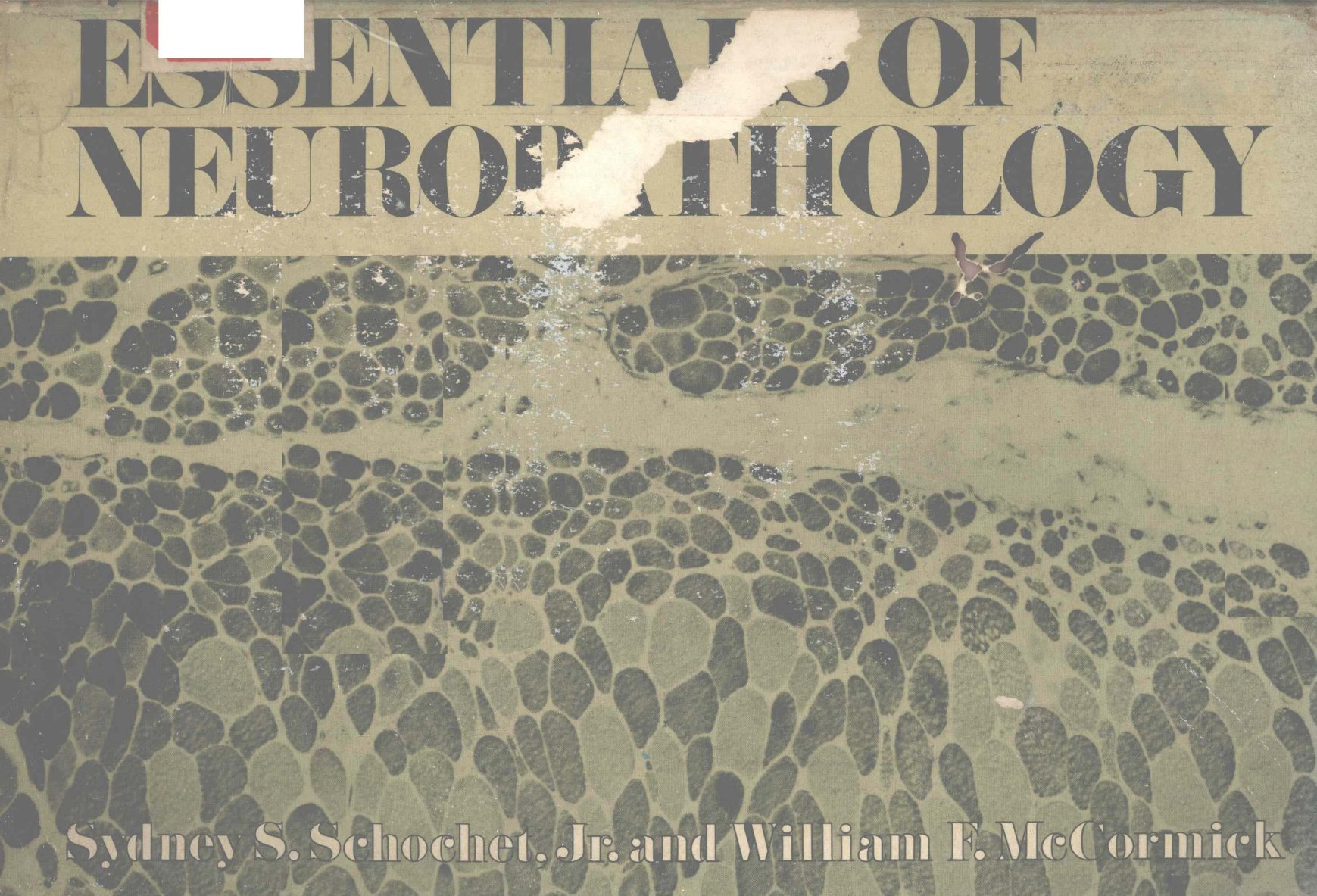
ESSENTIALS OF NEUROPATHOLOGY



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This book is dedicated to Dr. A. L. Sahs, Professor of Neurology, Emeritus, our teacher and colleague.

PREFACE

Essentials of Neuropathology is intended primarily for the student who wants more informaton than is available in the usual pathology or neurology textbook. It addresses the topics that we have found in our practice to be the most important or confusing, but is clearly not intended to be encyclopedic. The relatively extensive lists of references have been selected to assist the reader in finding additional and more detailed informaton, to augment our necessarily brief text.

We wish to thank our secretary, Ms. Gail Stewart, for the task of typing the manuscript, Ms. Pam Collins for patiently preparing the photographic prints, and Dr. Clyde Meyers for his diligent proofreading.

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1

BASIC NEUROPATHOLOGY

SAMPLING OF THE CENTRAL NERVOUS SYSTEM AT AUTOPSY

Because of the relatively large volume of the brain and spinal cord, careful sampling, to furnish the maximal information within the practical limits, becomes an important problem. All too often, a small number of poorly oriented and often unidentifiable fragments of tissue are taken for examination. This makes a critical review at a later date or by another observer virtually impossible. For these reasons, we have established a uniform procedure for sampling the brain and spinal cord. In our experience, this has provided the maximal amount of information for the time and money expended. A basic set of samples is taken on all cases regardless of the abnormalities present. Additional blocks are taken in cases with specific gross lesions that are not included in the routine samples.

Ideally, samples should include the important arterial border zones, areas that undergo specific types of degeneration (senile plaques, neurofibrillary tangles, Pick and Lewy bodies, etc.), areas that are involved in the various "system degenerations," and areas that are commonly involved by the forms of encephalomyelitis and demyelinating diseases. Our routine samples consist of:

The left frontal lobe to include the border zone between anterior and middle cerebral arteries
Both striata from the insula to the lateral ventricles at the level of the mammillary bodies
The hypothalamus to include the mammillary bodies and optic tracts
The unci
Both hippocampi at the level of the geniculate bodies
The glomi of the choroid plexi
The left occipital lobe to include the visual cortex
The mesencephalon at the level of the third nerve nuclei
The pons at the level of the fifth cranial nerves
Rostral medulla
Caudal medulla
The right and left cerebellar hemispheres to include vermis, roof nuclei, and lateral hemispheric folia
Cervical spinal cord at two levels

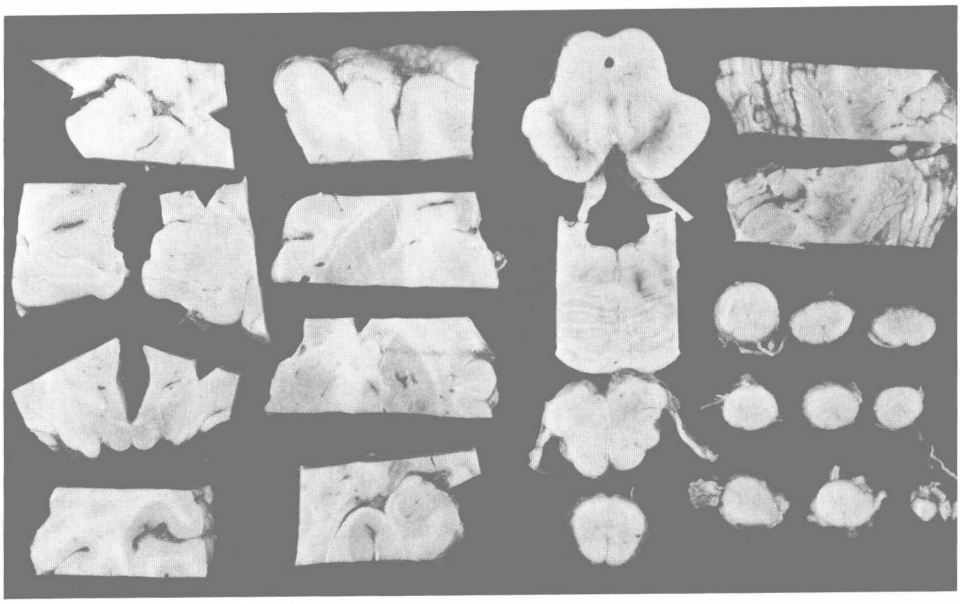

FIG. 1. Blocks routinely taken for sampling the brain and spinal cord.

Thoracic spinal cord at three levels
Lumbar spinal cord at two levels
Sacral spinal cord at one level

Only rarely are additional blocks necessary to adequately evaluate brains and spinal cords sampled in this manner.

Figure 1 illustrates the typical appearance and size of the samples mentioned above. All of these pieces fit readily on conventional 1-inch-wide microscope slides. In occasional cases where the brain stem will not fit, careful bisection in the midline with proper identification of right and left sides should be carried out. It is often important to know from which side a sample was taken. We routinely remove a V-shaped wedge of tissue from the blocks from the right side of the brain.

STAINS AND TECHNIQUES FOR DIAGNOSTIC NEUROPATHOLOGY

Brain and Spinal Cord

These tissues are routinely embedded in paraffin and the following stains may be performed.

HEMATOXYLIN AND EOSIN (H&E). This is a satisfactory routine stain with which most lesions can be seen. It has the advantage of being familiar to the technicians who prepare the sections and all pathologists. Viewing the sections with polarized

light helps to detect neurofibrillary tangles, discloses retained paraffin, and vividly displays certain crystals such as oxalates.

TRICHROME STAINS. These are excellent stains for central nervous system tissues and, if done well, are perhaps, the most useful routine stains. Inclusions such as the Hirano and Lewy bodies are demonstrated very clearly. In our laboratory, we use the Gomori one-step procedure.

NISSL STAINS. When applied to sections 20 μ or thicker and examined at low magnification, these are the best stains for evaluating neuronal populations. They are of little use for other purposes. They can be combined effectively with the luxol fast blue myelin stain.

LUXOL FAST BLUE (LFB). This stain provides a simple method for myelin that stains central and peripheral myelin somewhat differently. Luxol fast blue also demonstrates the lipid deposits in neuronal ceroid lipofuscinosis and Fabry's diseases effectively. This stain is often used in combination with periodic acid–Schiff–hematoxylin or a Nissl stain. The latter is somewhat "sharper."

WEIL, WEIGERT, WOELKE, ETC. These traditional hematoxylin techniques for myelin are more sensitive but more difficult to perform than the luxol fast blue technique.

BODIAN, BIELSCHOWSKY, HOLMES, ETC. These are silver stains for neurofibrils and nerve processes. The staining results from selective deposition of silver from solutions of relatively unstable silver compounds. Good preparations are sometimes difficult to obtain; extremely clean glassware is important. These silver stains are employed most commonly to demonstrate neurofibrillary tangles and senile plaques.

PERIODIC ACID–SCHIFF–HEMATOXYLIN (PASH). Alone or in combination with luxol fast blue for myelin, this stain is commonly used to demonstrate carbohydrate deposits, fungi, certain parasites and senile plaques.

CONGO RED. Staining with Congo red is the preferred technique for the demonstration of amyloid. For confirmation, a yellow-green birefringence color must be seen when the sections are examined with polarized light.

PHOSPHOTUNGSTIC ACID–HEMATOXYLIN (PTAH). In addition to being the traditional method for demonstrating glial fibrils, phosphotungstic acid–hematoxylin is also used to stain fibrin and blepharoplasts.

"RETICULIN" STAIN. This special type of silver stain is occasionally used to demonstrate the margins of vascular channels.

GROCOTT OR GOMORI METHANAMINE SILVER STAINS. These are very effective techniques for staining fungi.

TISSUE GRAM STAINS. Many types of bacteria can be stained by these methods, although differentiation as to Gram positive or Gram negative is not always reliable.

ZIEHL–NEELSEN STAIN. Acid-fast organisms can be stained with this carbol fuchsin–methylene blue technique.

FITE–FARACO STAIN. For demonstrating lepra bacilli, this is a superior acid-fast stain.

ALCIAN BLUE. When performed at the appropriate pH, this technique can be used to demonstrate acid mucopolysaccharides and capsules of cryptococci.

SUDAN STAINS. These oil-soluble compounds are used to demonstrate fat emboli and myelin breakdown products.

VERHOEFF'S ELASTIC STAIN. Elastic fibers in vessel walls are clearly demonstrated by this relatively simple technique.

FONTANA'S SILVER STAIN. Melanin, including neuromelanin, is stained black by this method.

VON KOSSA'S STAIN. This procedure is often described as a stain for "calcium." It actually demonstrates the phosphates that are combined with the stainable "calcium."

PRUSSIAN BLUE STAIN. This reaction is used to demonstrate iron.

Muscle

Whenever possible, specimens of muscle should be frozen rapidly with liquid nitrogen and sectioned in a cryostat. Even specimens obtained at autopsy several hours postmortem can be processed in this fashion. The following stains are commonly performed on the frozen sections.

HEMATOXYLIN AND EOSIN (H&E). This stain is routinely employed for a general evaluation of the specimens.

"MODIFIED" TRICHROME STAIN. In unfixed frozen sections, both muscle and connective tissue stain varying shades of green. This stain is routinely performed for general evaluation of the specimens and for the detection of certain specific pathologic processes such as target fibers, "ragged-red" fibers, nemaline rods, and cytoplasmic bodies.

PERIODIC ACID–SCHIFF–HEMATOXYLIN (PASH). Although intended primarily for the recognition of abnormal carbohydrate deposits, this technique is useful for the general evaluation of specimens and for revealing ring fibers.

ADENOSINE TRIPHOSPHATASE (ATPase). This reaction is routinely performed twice—after incubation at pH 9.4 and at pH 4.3. At pH 9.4, the type 1 myofibers are light and the type 2 myofibers are dark. At pH 4.3, the type 1 myofibers are dark and the type 2 myofibers are light. These reciprocal staining reactions are used for the evaluation of the number, size, and distribution of the two major fiber types.

NICOTINAMIDE ADENINE DINUCLEOTIDE–TETRAZOLIUM REDUCTASE (NADH-TR). This reaction stains the type 1 fibers darker than the type 2 fibers. It demonstrates target fibers very distinctly and tends to stain denervated fibers darkly regardless of their fiber type.

MYOPHOSPHORYLASE. This histochemical reaction is used primarily for the diagnosis of McArdle's disease.

For the preparation of paraffin-embedded sections of skeletal muscle, fixation in Heidenhain's SUSA solution is superior to the use of formalin. Staining with hematoxylin and eosin, trichrome, periodic acid–Schiff–hematoxylin and phosphotungstic acid– hematoxylin provide the maximal information.

Useful information also can be obtained by light microscopy of epoxy-embedded sections of skeletal muscle. For these preparations, the tissue is fixed in glutaraldehyde and postfixed in osmium tetroxide solution. The sections can be stained satisfactorily with toluidine blue. Pathologic changes such as "Z disk streaming," target fibers, cytoplasmic bodies, nemaline rods, tubular aggregates, and vacuoles can be seen readily. When indicated, the same blocks can be sectioned for electron microscopy.

Peripheral Nerves

Whenever possible, peripheral nerve specimens should be processed by a variety of techniques, each of which having special merit. The following stains are commonly performed on paraffin-embedded sections.

HEMATOXYLIN AND EOSIN (H&E). Although this procedure is routinely employed for a general evaluation, it provides relatively little information on peripheral nerve specimens. Probably it is most useful for the detection of vasculitis.

TRICHROME STAINS. These stains are more useful than H&E for the general evaluation of peripheral nerve specimens, since the myelin sheaths are stained red to orange.

LUXOL FAST BLUE–PERIODIC ACID–SCHIFF–HEMATOXYLIN (PASH-LFB). Although this is a simple method for staining myelin, its use on peripheral nerve is complicated by the heavy staining of the connective tissue.

CONGO RED. As in the central nervous system, this is the preferred technique for the light microscopic identification of amyloid. The staining must be confirmed by the demonstration of a yellow-green birefringence color when examined with polarized light.

BODIAN, BIELSCHOWSKY, ETC. The use of these silver stains for the evaluation of axons in peripheral nerves is complicated by extensive staining of connective tissue.

Epoxy-embedded sections stained with toluidine blue or p- phenylenediame are almost always superior to paraffin-embedded sections for the light microscopic examination of peripheral nerve specimens. Furthermore, the same blocks can be sectioned for electron microscopy. Electron microscopy is the only reliable technique for examination of unmyelinated axons.

Teased nerve preparations are highly informative but are tedious to prepare. Even incompletely teased nerve specimens can be useful. Examination with polarized light will often enhance visualization of the myelin sheaths. These preparations are the most reliable means for detecting segmental demyelination. (See Chapter 11, Peripheral Nerves and Neuropathies, for discussion of preparative technique and interpretation.)

Pituitary

Unfortunately, formalin fixation and simple stains such as hematoxylin and eosin, trichrome, and periodic acid–Schiff–hematoxylin are inadequate for the examination of the pituitary. For the routine evaluation of pituitary lesions, we fix the specimens in Heidenhain's SUSA solution. Paraffin-embedded sections are stained with hematoxylin and eosin, aldehyde thionine–PAS–hematoxylin–orange G, and PAS–hematoxylin–light green–orange G. These techniques allow clear differentiation of acidophils, β_1 basophils, β_2 basophils, and delta cells. For the practical diagnosis of most pituitary adenomas, they are quite sufficient. The procedural details for these stains can be found in McCormick and Halmi (see Bibliography).

NEURONAL FIBROUS PROTEINS

The neuronal fibrous proteins have been the subject of intensive investigation in recent years. The current classification is based on ultrastructural and biochemical criteria. Much confusion has arisen because of changing terminology. Furthermore, these categories cannot be distinguished from one another by light microscopy of silver-stained sections, the classical histologic technique for demonstrating "neurofibrils" and "neurofibrillary tangles."

NEUROTUBULES. Neurotubules are long, smooth tubules with a circular cross section and a diameter of 24 nm. Short sidearms are sometimes demonstrable. Neurotubules are present in normal neurons and are more numerous in dendrites than in axons. They are analogous to the microtubules that are found in all animal and plant cells. Neurotubules have been extensively characterized chemically and are thought to be involved with maintenance of form and rapid transport in neurons.

NEUROFILAMENTS. Neurofilaments are long, thin filaments with a circular cross section and a diameter of 10 nm. Sidearms are frequently demonstrable. The neurofilaments are present in normal neurons and act as a cytoskeletal element. They proliferate in neurons undergoing axonal reaction or transsynaptic degeneration. Marked proliferations of neurofilaments are found in cases of Pick's disease, neuroaxonal dystrophy, and certain cases of motor neuron disease.

Accumulations of morphologically similar filaments that may have a different chemical composition are found in neurons exposed to various mitotic spindle inhibitors, aluminum compounds, or certain lathyrogenic agents.

MICROFILAMENTS. Microfilaments are thin filaments with a circular cross section and a diameter of 4 to 7 nm. They are chemically similar to actin and are found clustered beneath the axolemma of growth cones.

PAIRED HELICAL FILAMENTS ("TWISTED TUBULES"). These are elongated helical structures formed by a pair of filaments. They have a maximal diameter of 22 nm and periodically constrict to about 10 nm at intervals of about 80 nm. Paired helical filaments are regarded as pathologic intraneuronal structures. They comprise the Alzheimer's neurofibrillary tangles found in old age, Alzheimer's disease (senile and presenile dementia), and Down's syndrome; the mesencephalic neurofibrillary tangles found in certain cases of parkinsonism; and Pick bodies in certain cases of Pick's disease.

SMOOTH FILAMENTS OR TUBULES. Long, smooth filaments or tubules with a maximal diameter of 15 nm have been reported to comprise the neurofibrillary tangles found in the brain stem of some patients with the Steele-Richardson-Olszewski syndrome.

SELECTED NEURONAL ALTERATIONS

"ISCHEMIC" CHANGE. Ischemic, or severely anoxic, neurons are characterized by shrunken angular perikarya, intensely eosinophilic cytoplasm, and pyknotic nuclei. Similar changes can occasionally result from autolysis. A similar configuration but lacking the acidophilia can result from mechanical trauma, the so-called biopsy artifact.

CHROMATOLYSIS. This neuronal alteration follows axonal injury and is characterized by an enlarged globular perikaryon and loss of the Nissl granules, especially from the central portion of the cell. This change is probably a manifestation of attempted cellular repair rather than merely a reaction to injury.

"STORAGE." Neurons containing abnormal accumulations of lipids, carbohydrates, or lipofuscin are often characterized by a globular configuration of the perikaryon, a finely granular or vacuolated cytoplasm, and displaced Nissl granules. Conventional light microscopy and histochemistry are of limited value in distinguishing among the various metabolic disorders that produce neuronal storage.

GRANULOVACUOLAR "DEGENERATION" (OF SIMCHOWICZ). This process results in the presence of one or more vacuoles 4 to 6 μ in diameter that contain a central granule. This alteration is most prevalent in the pyramidal cells of the hippocampus from individuals with Alzheimer's disease.

COWDRY TYPE A INCLUSIONS. There are single, large intranuclear inclusions often surrounded by a halo resulting from margination of the chromatin. They are characteristic but not pathognomonic of viral infections and may be found in patients with herpes simplex, herpes simiae, varicella zoster, cytomegalovirus, and subacute sclerosing panencephalitis.

COWDRY TYPE B INCLUSIONS. These are small, often multiple intranuclear inclusions lacking a halo. They may be seen in viral infections but are less characteristic. They may be seen in some cases of subacute sclerosing panencephalitis. The Marinesco body is a common example of a nonviral Cowdry type B inclusion.

NEGRI (LYSSA) BODIES. These eosinophilic intracytoplasmic inclusions are found in about 70 percent of patients with rabies.

ALZHEIMER'S NEUROFIBRILLARY TANGLES. These are torch- or flame-shaped intracytoplasmic fibrillary structures, classically demonstrated by silver stains. Ultrastructurally, they are composed of skeins of distinctive paired helical filaments. In large numbers, they are typical of Alzheimer's disease.

PICK BODIES. These are spherical intracytoplasmic bodies classically demonstrated by silver stains. Ultrastructurally, they are composed of aggregates of paired helical filaments and/or neurofilaments. They are typically seen in patients with Pick's disease.

LEWY BODIES. These are spherical to elongated, often concentrically laminated inclusions that are most abundant in the cytoplasm of pigmented neurons, e.g., substantia nigra, locus caeruleus, and dorsal motor nucleus of the vagus. They are characteristic of idiopathic parkinsonism.

LAFORA BODIES. These are variable-sized spherical inclusions found in the perikarya and even more abundantly in the processes of neurons. Ultrastructurally, they consist of unbounded radiating masses of branched fibrils. They are composed predominantly of glucose polymers. They are characteristic of myoclonus epilepsy.

HIRANO BODIES. These are spheroidal to spindle-shaped bodies found most abundantly in the hippocampi of patients with dementias or degenerative diseases. Ultrastructurally, they consist of multiple strata, each composed of intersecting arrays of parallel filaments. Hirano bodies are currently regarded as a nonspecific manifestation of chronic neuronal degeneration.

DENDRITIC "CACTI." This term is employed to describe prominent focal enlargements of Purkinje cell dendrites. They are encountered in certain storage diseases (e.g., Tay–Sachs' disease, ceroid–lipofuscinosis) and in certain cerebellar degenerations.

REACTIVE AXONAL SWELLINGS. These are focal enlargements that rapidly develop proximally and distally to the site of axonal transection. Ultrastructurally, the enlargements are filled with large numbers of axonal organelles.

DYSTROPHIC AXONS. These are prominent terminal and preterminal axonal swellings. They resemble reactive axons by light microscopy but differ ultrastructurally. They are found in certain degenerative diseases (neuroaxonal dystrophies), deficiencies, intoxications, and in the gracile and cuneate nuclei as a consequence of aging.

GLIA AND SELECTED GLIAL REACTIONS

NORMAL ASTROCYTES. These cells can be classified as protoplasmic or fibrous astrocytes according to the configuration of their processes, which are best demonstrated by metallic impregnation techniques. These techniques are not generally employed, and with the conventional stains, only the nuclei of normal astrocytes are apparent. One of the most significant structural features is the

presence of processes that extend to and encircle the capillaries. The pericapillary expansions are termed *foot plates*.

ASTROCYTIC REACTIONS. Astrocytes are sensitive to a wide variety of noxious stimuli and may respond by swelling and accumulating glycogen. This cytoplasmic swelling is the morphologic substrate of cytotoxic edema in the gray matter and accounts for the pericapillary and juxtaneuronal clear spaces seen in conventional sections. Other reactions to injury are cell multiplication and enlargement due to proliferation of intracytoplasmic glial filaments. The perikaryal cytoplasm of reactive astrocytes is conspicuous in conventionally stained sections. With long-standing but mild noxious stimuli, the glial filaments may degenerate and give rise to compact, finely granular masses termed *Rosenthal fibers*. By light microscopy, these appear as rounded or spindle-shaped acidophilic bodies. Astrocytic nuclei may harbor Cowdry type A inclusions in certain viral infections such as subacute sclerosing panencephalitis. Alzheimer's type II glia are enlarged astrocytes with pale lobulated nuclei that often contain spheroidal deposits of glycogen. These cells are often seen in hepatic disorders and are thought to be a response to elevated ammonia.

CORPORA AMYLACEA. These are amphophilic spheroids that are found predominantly in subpial, perivascular, and subependymal locations and increase in number with advancing age. Ultrastructurally, they appear as unbounded masses of granular and branched fibrillar material within astrocytic processes. Corpora amylacea are composed of glucose polymers similar to starch. The metabolic basis for their formation has not been ascertained.

OLIGODENDROCYTES. Oligodendrocytes are found as perineuronal satellite cells and as interfascicular glial cells responsible for the formation and maintenance of the myelin sheaths in the central nervous system. In contrast to the Schwann cell, a single oligodendrocyte is connected by long, thin processes to multiple internodal segments of myelin. Destruction of the oligodendrocytes results in breakdown of the myelin sheaths with preservation of the axis cylinders (primary demyelination), but destruction of the axis cylinders results in loss of the myelin sheaths and oligodendrocytes (secondary demyelination).

OLIGODENDROGLIAL REACTIONS. Cytoplasmic swelling, especially of the interfascicular oligodendrocytes produces a perinuclear halo that is commonly observed as an artifact in routinely processed nervous system tissue. Inclusions are regularly encountered in oligodendroglial nuclei in patients with certain viral infections, e.g., progressive multifocal leukoencephalopathy and herpes simplex encephalitis.

EPENDYMA. These are specialized glial cells that line the ventricular system, give rise to the choroid plexi, and line the patent or obliterated central canal of the spinal cord. The cells are characterized by specialized contacts between adjacent cells and the presence of blepharoplasts and/or cilia.

EPENDYMAL REACTIONS. The ependyma give rise to relatively few distinctive nonneoplastic reactions. Noxious stimuli can produce focal destruction of the ependymal cells with subsequent proliferation of the underlying astrocytes and residual ependymal cells. This produces grossly visible but fine elevations on the ventricular surfaces that are described somewhat incorrectly as "ependymal granulations." As a consequence of intraventricular bleeding, the epithelial cells of the choroid plexus may contain hemosiderin.

MICROGLIA. These nonneuroectodermal cells are thought to be derived from reticuloendothelial cells that are formed in the bone marrow. They are the principal phagocytic cells in the central nervous system. They may assume an elongated shape in certain chronic infections and are described as *rod cells* or they may become enlarged and filled with phagocytosed lipid and are described as *gitter cells*. Merely referring to them as *macrophages* would be more suitable and consistent with general pathologic terminology.

BLOOD–BRAIN BARRIERS

The blood–brain barriers are those structures and/or phenomena that regulate the passage of various substances between the blood and the central nervous system. Ehrlich (1885) had observed that certain intravenous dyes stained all tissues of the body except the brain and spinal cord. Goldman (1913) established the concept of a blood–brain barrier by contrasting the effect of intravenous trypan blue with subarachnoid trypan blue, which stained the central nervous system.

The anatomic structure of the blood–brain barrier has been investigated intensively by a variety of techniques. Chromatic and fluorescent dyes have been employed, but these compounds bind to serum proteins and thus reflect the location of the protein molecules. Electron-dense tracers have been selected according to desired molecular size and visualized with the electron microscope.

A barrier to molecules the size of serum proteins and the electron-dense tracers is present throughout most of the adult central nervous system (Fig. 2, top). The lumenal surface of the capillary endothelium is generally regarded as the site of this barrier. These capillaries are lined by nonfenestrated endothelium, and the adjacent endothelial cells are joined by tight junctions that are permeable to very small molecules and ions but impermeable to large molecules, including the tracers. Only a small number of pinocytotic vesicles are present in these endothelial cells, and vesicular transport is thought to play only a minor role in the central nervous system. The endothelium is surrounded by a basal lamina, but this is not a barrier to electron-dense tracers and may actually facilitate transport of certain substances. The capillaries are encircled by astrocytic processes that are joined to one another by "gap" junctions. These structures impose no barrier. The intercellular spaces throughout the neuropil are narrow but adequate to provide a functional pathway.

The blood–brain barrier is absent in special regions, including the area postrema, median eminence, intercolumellar tubercle, subcommissural organ,