One of the greatest challenges in evaluating central nervous system (CNS) biopsies of non-neoplastic conditions is the extraordinary cytologic and architectural diversity of the CNS. Knowledge of this remarkable diversity is necessary for the proper evaluation of non-neoplastic biopsy specimens since recognition of pathologic features often entails comparison with a mental image of the normal structure of what has been biopsied.

Certain regions of the CNS are more amenable to biopsy than others because biopsy of some structures poses a high risk of neurologic morbidity and because neurosurgical access in some regions poses difficulties. Biopsies of neoplastic diseases must target the neoplastic mass, which is in many cases a single lesion. Even in the setting of probable neoplasm, however, some locations and clinicopathologic situations present problems that argue against biopsy, for example, in the case of a suspected diffuse pontine glioma or pineal germinoma. Non-neoplastic diseases less often feature a distinct single lesion, and thus sometimes allow more choice in terms of biopsy sites. In such situations, the neurosurgeon will select to biopsy a more readily accessible, less “eloquent” area, rather than biopsy a deep-seated nucleus or a region likely to lead to morbidity. As a result, some CNS regions are almost never biopsied. The following chapter reviews the cellular constituents of the CNS and its surroundings, as well as the architectural features of regions that are subject to biopsy.

**REGIONAL NEUROANATOMY**

The following section is oriented toward understanding the regional neuroanatomy of the CNS in the context of surgical neuropathology specimens. As such, the discussion is biased toward structures that are encountered by the pathologist when evaluating surgical specimens. Recognition of specific gray and white matter structures is important when interpreting neuropathologic findings, and can be of intraoperative help to neurosurgeons, particularly during stereotactically guided needle biopsies and microneurosurgical procedures.

By far the most common regions biopsied when non-neoplastic diseases are suspected are the meninges, cerebral cortex, and underlying white matter. In addition, the non-“eloquent” areas of the cerebrum are commonly removed for non-neoplastic processes, such as for epilepsy surgery or resections of infarcted or edematous brain. Although never resected, deep structures are sometimes biopsied, particularly if specific deep lesions suggest a greater likelihood of establishing a diagnosis. The following section discusses the architectural features of different regions that may be included in biopsy or resection material. For further information on neuroanatomy, the reader is referred to excellent reference texts (1,2).

**Meninges**

The meninges are the tripartite coverings of the CNS and are often included in biopsy material. The meninges may be the primary sites of certain infectious and inflammatory diseases, and are often biopsied to detect more global CNS conditions such as vasculitis. The meninges are composed of three layers: the dura mater, the arachnoid mater, and the pia mater.

The dura mater (pachymeninx) is the most external of the three membranes. In the cranial cavity, the dura is closely affixed to the overlying cranium, whereas in the vertebral cavity, the dura is free; as a result, there is only a potential epidural space in the head, but an actual spinal epidural space. The dura is a thick, densely collagenous, hypocellular structure composed of two layers (fig. 1-1). The two layers are histologically similar, but have collagen fibers running in different directions. Each layer features dense collagen, fibroblasts, and both arterial and venous blood vessels (fig. 1-2). In places where layers of the dura come together, large venous sinuses are
present. These sinuses are lined by endothelial cells but are indented in places by arachnoid (pacchionian) granulations (see below).

The arachnoid mater (one of the leptomeninges) is not often biopsied by itself, but most biopsies of the cerebral cortex purposefully include the overlying arachnoid and the subarachnoid space (fig. 1-3). The arachnoid is a thin membrane, only a few cells thick, consisting of fibroblasts and arachnoidal cells (fig. 1-4). Arachnoidal cells vary from spindled to cuboidal. They resemble the cells commonly encountered by pathologists in meningiomas: cells that often have oval nuclei, open chromatin, and sometimes, intranuclear pseudoinclusions. Ultrastructurally, as in meningiomas, arachnoidal cells contain prominent intermediate filaments and desmosomes. In many places, they form small multicellular clusters (fig. 1-5); these clusters resemble little meningiomas, with prominent whorls and often with psammoma bodies. Along the large venous sinuses, the arachnoid aggregates further into granulations that protrude into the sinuses. These granulations feature arachnoidal cells, blood vessels, and a hyalinized, collagenous stroma (fig. 1-6). Scattered pigmented melanocytes are also present in the arachnoid and subarachnoid space (fig. 1-7), particularly along the base of the brain and in dark-skinned individuals.
DURA MATER
Dense collagen bundles with scattered small blood vessels.

ARACHNOID MATER AND SUBARACHNOID SPACE
The subarachnoid space is found between the thin overlying arachnoid and the underlying pia mater at the surface of the cerebral cortex. The subarachnoid space contains medium-sized blood vessels and the cerebrospinal fluid.

ARACHNOID MATER
The arachnoid is a thin membrane consisting of cuboidal to oval arachnoidal cells and fibroblasts.
The subarachnoid space is of major importance in surgical neuropathology, since it is targeted by many pathologic processes. The subarachnoid space primarily contains blood vessels and cerebrospinal fluid (CSF) (fig. 1-3). In older individuals, the subarachnoid space and overlying arachnoid may be fibrotic, particularly along the parasagittal convexities (fig. 1-8). The vessels are both arterial and venous. In surgical specimens that are compressed during removal, the subarachnoid vessels may be artifactually grouped closely together, mimicking vascular malformations. The surgical pathologist must be careful not to overcall a vascular malformation in such situations. In addition, occasional lymphocytes may be present in an otherwise unremarkable subarachnoid space.

The pia mater is not a separate membrane, but a layer of cells tightly affixed to the brain and spinal cord. Aside from maldevelopmental processes, there is little diagnostic pathology directly related to the pia mater.

**Cerebral Cortex**

Along with the meninges, the cerebral cortex is the single most frequently biopsied site for non-neoplastic diseases. In addition, along with the cerebellum, it is the only structure that is commonly removed as part of resection specimens, e.g., for epilepsy or stroke debulking. With

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**Figure 1-5**

**ARACHNOID MATER**

Nests are formed by clusters of arachnoid cells, resembling small meningiomas, complete with whorls and psammoma bodies.

**Figure 1-6**

**ARACHNOID GRANULATION**

Fibrovascular cores with clusters of arachnoidal cells project into a dural sinus. A psammoma body is present.
Microscopic Neuroanatomy

Figure 1-7
ARACHNOIDAL MELANOCYTES
Elongated, densely pigmented melanocytes are within the arachnoid membrane.

Figure 1-8
ARACHNOID MATER AND SUBARACHNOID SPACE
Fibrosis is common, particularly in the parasagittal regions of elderly patients.

the exception of the medial temporal lobe structures included in resection specimens (discussed below), nearly all sampled cortex is the six-layered neocortex. The neocortex varies from region to region, but has certain consistent features (figs. 1-9–1-13). Most strikingly, it is a laminated structure with large and medium-sized neurons “pointing” in the same direction: the apical dendrites, arising from the “tops” of the triangular (pyramidal) cells, are all oriented toward the cortical surface (fig. 1-11). This is readily apparent for the large pyramidal neurons, which are present in all cortical areas, but is not discernible for the smaller, more rounded granular neurons.

The six layers of neocortex are, beginning from the pial surface: 1) the cell-poor molecular layer; 2) the external granular cell layer; 3) the external pyramidal cell layer; 4) the internal granular cell layer; 5) the internal pyramidal cell layer; and 6) the polymorphous or transitional layer. Different regions of the brain have cortices that have different appearances, which are largely the result of variations in the prominence and cell types of the six different layers and the amount and pattern of myelin. Detailed
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Figure 1-9
CEREBRAL CORTEX
Laminations and large neurons of frontal lobe cortex.

Figure 1-10
CEREBRAL CORTEX
Frontal cortex features large pyramidal neurons in layers 3 and 5.

Figure 1-11
CEREBRAL CORTEX
Pyramidal neurons in frontal cortex point toward the pial surface.
classifications of cortical cytoarchitecture and myeloarchitecture reflect these differences, the most famous of which is the Brodmann scheme (2). In general, however, cortices that subserve motor functions have prominent pyramidal cell layers. Most neurosurgical specimens that include the frontal lobe contain easily identifiable pyramidal cell layers (fig. 1-9). Although not often biopsied, the most striking example of such pyramidal cell prominence is the precentral motor cortex, with its extremely large Betz cells in the internal pyramidal layer (fig. 1-14). On the contrary, primary and secondary sensory cortices have smaller pyramidal cells and thicker granular cell layers. In general, samples of the parietal lobe have this more “sensory” appearance. Although not often biopsied, a striking example of this organization is found in the visual cortex of the occipital lobe (fig. 1-12).

The temporal lobe neocortex appears similar to other neocortical regions, with six layers and clearly discernible pyramidal cell layers. The only notable distinctions, which are primarily of significance in the differential diagnosis of infiltrating gliomas, are the presence of multiple perineuronal oligodendrocytes (which can mimic perineuronal satellitosis of glioma cells) and the presence of multiple neurons within the subcortical white matter. However, the non-neocortical medial temporal lobe structures, which are commonly encountered in surgical specimens for neoplastic and non-neoplastic conditions, have unique histologic features. The proper appreciation of the histologic architecture of these structures is dependent on the appropriate coronal orientation and cutting of these tissues on gross examination (see chapters 3 and 13), one of the few times in which
macroscopic examination plays a crucial role in surgical neuropathology.

The hippocampus (fig. 1-15) is a multiply curved structure that has at least a superficial resemblance to a seahorse; hence the name. The medial temporal lobe structures of the hippocampus can be thought of as a skewed S-shaped combination of the entorhinal cortex/subiculum and cornu ammonis; the C-shaped dentate gyrus is located at the top of the skewed S (see chapter 3, fig. 3-4). On coronal sections, from lateral to medial, the temporal neocortex transitions to a cortical appearance in which clusters of large neurons ("clouds of Arnold") appear just below the pial surface. Proceeding into the cortical tissue immediately below the central part of the hippocampus, this primitive cortex becomes simpler, forming a three-layered area known as the subiculum. The subiculum, the "support" beneath the central hippocampus, consists of two relatively cell-free layers sandwiching large pyramidal neurons. The subiculum then transitions into the cornu ammonis (CA) of the hippocampus.

There are four distinct CA regions, CA1 to CA4, with CA1 directly adjacent to the subiculum; each contains prominent pyramidal cells (fig. 1-16). CA1 is known as the Sommer sector,
and is the region most sensitive to hypoxic damage and seizure-related changes (see chapter 13) as well as most affected in Alzheimer disease (see chapter 10). The central region of the hippocampus, following CA4, is the prominent dentate gyrus, consisting of a distinct line of small granular neurons (fig. 1-17).

The amygdala is located in the anterior temporal lobe, rostral to the hippocampus and temporal horn of the lateral ventricle. The structure is a combination of cortical and subcortical gray matter. Its histologic appearance is variable, but it is primarily composed of irregularly arranged globular, medium-sized neurons (fig. 1-18). White matter is sparse but in some areas is aggregated into small bundles that are reminiscent of the “pencils of Wilson” found in the striatum.

**White Matter**

The white matter is commonly sampled in neurosurgical procedures, in resection specimens, in cortical biopsies that include the underlying gyral white matter cores, and in deep needle biopsies. When stained with hematoxylin and eosin (H&E), white matter is characterized by numerous oligodendrocytes, often arranged in short lines of a few or more cells when sampled parallel to the direction of the axonal fibers (figs. 1-19, 1-20). Astrocytes are also present, but attention is drawn to the plentiful, dark oligodendrocyte nuclei. The background neuropil has a linear quality when the biopsy is parallel to the white matter tract, brought about by the parallel myelin sheaths and central, eosinophilic axons. When viewed
Medium-sized neurons are irregularly arranged, and bundles of white matter are often noted.

Subcortical cerebral white matter contains numerous oligodendrocytes and small vessels.

Oligodendrocytes and astrocytes may be arrayed in lines in white matter bundles such as the anterior commissure.
perpendicular to the tract, there is a “vacuolar”
quality that is occasioned by cross sectioning
the myelin sheaths, which sometimes artifac-
tually pull away from the central axons (fig.
1-21). Toluidine blue–stained, water-based
frozen sections highlight the myelin debris as
refractile purple-brown material. On paraffin
sections, Luxol fast blue stains provide ready
confirmation of myelin, and hence, of white
matter tracts (fig. 1-22).

Some white matter areas have distinct fea-
tures that suggest that region, and may therefore
be of help in providing intraoperative guidance:
the corpus callosum, internal capsule, and fornix
(figs. 1-20, 1-23). Both the corpus callosum and
the internal capsule are large and often-sampled
white matter tracts that have similar histologic
features. Perhaps because of their large size,
longitudinal sections of these structures dem-
onstrate longer rows of oligodendrocyte nuclei,
with larger groups of myelinated fibers between
the nuclear rows. Although only rarely sampled
during surgical procedures, the fornix has a
distinct organization when viewed in cross
section. The white matter bundles are grouped
into fascicles, in a manner reminiscent of the
optic nerve (see below).

**Deep Gray Matter**

Although the various structures of the deep
gray matter of the cerebral hemispheres differ
markedly from one another in terms of their
cytology and architecture (and obviously in
their functions as well), they can be discussed
together in the context of surgical neuropathol-
ogy. Because of the unacceptable morbidity
associated with any attempts to resect such structures, the deep gray matter nuclei are only visualized in small biopsy specimens. In fact, nearly all surgical specimens from deep gray matter are stereotactic needle biopsies. On the other hand, the more superficial gray matter regions that are not classic neocortex, such as the amygdala and hippocampus, are commonly included in temporal lobe resection specimens for either neoplastic or non-neoplastic conditions. These are discussed in the section on the cerebral cortex, above.

As a result of the small size of most deep gray matter biopsies, the architectural features of the three major deep gray matter regions—the basal ganglia, thalamus, and hypothalamus—are not often appreciated as they are depicted in standard neuroanatomy books. Nonetheless, cytologic features as well as some architectural features, such as the density of the neurons and the quality of the background neuropil, can hint at the origin of a deep gray matter specimen. Such information can be of substantial help to the neurosurgeon intraoperatively and to the interpretation of the final histologic sections. The three major regions are discussed below and illustrated in figures 1-24 to 1-28.

From the standpoint of surgical neuropathology, the basal ganglia consist of the caudate nucleus, putamen, and globus pallidus. Although standard neuroanatomy texts variably include a set of additional nuclei under the rubric of
“basal ganglia,” such as the subthalamic nucleus, these structures do not lend themselves to surgical biopsy. Histologically, the caudate and putamen are identical and the external and internal segments of the globus pallidus are very similar. For these reasons, there are two basic histologic patterns for surgical pathologists to recognize in the basal ganglia: that of the striatum (caudate nucleus and putamen) and that of the globus pallidus.

The caudate nucleus and putamen feature a combination of large and medium-sized neurons (fig. 1-24). These neurons are polygonal to round-ed, are moderately densely packed (fig. 1-25), and are located in a neuropil that restricts myelin to fiber tracts known as “pencils of Wilson.” These bundles are visible on H&E stains as small, short tracts of parallel fibers and arrays of oligodendro-

cytes; on Luxol fast blue stains, there is little visible myelin in the caudate and putamen except in these pencil fibers. This appearance contrasts markedly with the globus pallidus, which has a sparse collection of large, polygonal neurons in a neuropil that features numerous white matter fibers running in different directions (fig. 1-26). This abundance of myelinated fibers within a gray matter structure accounts for the relatively “pale” appearance of the globus pallidus on macroscopic examination; hence its name.

The thalamus and hypothalamus, in contrast to the caudate, putamen, and globus pallidus, are microscopically heterogeneous. Some regions of the thalamus, particularly the ventral (or laterally placed) tier of nuclei feature a background neuropil rich in myelinated fibers (fig. 1-27), whereas the remaining nuclear groups

Figure 1-25

CAUDATE AND PUTAMEN

The striatum has conspicuous white matter bundles known as “pencils of Wilson” (lower right to middle).

Figure 1-26

GLOBUS PALLIDUS

Scattered large neurons are in a background of numerous axons.
Non-Neoplastic Diseases of the Central Nervous System

tend to have more restricted white matter bundles and delicate neuropil (fig. 1-28). Most thalamic neurons are moderate in size, but they vary in shape and density from nucleus to nucleus. White matter lamina separate many of the thalamic nuclei from one another, but, with the exception of the mamillothalamic tract (tract of Vicq d’Azyr), are not prominent.

Similarly, the histologic appearance of the hypothalamus varies from region to region. Most hypothalamic neurons are moderate in size and range from polygonal to globular in shape. In some of the well-delineated hypothalamic nuclei, such as the supraoptic and paraventricular, the globular neurons are tightly packed together, but much of the more lateral hypothalamic features scattered neurons and moderate amounts of interspersed white matter.

Pineal Gland

A wide variety of non-neoplastic processes can involve the pineal region, and biopsies of the pineal gland are essentially always performed for tumor diagnosis or treatment. Occasionally, normal gland is sampled rather than tumor and so familiarity with the histology of the pineal gland is important for surgical pathologists. The pineal is composed of medium-sized neuronal cells as well as glia (fig. 1-29). The neuronal cells are polygonal, with short processes that can be highlighted with particular silver impregnations, such as the DeGirolami-Zvaigzne modification of the Achucarro-Hortega method (3), as well as with immunohistochemistry for synaptophysin and retinal S-antigen. The important feature to appreciate is the lobularity of the normal pineal...
architecture, with cells packaged into large lobules by glial and vascular septa, and with large, irregular calcifications (fig. 1-30).

**Brain Stem**

The brain stem is seldom biopsied, for either suspected neoplasm or for non-neoplastic processes, because of the high risk of morbidity following biopsy. Occasional biopsies may target the middle cerebellar peduncle that joins the pons and deep cerebellar white matter. This white matter is indistinguishable from the deep hemispheric cerebral and cerebellar white matter. Rarely, exophytic lesions of the dorsal brain stem are biopsied via the fourth ventricle. In such situations, specimens may show the ependymal lining of the floor of the fourth ventricle, choroid plexus from the fourth ventricle itself, and occasional neurons from superficially located nuclei in the floor of the fourth ventricle.

These are most often large neurons with typical neuronal cytologic features.

**Cerebellum**

The cerebellum is frequently included in posterior fossa biopsies, both as a target for biopsies and for access to deeper structures. It has a unique architecture that is easily recognized, but which can be mistaken for densely cellular pathologic processes in the setting of tiny biopsies and smear preparations.

The cerebellum is arranged in small folia: frond-like arrangements around a central white matter core (fig. 1-31). The cerebellar cortex has a trilaminar appearance, although at low power only the outer and inner layers are noticeable, given the thinness of the middle, Purkinje cell, layer. Beneath the pial surface is the outermost lamina, the paucicellular molecular layer (fig. 1-32). In addition to scattered glia, the molecular...