts are based on erroneous *scala naturae* thinking and also fail to take into account the multitude of features that were gained quite suddenly with the evolution of neural crest and placodes (see Chapter 9) in ancestral vertebrates.

As in many incorrect ideas, there nonetheless is a grain of truth in the ontogeny-phylogeny idea. In the early 1800s, Karl von Baer realized that developmental sequences do not recreate stages from "lower" to "higher" groups of animals. He did note, however, that resemblances occur among embryos within a group, and that the resemblances decrease as development proceeds. von Baer concluded that those features that are common to a group appear earlier in development than the more specialized features of individual taxa within the group. Thus, in the development of the brain of a seagull, for example, we would expect features common to chordates to develop first, followed by features common to all vertebrates, and so on in sequence through features common to jawed vertebrates, sarcopterygians, tetrapods, amniotes, birds, and finally seagulls. von Baer thus believed that over evolution, there is conservation of a number of developmental stages. This concept is referred to as "**von Baerian recapitulation**," and a growing body of data supports it.

The von Baerian view makes sense when we note that adult phenotypes are produced by a series of ontogenetic sequences. Changes over evolution in the phenotype are the direct result of changes in the ontogenetic sequences, which in turn are produced by mutations established in the genome,

shifts in the timing during development of some events relative to others (**heterochrony**), and other developmental factors, as discussed in Chapter 1. Features that are common to all vertebrates, such as the neural tube, arise before more specialized features present only in one radiation, such as the dorsal ventricular ridge in nonmammalian amniotes. Given the complexity and interactions of developmental events, modifications in early sequences would have much more profound, and in most cases disruptive, effects than modifications in later sequences. The reduction of particular systems and the maintenance of neotenic (embryonic) characteristics in the adults of some groups may in fact result from relatively early modifications in the rates of cell proliferation, differentiation, and migration.

Although some of the later modifications constitute terminal or near terminal additions, the radiations of extant vertebrates have been separated long enough that such terminal additions reflect their independent histories rather than allowing for the construction of a single line of evolutionary history. Marked differences in the development of the telencephalon between as well as within the major vertebrate radiations clearly demonstrate the separateness and independence of the radiations over a long period of time. On the other hand, those features that are common to most or all groups, in developmental structures and sequences and in the adults, can be used to reconstruct the condition of the brain in the common ancestral vertebrate stock.

THE BRAIN AND SPINAL CORD

In the head region of early vertebrates, the elaboration of neural crest and placode tissues resulted in the formation of most of the paired sense organs and a new rostral (front) part of the head to house them. The central nervous system was likewise enlarged and elaborated so that is was able to play a greater role in sensory and motor integration. A new rostral part of the brain, called the telencephalon, was also added in which sensory information could be further analyzed, integrated, and remembered, allowing for sophisticated decision-making capabilities and for appropriate and learned motor responses to a variety of stimuli.

The central nervous system consists of the brain and the spinal cord. Figure 3-11 illustrates the location of the brain and the rostral end of the spinal cord in the head of an adult vertebrate, a lizard in this example, and demonstrates some of the standard terms of orientation (also see the Appendix). While the distinction between brain and spinal cord is of some importance in medical education and neurology, it suggests a much greater dichotomy of function than actually exists. Indeed, this subdivision is often confusing to newcomers to the neurosciences because it emphasizes the relatively few differences and directs attention away from the many similarities between the two regions.

The boundary between the brain and spinal cord is not nearly as sharp as some textbooks suggest, nor does it correspond precisely to the junction of the skull and the vertebral column (spinal column or backbone), which surrounds and protects the spinal cord. Although a substantial portion of the brain consists of unique structures that have no counterpart in

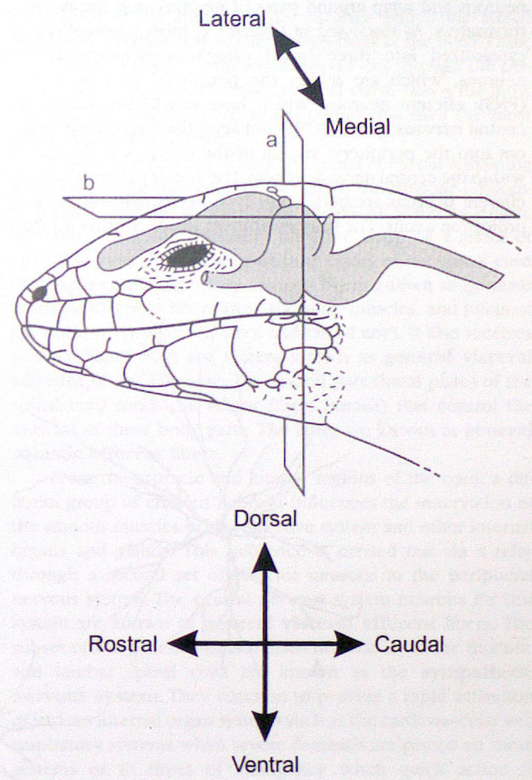

FIGURE 3-11. Lateral view of the head of a lizard (*Lacerta sicula*) with the position of the brain and the rostral part of the spinal cord (indicated by shading) shown *in situ*. Rectangle "a" represents the transverse plane, which runs from dorsal to ventral and medial to lateral. Rectangle "b" represents the horizontal plane, which is approximately parallel to the line of the mouth and runs from rostral to caudal and medial to lateral. The sagittal plane is parallel to the lateral view shown in the figure and runs from rostral to caudal and dorsal to ventral. Adapted from Senn (1979). Used with permission of Elsevier.

the spinal cord, much of the brain, especially its caudal region, is actually a continuation of the structures and general organization of the spinal cord.

The spinal cord is organized for the control of the body's limbs and trunk; similarly, the caudal brain is organized for the control of specialized structures in the head, such as the jaws, tongue, eye muscles and lids, and vocal organs. Moreover, the caudal brain and spinal cord share the task of control and regulation of the viscera, or internal organs, such as the heart, digestive system, and respiratory system.

CELLULAR ORGANIZATION OF THE CENTRAL NERVOUS SYSTEM

The cells in the brain and spinal cord are of two types: nonneural cells called glia, which fill in the spaces between

neurons and wrap around parts of neurons, and the neurons themselves. As discussed in Chapter 2, most neurons can be categorized into three broad categories—sensory afferent neurons, which are within the peripheral nervous system (PNS); efferent neurons, which have cell bodies within the central nervous system (CNS) but send their axonal processes out into the periphery; and all of the other neurons that lie within the central nervous system. The sensory afferent and the efferent neurons are both Golgi Type I cells, which have long projection axons. The sensory afferent neurons bring information about the internal and external environments into the central nervous system. The efferent neurons are motor or effector cells that carry (either directly or via a second neuron in the peripheral nervous system) instructions from the central nervous system to the body's effector organs, the muscles and glands. The third category—the vast majority of the neurons that constitute the CNS—consists of both Golgi Type I and Golgi Type II cells. The Golgi Type I cells are sometimes referred to as **projection neurons** and the Golgi Type II cells as local-circuit neurons or **interneurons** (Fig. 3-12).

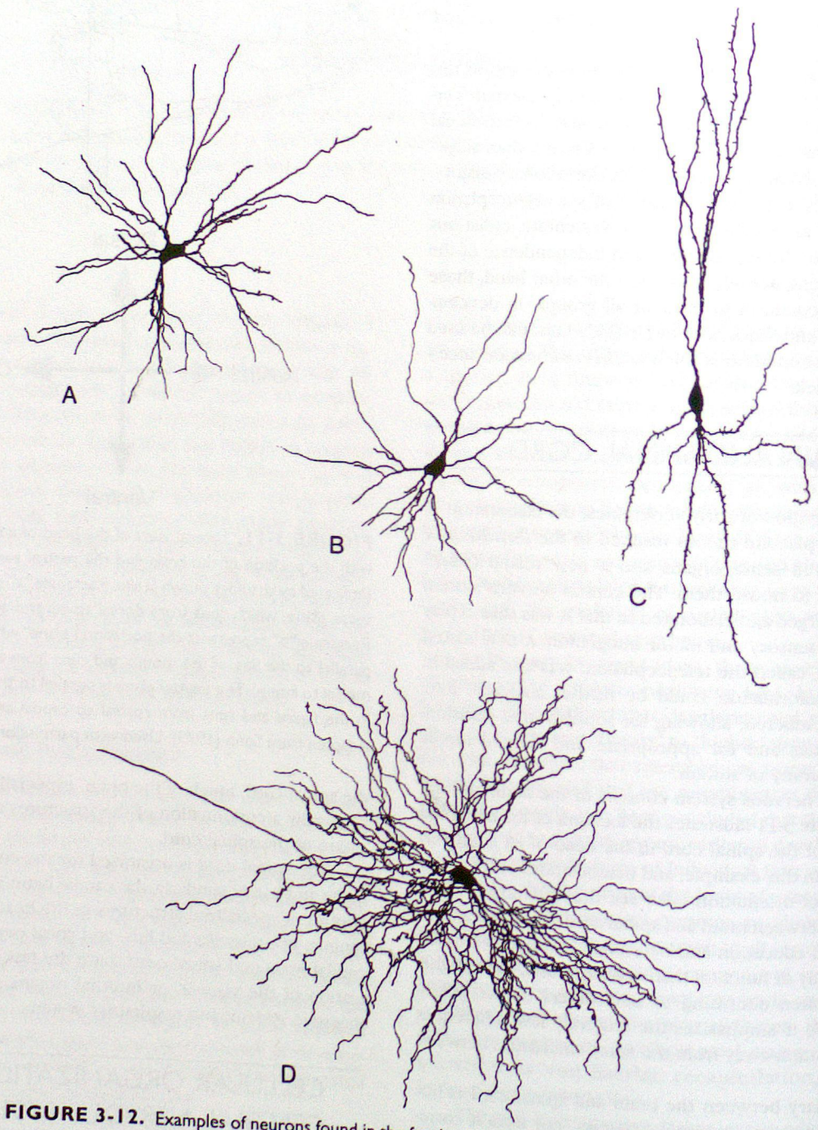

FIGURE 3-12. Examples of neurons found in the forebrain in various mammals, from the dorsal thalamus of a cat (A and B), after Robson (1993); from the cerebral cortex of a monkey (C), after Lund and Lewis (1993); and from the dorsal thalamus of a monkey (D), after Havton and Ohara (1993). Figures used with permission of John Wiley & Sons.

We should note that the terms "afferent" and "efferent" may be used in conjunction with the primary sensory and the motor or effector neurons, respectively, or in reference to the direction of information relay within the central nervous system. In the latter sense, afferent means "coming into," and efferent means "going out of." The axon of a Golgi Type I neuron that comes into and terminates within a specified neuronal population, which we will call A, is afferent to A. The axon of another Golgi Type I neuron that goes from A to a different neuronal population, which we will call B, is efferent from A and afferent to B.

The CNS intermediary neurons form a neural chain between the primary sensory afferent neurons and the efferent neurons. Rarely does a primary sensory neuron make direct contact with a motor neuron. Rather, a few or many thousands of other neurons typically receive the flow of information from sensory neurons into the central nervous system, process that information, and send the resultant outflow of instructions to muscles or glands via the effector neurons. The processing of information that is carried out within the CNS determines whether the instructions will be for action or for inaction and whether a response will be rapid or leisurely, vigorous or delicate, toward an object or away from it.

This general description of central nervous system organization applies to both the spinal cord and brain. The rostralmost parts of the brain have fewer primary sensory, afferent components and fewer effector, efferent components than are present in the brainstem. The rostral brain consists mostly of neurons arranged in a variety of specialized Golgi Type II local-circuit populations that are interconnected by long-axon, Golgi Type I projection neurons. Ascending projections from nuclei in the brainstem bring sensory information and also feedback information up to the rostral brain, and descending projections from the rostral brain carry its output. The heavy concentration of neurons in the rostral brain has served to focus attention on this region as the possible "executive" component of the central nervous system, with major responsibilities for decision making, memory, attention, communication, emotion, and other important, complex behavioral processes.

To summarize, the brain and spinal cord are organized to allow for the input of primary sensory information, the analysis and processing of the information, and the production and transmission of appropriate responses to the information. The axons of incoming, primary sensory, afferent neurons bring sensory information into the brain and spinal cord. Long-axon, projection (Golgi Type I) neurons carry this information between multiple nuclei and cortices. Short-axon, local circuit (Golgi Type II) neurons within nuclei and cortices are involved with processing the information. Additional sets of projection neurons carry the output for responses to the outgoing motor or effector neurons in the brain and spinal cord.

REGIONAL ORGANIZATION OF THE NERVOUS SYSTEM

The Spinal Cord

Both the brain and spinal cord can be subdivided into individual regions. The subdivisions of the spinal cord are named for regions of the spinal column through which the spinal nerves exit on their way to the various parts of the body. Thus, the region of the cord from which nerves exit through the cervical (neck) bones is called the **cervical cord**. This is the most rostral division of the cord and is continuous with the most caudal region of the brain.

Proceeding caudally within the spinal cord, the remaining divisions are the **thoracic** (chest) **cord**, the **lumbar** (abdominal) **cord**, and the **sacral** (pelvic) **cord**. All along its length, the spinal cord communicates with the body via a series of **spinal nerves**. The dorsal part (alar plate) of the spinal cord receives incoming, primary sensory fibers known as **general somatic afferent** fibers from the skin, muscles, and joints of the neck, body, limbs (if any), and tail (if any). It also receives sensory fibers from the viscera known as **general visceral afferent** fibers. Likewise, the ventral part (basal plate) of the spinal cord sends out motor fibers (axons) that control the muscles of these body parts. The latter are known as **general somatic efferent** fibers.

From the thoracic and lumbar regions of the cord, a different group of efferent neurons influences the innervation of the smooth muscles of the digestive system and other internal organs and glands. This influence is carried out via a relay through a second set of effector neurons in the peripheral nervous system. The central nervous system neurons for this system are known as **general visceral efferent** fibers. The subset of the general visceral efferents that lie in the thoracic and lumbar spinal cord are known as the **sympathetic nervous system**. They function to provide a rapid activation of various internal organ systems such as the cardiovascular and respiratory systems when severe demands are placed on these systems or in times of emergency when quick action is required. This system serves "fight or flight" and related responses.

The sympathetic nervous system is complemented by another general visceral efferent system, the **parasympathetic nervous system**, which is composed of visceral efferent neurons from the sacral division of the spinal cord and from the caudal regions of the brain. The parasympathetic system controls (via a second set of effector neurons in the peripheral nervous system) the same organs as does the sympathetic system, but it does so under normal conditions, when no special stresses are present. This system functions in promoting the digestion of food, allowing urination to occur, and other related, normal functions of the organs. Thus, when a high-demand situation arises, the sympathetic system takes control; when the high-demand situation ceases, control returns to the parasympathetic system. The sympathetic and parasympathetic systems together are known as the **autonomic nervous system**.

The Brain

Figure 3-13 is a drawing of the brain and rostral spinal cord of a vertebrate, in this case a ray-finned fish, which will serve as an example for the general organization of vertebrate brains. Each of the lobes and other swellings of the brain surface has a specific name, as briefly introduced above, such as the midbrain roof (tectum) or cerebellum. Groups of lobes or swellings are known by regional names, such as the mesencephalon

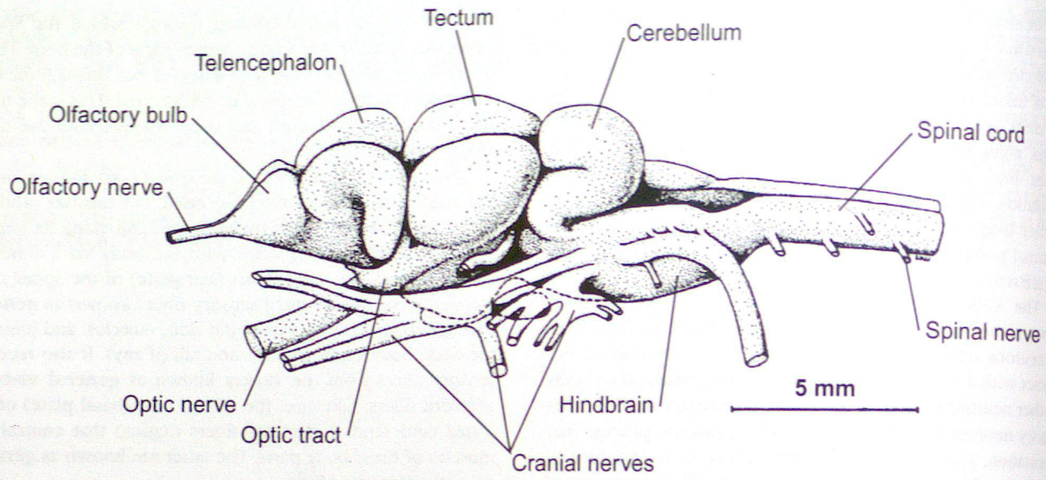

FIGURE 3-13. Drawing of a lateral view of the brain of a ray-finned fish, the longnose gar (*Lepisosteus osseus*). Rostral is toward the left. Adapted from Northcutt and Butler (1976).

(midbrain). Still more-encompassing regional names are used, such as forebrain and brainstem.

The nerves entering and leaving the brain are the **cranial nerves**. Like the spinal nerves, the cranial nerves carry primary sensory afferent axons (mainly from the head rather than the body) into the central nervous system and the axons from motor or effector efferent neurons that control the muscles and glands of the head and neck. Although these nerves are given special names, such as trigeminal nerve or oculomotor nerve, the organization of at least some of them is essentially the same as that of the spinal nerves. Moreover, some of the neuronal populations (nuclei) of the more caudal cranial nerves are directly continuous as a cell column with equivalent cell populations in the spinal cord.

Hindbrain. The caudal-most region of the brain is the **rhombencephalon**, or **hindbrain**, which comprises the **myelencephalon**, or **medulla oblongata**, and the **metencephalon**, which consists of the **pons** and **cerebellum**. The cranial nerves of this area include motor efferents that innervate the muscles of the jaws and the superficial facial muscles, such as those of the lips, cheeks, and forehead, the muscles of the tongue (where present) and throat, and one of the extraocular muscles of the eyeball. They also include components that comprise most of the cranial division of the parasympathetic nervous system. On the sensory side, some senses that traditionally have been called "special senses" are represented by cranial nerves that enter the brain at this level. Such special senses are those that are unique to the head region, such as hearing and the sense of balance and acceleration (vestibular sense). Other so-called special senses, not present in all vertebrates, include the lateral line system for the detection of water displacement over the body surface and of electric fields in the aquatic environment and the infrared (IR) sense for the detection of body heat radiated by other animals. The general senses of touch, position, temperature, and pain for much of the head region are also afferent to hindbrain sensory nuclei.

In addition to the nuclei associated with some of the cranial nerves, the medulla and pons contain other nuclei and a number of fiber tracts. Many of the fiber tracts are long pathways between the spinal cord and the more rostral parts of the brain, while others are shorter and run between nuclei within this area. Some of the cell populations in the medulla and pons are more widely scattered and diffuse than most other nuclei in the brain. These scattered populations are collectively referred to as the **reticular formation**. The nuclei of the reticular formation are involved in integrating inputs from a variety of sources, including the cranial nerve nuclei and more rostral parts of the brain. The reticular formation regulates and modulates activities elsewhere in the brain on the basis of the incoming information. A transverse section through the hindbrain in a fish (Fig. 3-14) illustrates the distribution of nerve cell bodies within this part. Fiber tracts run in the areas in which there are few or no cell bodies. Closely related to the pons, both geographically and functionally, is the cerebellum (Fig. 3-13). The **cerebellum** is a cortical structure in the roof of the hindbrain. Among its other functions, the cerebellum is involved in balance, coordination, and the smooth execution of rapid movements.

Midbrain. The next major subdivision of the brain is the **mesencephalon** or **midbrain**. The most prominent external feature of this area in most vertebrates is the roof of the midbrain, or **tectum** (Fig. 3-13). This structure is also often referred to as the **optic lobe**, or **optic tectum** (Fig. 3-14), due to the large number of neurons of the optic nerve that terminate within its superficial layers. The ventral portion of the mesencephalon, the region underneath the tectum, is known as the **tegmentum**. The mesencephalic tegmentum contains a number of nuclei and fiber tracts, including the nuclei of two motor cranial nerves that innervate most of the extraocular muscles for control of eye movements. The operation of the intraocular eye muscles, which mediate constriction of the pupil and the focus of the lens, is controlled from this

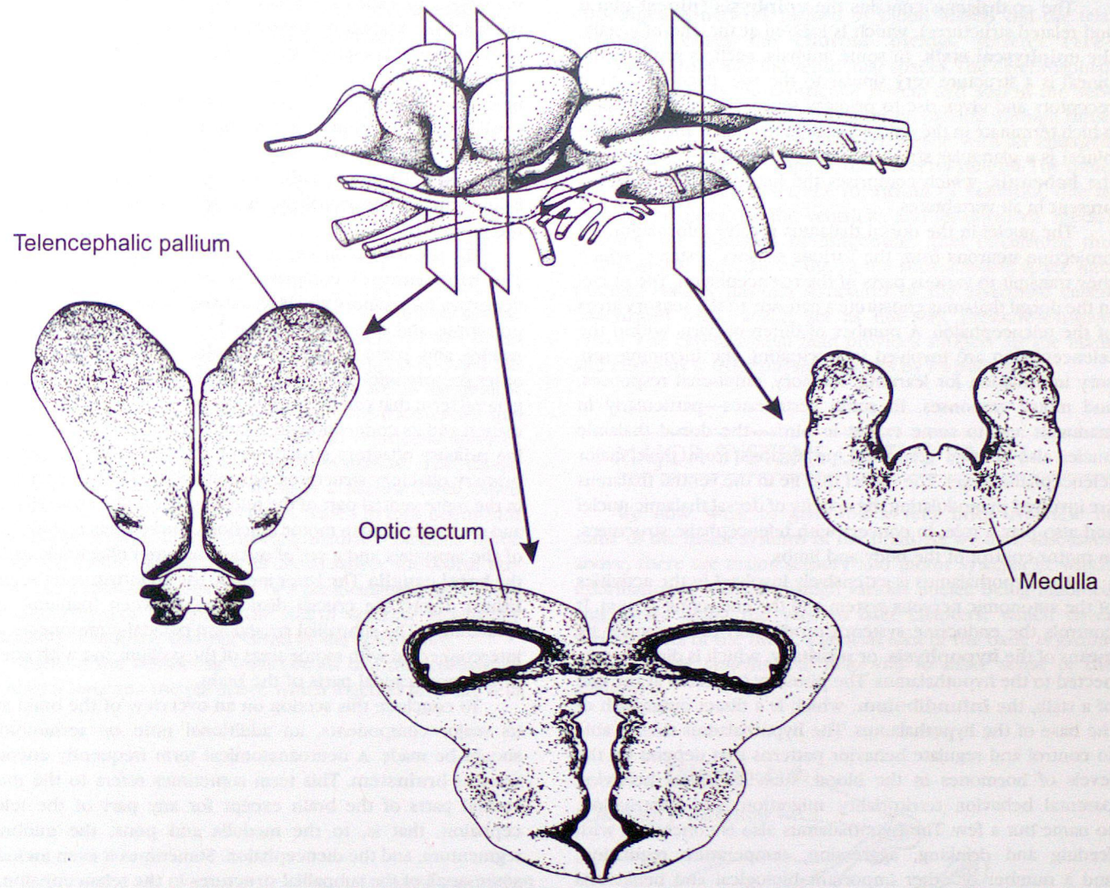

FIGURE 3-14. The brain of the longnose gar, as shown in Figure 3-13, with transverse sections through the telencephalon, midbrain, and hindbrain. Adapted from Northcutt and Butler (1976).

region as well via parasympathetic efferent fibers. The midbrain does not directly receive any afferent cranial nerve components.

Forebrain. The **prosencephalon**, or **forebrain**, is the most rostral division of the brain. It contains two major parts: the **diencephalon** and the **telencephalon** (Fig. 3-13). The diencephalon, not labeled in the figure, lies rostral to the midbrain, caudal-ventral to the telencephalon, and medial to the axons that form the optic tract, the central nervous system continuation of the optic nerve. The diencephalon is a large division composed of six principal areas. The caudal part of the diencephalon contains a dorsal area called the **pretectum** and a more ventral area called the **posterior tuberculum**. More rostrally, four areas are present. In dorsal to ventral sequence, these areas are the **epithalamus**, the **dorsal thalamus**, the **ventral thalamus**, and the **hypothalamus**. Each of these areas is composed of a number of nuclei, and there are also major fiber tracts that pass through this region. In contrast to the midbrain, the forebrain receives sensory afferent information and does not give rise to any cranial nerve effector components.

A number of the nuclei in the pretectum receive visual input from the retina and are involved in visuomotor behaviors. Pretectal nuclei and other visually related nuclei in the tegmentum influence eye movements (via midbrain and hindbrain motor nuclei) in relation to prey and predator detection and to orientation of the body within space. The posterior tuberculum consists in part of a medially lying nucleus that contains neurons involved in regulating motor functions. In ray-finned fishes, more laterally lying nuclei of the posterior tuberculum are also present. These nuclei relay sensory inputs (from hindbrain sensory nuclei) to the telencephalon. Similar nuclei may be present in cartilaginous fishes, but migrated posterior tubercular nuclei have not yet been identified in amphibians or land vertebrates.

The epithalamus contains the **epiphysis** (**pineal gland** and related structures), which is located at the end of a stalk, the **epiphyseal stalk**. In some animals, such as reptiles, the pineal is a structure very similar to the eye. It contains light receptors and gives rise to primary sensory afferent neurons, which terminate in the epithalamus. In mammals and birds, the pineal is a glandular structure. The epithalamus also contains the **habenula**, which comprises the habenular nuclei and is present in all vertebrates.

The nuclei in the dorsal thalamus receive information via projection neurons from the various sensory systems, which they transmit to various parts of the telencephalon. The nuclei in the dorsal thalamus constitute a gateway to the sensory areas of the telencephalon. A number of different parts within the telencephalon are involved in integrating the incoming sensory information for learning, memory, emotional responses, and motor responses. In some vertebrates—particularly in mammals and to some extent in birds—the dorsal thalamic nuclei also receive reciprocal projections from their major telencephalic target. The nuclei that lie in the ventral thalamus are involved in modulating the activity of dorsal thalamic nuclei and also play a role, in concert with telencephalic structures, in motor control of the body and limbs.

The hypothalamus is extensively involved in the activities of the autonomic nervous system and the endocrine system. It controls the endocrine system's production of hormones by means of the **hypophysis**, or **pituitary**, which is directly connected to the hypothalamus. The pituitary is located at the end of a stalk, the **infundibulum**, which is a direct outgrowth of the base of the hypothalamus. The hypothalamus thus is able to control and regulate behavior patterns that depend on the levels of hormones in the blood, such as sexual behavior, parental behavior, territoriality, migration, and hibernation, to name but a few. The hypothalamus also is concerned with feeding and drinking, aggression, temperature regulation, and a number of other important biological and behavioral functions.

The most rostral region of the brain, the **telencephalon** (Figs. 3-13 and 3-14), includes an upper part, the **pallium**, which includes the **cerebral hemisphere** (also called the **cerebrum**). At the rostral end of the cerebrum is the **olfactory bulb**, in which axons of olfactory receptor cells in the nasal mucosa terminate. In animals in which the sense of smell is highly developed, such as some sharks and bloodhounds, the olfactory bulb is rather impressive in size. In animals such as many birds and some mammals, in which the sense of smell is not especially important for survival, the bulb is relatively small in comparison. The olfactory bulb projects to the olfactory part of the pallium in the telencephalon via **olfactory tracts**, which can be short if the olfactory bulb lies adjacent to the telencephalon (as in the brain of the fish shown in Fig. 3-13) or elongated.

The cerebrum itself has a relatively smooth surface in most vertebrates. It is composed of nuclear areas in some vertebrate groups, such as cartilaginous and most ray-finned fishes; in other vertebrate groups, particularly tetrapods, it is composed of both nuclei and cortex. In some animals, mostly among the mammals, although there are other instances as well, the surface of the cerebrum develops ridges and valleys known as convolutions. The ridges are called **gyri** (singular = **gyrus**) and the valleys are called **sulci** (singular = **sulcus**). The deepest of the sulci are known as **fissures**. Among mammals, gyri and sulci tend to be present in those species within each genus that have larger body and brain size in absolute terms, and these hemispheres are described as **gyrencephalic**. In contrast, the smaller species within each mammalian order have few or no gyri and sulci. The smooth surface of their hemispheres is described as **lissencephalic**. Most of the surface of the cerebrum, whether lissencephalic or gyrencephalic, is occupied by the neocortex.

The telencephalon also includes several other major areas. The **hippocampus** comprises several cortical regions; it is necessary for memory and is also involved in emotion. The hippocampus and some nuclei related to it, including the **septal nuclei** and parts of the **amygdala**, receive olfactory and other sensory information. The adjective **limbic** is a somewhat general term that can be applied either to the hippocampal formation and its connectionally related structures but not including primary olfactory structures or to both hippocampal and primary olfactory structures. Several additional major areas lie in the more ventral part of the telencephalon, the **subpallium**, and are involved with motor functions. These areas include part of the amygdala and a set of nuclei that are collectively called the **basal ganglia**. The latter include the **striatum** and the **pallidum**. (Note the crucial distinction between "pallium" and "pallidum.") The subpallial striatal and pallidal components are interconnected with motor areas of the pallium and with nuclei in the more caudal parts of the brain.

To conclude this section on an overview of the brain and its major components, an additional note on terminology should be made. A neuroanatomical term frequently encountered is **brainstem**. This term sometimes refers to the more ventral parts of the brain except for any part of the telencephalon, that is, to the medulla and pons, the midbrain tegmentum, and the diencephalon. Sometimes it even includes some or all of the subpallial structures in the telencephalon. It is alternatively used to refer only to the medulla, pons, and midbrain tegmentum (and sometimes the midbrain tectum) without including the diencephalon. Context must be used to determine the specific sense in which this somewhat loose term is being discussed.

The Meninges and the Ventricular System

The brain and spinal cord are covered by one or more layers of connective tissue, which are called the **meninges**, from the Greek word **meninx**, which means membrane. In fishes, only a single layer, the **primitive meninx**, is present. Amphibians and reptiles have two meningeal layers, an outer **dura mater** (meaning "hard mother") and an inner thin layer, the **secondary meninx**. In mammals and birds, three meningeal layers are present. The layer closest to the brain is a thin layer called the **pia mater** (meaning "tender mother"). The middle layer is a thin, avascular layer called the **arachnoid** due to its spider web-like appearance. The space between the pia mater and the arachnoid is the **subarachnoid space**. Blood vessels lie within it. The outermost layer is the **dura mater** and is actually composed of two layers: an inner layer enclosing the central nervous system and an outer layer that lines the inside of the skull. The use of the word "mother" to describe these membranes comes from an ancient notion that they were the origin, or mother, of all membranes in the body.

As discussed above, the central nervous system develops embryologically from a hollow tube. The walls of the tube thicken to form the brain and spinal cord, and the hollow within the tube becomes the fluid-filled **ventricular system** of the adult. Instead of remaining a straight tube of uniform diameter, the ventricular system extends laterally into the variously expanded parts of the brain in different vertebrate groups, such as the olfactory bulbs, telencephalic hemispheres, the midbrain roof, and/or the cerebellum. This arrangement is shown in Figure 3-15.

In most groups of vertebrates, the ventricular system expands laterally within each of the telencephalic hemispheres, and this pair of laterally extending spaces is called the **lateral ventricles**. The lateral ventricles are in continuity, through paired openings called the **interventricular foramina of Monro**, with the unpaired, medial ventricular space of the diencephalon, called the **third ventricle**. The caudal continuation of the third ventricle is a narrow canal called the **cerebral aqueduct of Sylvius**, which in turn opens into the **fourth ventricle**, the unpaired, medial ventricular space of the hindbrain. Viewed from its dorsal aspect, the fourth ventricle has a rhombic shape (that of a parallelogram), giving the rhombencephalon its name. The fourth ventricle is caudally continuous with the **central canal** of the spinal cord.

Parts of the ventricular walls consist of a thin ependymal epithelial layer and the pia mater, which together form the **tela choroidea**. A network formed by blood vessels and the tela choroidea, called the **choroid plexus**, secretes **cerebrospinal fluid** into the ventricular spaces. The cerebrospinal fluid circulates in the ventricular system and also in the subarachnoid space; it reaches the latter by passing through three openings that connect the fourth ventricle with an enlarged part of the subarachnoid space, the **cisterna magna**. The three openings are a paired set, the **foramina of Luschka**, one at each lateral aspect of the ventricle, and an unpaired, medial foramen, the **foramen of Magendie**. After circulating, the cerebrospinal fluid passes out of the subarachnoid space into vascular sinuses through structures in the arachnoid called **arachnoid villi**, which act as one-way, pressure-sensitive valves. The cerebrospinal fluid provides support for the brain and cushions it from physical shocks by its buoyancy.

MAJOR SYSTEMS OF THE BRAIN

We now want to give you a very brief overview of some of the major systems of the brain. As we have discussed above, there are major sensory and motor systems in which information is relayed through various nuclei, being modified and sorted along the way. In later chapters, which cover various parts of the brain, a general idea of the basic organization of these systems will help you to make sense of the anatomy.

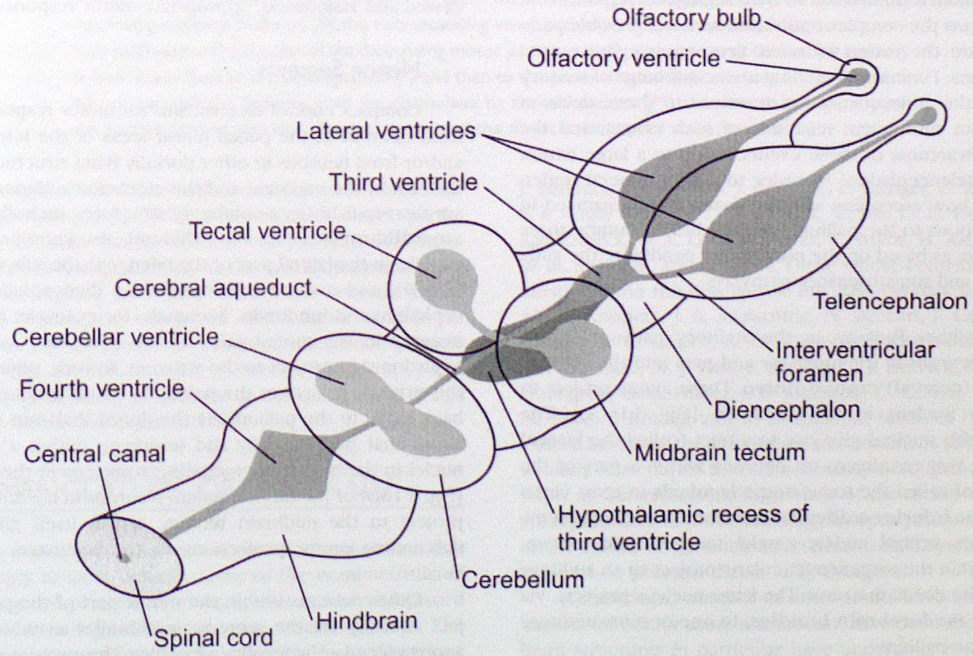

FIGURE 3-15. Dorsolateral schematic drawing of a generalized ray-finned fish brain to represent the general vertebrate condition of the ventricular system, indicated by shadings. Not all vertebrates have a hypothalamic recess of the third ventricle or tectal or cerebellar ventricles. Rostral is toward the upper right.

Sensory Systems

All of the receptors for touch and position sense, radiant-energy sense, pain and temperature, lateral line (for wave displacement and electrical field detection), hearing, vestibular sense, and gustatory sense have their initial points of termination within the central nervous system either in the spinal cord or in the hindbrain (in the medulla and/or pons). As mentioned in Chapter 2, the target cell populations of these primary pathways can be referred to as **first-order multipolar neurons (FOMs)**, since they are the first of several groups of multipolar neurons that form the sensory pathway within the central nervous system. The FOMs receive the sensory bipolar neuron inputs and then project to more rostral levels of the brain, particularly the dorsal thalamus and the optic tectum, which itself then projects to the dorsal thalamus as well. Similarly in the visual system, retinal bipolar neurons receive receptor inputs and terminate on retinal ganglion cells, which are the FOMs for the visual pathways. Most of the retinal ganglion cell axons terminate in part of the dorsal thalamus and in the optic tectum. From the dorsal thalamus, the various pathways project to part(s) of the telencephalic pallium, and, in some cases, to part of the subpallium as well. The olfactory pathways, in contrast to the more caudal sensory pathways, project directly into part of the telencephalon. Topographic organization is an important characteristic of all of these pathways; this feature provides for orderly maps of the sensory input within particular parts of the brain that correspond to the spatial map of the external world.

Each of the ascending sensory pathways to the telencephalic pallium terminates in its own segregated region. From that site begins the complex and varied series of possible pathways that are the routes to other sensory, integrative, and motor systems. Functions including memory storage of sensory events and the consequences of reactions to them, decision making about subsequent reactions to such events, and the conscious awareness of these events reside to a large extent within the telencephalon. In order to gain a general understanding of how ascending sensory systems are organized in their projections to the pallium, we will briefly outline three of them here, as based on the mammalian condition: the auditory, visual, and somatosensory pathways.

The Auditory Pathway. In the auditory pathway, axons arise from neurons in the inner ear and pass into the brain in the **eighth (octaval) cranial nerve**. These axons project to an auditory nucleus in the hindbrain [Fig. 3-16(A)]. The neurons in this nucleus give rise to a tract (called the **lateral lemniscus**) that terminates on neurons within a part of the midbrain roof called the **torus semicircularis** in most vertebrates and the **inferior colliculus** in mammals. The torus semicircularis lies ventral and/or caudal to the optic tectum. Neurons within the torus semicircularis project to an auditory nucleus in the dorsal thalamus. The latter nucleus projects, via tracts called the **forebrain bundles**, to one or more auditory regions of the pallium.

The Visual Pathways. Neurons in the retina give rise to axons that enter the brain via the **optic nerve** [Fig. 3-16(B)] and its continuation, the **optic tract**. Most retinal axons terminate on neurons located either in the optic tectum of the midbrain (called the **superior colliculus** in mammals) or in a visual nucleus in the dorsal thalamus. Visual neurons in the optic tectum also project to a second visual nucleus in the dorsal thalamus. Each of the two visual dorsal thalamic nuclei projects to the telencephalon via the forebrain bundles and terminates in one or more visual areas within the pallium.

The Somatosensory Pathways. Axons that carry somatosensory information [Fig. 3-16(C)] enter the spinal cord and pass rostrally to terminate on neurons within two cell groups called the **dorsal column nuclei**. These nuclei lie in the junctional area between the spinal cord and the brainstem. Neurons in the dorsal column nuclei give rise to axons that pass rostrally in a tract called the **medial lemniscus**. Some of these axons terminate on neurons in a somatosensory part of the midbrain tectum. Other somatosensory axons from the dorsal column nuclei bypass the midbrain and terminate in a somatosensory nucleus in the dorsal thalamus. Neurons in the somatosensory part of the midbrain also give rise to projections to a second somatosensory nucleus in the dorsal thalamus. Each of the two dorsal thalamic somatosensory nuclei projects to the telencephalon via the forebrain bundles and terminates in two or more somatosensory areas within the pallium.

In the telencephalon, sensory information is relayed through multiple sets of projection (Golgi Type I) and local circuit (Golgi Type II) neurons—to secondary, tertiary, and further sensory and association pallial areas, into the limbic system for memory, into multisensory association pallial areas for integration, and so on. When the information has been processed and assimilated, appropriate motor responses follow.

Motor Systems

Complex control mechanisms for motor responses derive from neurons in the pallial motor areas of the telencephalon and/or from neurons in other dorsally lying structures, such as the roof of the midbrain and the cerebellum. Motor responses are also regulated by a number of structures, including the **striatopallidum** (striatum and pallidum), also known as the basal ganglia, in the lateral part of the telencephalic subpallium [Fig. 3-16(D)] and nuclear areas within the diencephalon, mesencephalon, and hindbrain. Mammals, for example, have motor neurons in the motor parts of the neocortex in the telencephalon that project to the striatum. In turn, neurons within the striatum project to the pallidum, which gives rise to feedback loops to the pallium via the dorsal thalamus and also to axons that pass caudally and terminate within a number of nuclei in the brainstem, including a nucleus in the pretectum [Fig. 3-16D] of the diencephalon. Neurons in the latter nucleus project to the midbrain tectum, which itself gives rise to descending motor projections to the brainstem and spinal cord.

Other neurons within the motor part of the pallium project caudally via the same major bundles in which sensory axons ascend—the forebrain bundles. These axons collectively form a tract that is rather like a major interstate highway. They pass caudally to synapse within nuclei in the midbrain and the brainstem and, in some cases, directly on neurons in the spinal cord. The latter, direct tract is present in mammals and is called

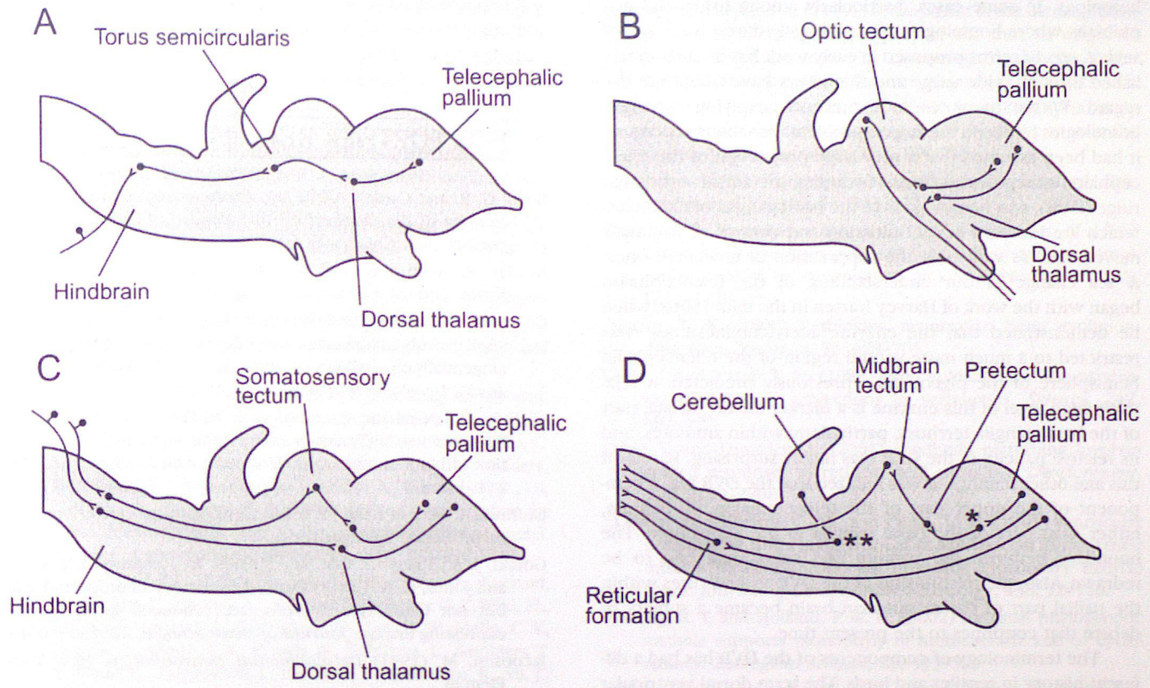

FIGURE 3-16. Schematic representation of the major sensory and motor pathways. Rostral is toward the right. Dots represent neuronal cell bodies, and lines represent the axons of the cell bodies with their terminal endings. Dendrites of cell bodies, on which the axons actually synapse, are not represented. (A) Ascending auditory pathway; (B) the two ascending visual pathways; (C) the two ascending somatosensory pathways; and (D) some of the descending motor pathways. In D, the uppermost descending pathway is from the pallium to the striatopallium (*) and then to the pretectum, midbrain tectum, and spinal cord. Also shown are the pathway from the cerebellum to the red nucleus (**) and then to the spinal cord, the corticoreticular and reticulospinal tracts, and the direct corticospinal tract (lowermost).

the **corticospinal tract**. Motor nuclei of the cerebellum similarly contain neurons that project to brainstem nuclei, particularly the vestibular nuclei and the red nucleus. The latter nuclei project to the spinal cord via the **vestibulospinal tract** and the **rubrospinal tract**, respectively. The reticular formation of the brainstem is composed of a number of different nuclear areas that also are involved in these descending motor pathways. Like the red nucleus, it receives pallial input and gives rise to descending projections to the spinal cord, in this case called the **reticulospinal tract**.

NOMENCLATURE OF THE BRAIN

Just as brains evolve, so too does the nomenclature that humans apply to its structures. Some of the nomenclature of the founding comparative neuroanatomists has been replaced with new terminology during the past several decades. The early comparative neuroanatomists include many illustrious workers, whose legacy is only sometimes given the great respect that it merits. To name just a few here, some of the earliest workers (19th century into the early 20th century) include S. Ramón y Cajal and his brother, P. Ramón, as well as J. Bellonci, G. Cuvier, S. J. deLange, L. Edinger, G. Elliott Smith, S. P. Gage, C. Golgi, C. L. Herrick, W. His, O. D. Humphrey, H. Kuhlenbeck, W. A. Locy, A. Meyer, F. Pinkus, H. Rabl-Rückhard, W. M. Shanklin, and L. Stieda. Those whose contributions came mostly within the first half of the 20th century include C. U. Airëns Kappers, J. A. Armstrong, N. Beccari, J. Cairney, E. H. Craigie, E. C. Crosby, A. O. Curwen, A. Durward, T. Edinger, A. Frederikse, M. J. Gisi, F. Goldby, C. J. Herrick, M. Hines, N. Holmgren, G. C. Huber, J. B. Johnston, O. Larsell, R. N. Miller, M. Rose, P. Röthig, and R. E. Sheldon. Much of their nomenclature has stood the test of time and continues to be used, particularly those terms that are accurately descriptive and do not imply an incorrect homology. Many of the earlier workers also are represented in the terminology by eponymous terms—such as the nuclei of Bellonci, Darkschewitsch, Luys, Meader, and Meynert—a practice that is sadly dying out.

A substantial number of other terms have become problematic for one or more reasons and have been replaced. Forebrain structures in particular have undergone name changes; the diversity of the forebrain within and across different vertebrate radiations is arguably more pronounced than in most other parts of the brain, and thus its structures have been subject to misnomers based on incorrect assumptions of

homology. In some cases, particularly among fishes and amphibians where homologies are still largely unresolved, one of several sets of terms proposed in early work has become established through wide usage and the others have fallen into disregard. Within amniotes, nomenclature implying incorrect homologies has been the largest problem. For almost a century, it had been assumed that a very large proportion of the telencephalon of reptiles and birds, including the dorsal ventricular ridge (DVR), was homologous to the basal ganglia of mammals, which are involved in the initiation and control of voluntary movements, as well as in the suppression of unwanted ones. A sea change in our understanding of the telencephalon began with the work of Harvey Karten in the mid- 1960s, when he demonstrated that the enzyme acetylcholinesterase was restricted to a much more ventral region of the telencephalic hemisphere of the pigeon than previously predicted. A relatively high level of this enzyme is a marker for the striatal part of the basal ganglia territory, particularly within amniotes, and its relative paucity in the DVR was highly surprising. Based on this and other findings, it was realized that the DVR was a component of the upper part of the telencephalon, or pallium, rather than part of the basal ganglia in the subpallium. The boundary between the pallium and subpallium had to be redrawn. Also, the relationship of the DVR to structures within the pallial part of the mammalian brain became a subject of debate that continues to the present time.

The terminology of components of the DVR has had a different history in reptiles and birds. The term dorsal ventricular ridge itself was introduced by J. B. Johnston in 1915. However, in some reptiles and in birds, various components of the DVR and/or other pallial areas were labeled with terms that included the suffix "striatum" in at least some of the early work, in keeping with the prevailing view that these areas were part of the basal ganglia. Such terms included "hyperstriatum," meaning "above the striatum," "neostriatum," meaning the "new striatum" and referring to the assumed homology with a similarly named part of the mammalian striatum, and "ectostriatum," meaning "out of the striatum." The "striatum" suffix died out in usage for these regions in reptilian telencephalons in the late 1960s, with reversion to Johnston's DVR term in most cases.

In birds, however, the use of the "striatum" suffix for some pallial areas persisted until very recently. This usage resulted in considerable communication problems between researchers working on different taxa of vertebrates, particularly those not well acquainted with the comparative nonmammalian literature. Recognizing this problem, Martin Wild and Anton Reiner proposed that a new set of terms be developed for the pallial regions in question and initiated a process that culminated several years and many discussions later with the Avian Brain Nomenclature Forum, which was organized by Erich Jarvis and held at Duke University in the summer of 2002. From this conference and the combined efforts of all its participants, a new nomenclatural system for the avian telencephalon was devised and published in two papers by Reiner et al., 2004 in the *Journal of Comparative Neurology*. The new nomenclature includes changes for some brainstem structures as well as for both pallial and subpallial regions of the telencephalon. The new terms either reflect well-established homologies or are neutral, descriptive terms that avoid promulgating disproved and discarded hypotheses of homology. The new nomenclature will be introduced in appropriate places throughout this text, and comprehensive tables of the new terms are presented in Chapters 15 and 19.

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