

NEUROPATHOLOGY

2009

COLLEGE OF PHYSICIANS & SURGEONS

COLUMBIA UNIVERSITY

New York, New York

NEUROPATHOLOGY SYLLABUS

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MESSAGE FROM THE COURSE DIRECTOR

Welcome to the Neuropathology Course. We hope that you will find this to be a pleasurable and challenging introduction to diseases of the nervous system. During this phase of your medical school experience, you are expected to become familiar with the vocabulary, basic pathologic concepts and morphologic aspects of neurologic diseases. Traditionally, diseases of the nervous system have been classified or divided etiologically into vascular, metabolic, neoplastic, infectious, degenerative, demyelinating, traumatic and developmental categories. Diseases of the neuromuscular system have been segregated somewhat, but can be divided similarly. This approach is still considered to be the most effective and understandable way to present this myriad of afflictions, but it often seems disjointed to the novice. So, be patient and we believe that things will fall into place by the end of the course.

We shall try to emphasize common entities in the lectures, the small groups and images reviews, but prototypes of rare diseases also will be presented to provide you with an overview and perspective. The main purpose of the formal lectures is the presentation of conceptual, nosological, or pathogenetic aspects of neuropathology. In the small groups, we will reinforce material from lectures largely through review of images. Additionally, we will illustrate the application of basic neuropathologic principles to problem solving and analysis in the clinical setting. To this end, we will discuss a series of clinical cases in the group sessions. We will enlist your help in generating differential diagnoses to give you a feel for how we approach neurological diseases. We have included a lecture on Neuroimaging since this area is currently expanding tremendously and a basic appreciation of techniques and the value, and limitations, of those techniques will assist you in many areas of your clinical training.

The Course Syllabus will be used in lieu of the textbook. We have intentionally listed somewhat extensive chapters, too much to be used in a short course. These readings are for those of you who wish to explore material in more detail.

Images for the small group sessions are online at the following website:

www.columbia.edu/itc/hs/medical/pathology/pathoatlas. This will lead you to the site that contains images for all pathology courses (topic bar will say 'General Pathology'). Scroll down to the 'Neuropathology' section to access images for this course. Access to this site is possible both on and off campus.

A large number of additional websites are available that may enhance your learning, if you wish to investigate them. At **www.neuropat.dote.hu/** you will find a large online resource with links to Neuroanatomy, Neuropathology and Neuroradiology. The website at University of Rochester (www.urmc.rochester.edu/neuroslides) is useful and contains neuroradiology along with pathologic images. If you want to review some normal neurohistology, there is an interesting "virtual slide box of histology" at www.medicine.uiowa.edu/pathology/nlm_histology. There are many others to explore.

Finally, constructive criticism and comments are welcome and should be referred to the course director. Phone and office numbers are given for the preceptors and we encourage you to make use of this resource outside of our formal teaching plan. We hope and expect that this will be a good learning experience for you.

NEUROPATHOLOGY SMALL GROUP SCHEDULE - 2008-2009

Tues., 12/8	11:00-12:50	Prec.Rms.	Introduction to Cellular Neuropathology/Cerebral Edema Cerebrovascular Diseases Review
Weds., 12/9	11:00-12:50	Prec.Rms.	Infectious Diseases Review Case 1: Cerebrovascular Diseases
Thurs., 12/10	11:00-12:50	Prec.Rms.	Dementia and Degenerative Diseases & Metabolic Diseases Review Case 2: Dementia
Fri., 12/11	11:00-12:50	Prec.Rms.	Developmental Disorders & Brain Tumors Review Case 3: Brain tumors
Mon., 12/14	11:00-12:50	Prec.Rms.	Diseases of Myelin Review Case 4: Myelin
Tues., 12/15	11:00-12:50	Prec.Rms	Diseases of Nerve & Muscle Review Case 5: Nerve/Muscle
Weds., 12/16	11:00-12:50	Prec. Rms	Trauma Review Review Session for exam

NEUROPATHOLOGY COURSE FACULTY

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CELLULAR NEUROPATHOLOGY

James E. Goldman, M.D., Ph.D.

CELLULAR NEUROPATHOLOGY

At the beginning of this course, it is useful to consider each class of cells in the nervous system separately and to examine the diverse pathologies that may affect each of them. You will discover that these alterations are common to a variety of neuropathological disorders.

NEURONS

A. Cell body

1. **Acute ischemic or hypoxic damage** produces a shrinkage of the cell body and a hyper eosinophilia. The nucleus becomes pyknotic. These are thought to be irreversible and lethal changes [CN-1].
2. **Atrophy**, a non-eosinophilic shrinkage of the cell body [CN-2], is the hallmark of many neurodegenerative disorders (eg. Alzheimer, Parkinson, and Huntington diseases). The neuron may be involved directly or indirectly, through retrograde (via efferents) or anterograde (via afferents) transneuronal or transsynaptic degeneration.
3. **Chromatolysis** results from axon damage (including axon transection). The cell body becomes hypertrophic and loses its Nissl substance (rough ER) [CN-3]. Chromatolysis may be followed by regrowth of the axon from the point of damage, a phenomenon more often seen in the peripheral than in the central nervous system.
4. In neuronal **storage** diseases, excessive amounts of lipids, carbohydrates, glycosaminoglycans, or glycoproteins accumulate within neurons, enlarging and distorting the normal geometry of the cell body and proximal processes. These are usually seen in the context of inherited disorders of lipid or glycosaminoglycan catabolism (eg. Tay Sachs disease, mucopolysaccharidoses). In many of these diseases, similar storage material accumulates in glial cells.
5. **Inclusions** represent abnormal nuclear or cytoplasmic structures. Some reflect the focal storage of metabolites, some the presence of viral proteins or nucleoproteins, and some the abnormal accumulation of structural proteins (eg. neurofibrillary tangles, Lewy bodies).
6. **Lipofuscin** is an insoluble mix of proteins, lipids, and minerals that accumulates in neurons and astrocytes during the normal aging process.
7. **Neuronophagia** is the phagocytosis of degenerating neurons, usually by macrophages. This is commonly seen after hypoxic or ischemic insults or during viral infections.

B. Axon

1. **Wallerian degeneration** is the loss of the axon (and its myelin sheath) distal to the point of axonal damage [CN-4].
2. **Dying back degeneration**, a degeneration of the most distal axon, followed by the progressive loss of more and more proximal regions, is often seen in toxic peripheral neuropathies.
3. **Demyelination** refers to the primary loss of myelin with relative preservation of the axon (eg. as in multiple sclerosis) [CN-5].
4. A **spheroid** is a focal enlargement of an axon due to damage, regardless of cause [CN-6]: trauma, local areas of necrosis, or toxic-metabolic insults. Spheroids contain mixtures of lysosomes, mitochondria, neurofilaments, and other cytoplasmic constituents. Slowing or cessation of axoplasmic transport at sites of damage presumably account for spheroids.

C. Dendrite

1. **Hypoplasia** refers to an inadequate development of dendritic branches. This is seen in many types of mental retardation, including congenital hypothyroidism (cretinism).
2. **Atrophy** is a reduction in the volume and surface area of dendritic branches, commonly seen in neurodegenerative diseases.

D. Neuropil

1. **Neuritic plaques** are collections of degenerating axons and dendrites, mixed with microglia and astrocytes and associated with the extracellular deposition of amyloid (beta-amyloid, see lecture on Neurodegenerative diseases).
2. **Status spongiosis** refers to a spongy state of the neuropil, the formation of fine to medium sized vacuoles representing swollen neuronal and astrocytic processes. This change is typical of transmissible spongiform encephalopathies, such as Creutzfeldt-Jacob disease.

ASTROCYTES

Astrocytes are found in all brain regions. They contact blood vessels, pial surfaces, and enfold synapses in their functions to maintain the concentration of ions, neurotransmitters, and other metabolites within normal levels in the extracellular space. They also play a fundamental role in inducing blood brain barrier functions in cerebral vessels [CN-7].

1. Astrocytes undergo **hypertrophy** (enlargement) and **hyperplasia** (proliferation) in response to a great many pathological processes, including hypoxic-ischemic damage and trauma. Astrocytes form the majority of scars in the CNS (unlike other organs, in which scars are typically collagenous, formed by fibroblasts). Astrocytes develop abundant pink cytoplasm, either due to imbibing plasma proteins and fluid in the short-term (when the blood-brain-barrier is broken) or filling up with intermediate filaments (in long-term scarring). The descriptive term of **reactive, hypertrophic** or **gemistocytic** is often used to describe this change.
2. **Alzheimer type II astrocytes**, which display a swollen, lucent nucleus and swollen cytoplasm, are found in gray matter in patients with chronic or acute liver disease. They are thought to be related to the hyperammonemia of hepatic failure (see notes on Metabolic diseases).
3. **Inclusions: Rosenthal fibers** are eosinophilic, refractile inclusions composed of intermediate filaments and small heat shock proteins, found in low grade, pilocytic type of astrocytomas, Alexander's disease (a rare leukodystrophy) and occasionally in old scars [CN-8]. **Corpora amylacea** are spherical accumulations of polyglucosan (branched-chain glucose polymers), which increase in numbers with age, particularly in a subventricular and subpial locations, and in glial scars. **Viral inclusions** occur in cytomegalovirus infections.
4. **Neoplasia:** Astrocytomas represent a common form of brain tumor (see notes on neoplasia)
5. Astrocytes become **phagocytic** after damage to the CNS.
6. **Storage:** see above.

OLIGODENDROCYTES

Oligodendrocytes are the myelinating cells of the CNS.

1. **Demyelination:** see under Axons (above). Note that oligodendrocytes or progenitors of oligodendrocytes are able to remyelinate demyelinated axons, and thus help to repair demyelinated lesions.
2. **Myelin edema:** In certain toxic and metabolic settings, fluid accumulates within myelin sheaths, leading to intramyelinic edema.
3. **Cell loss** of oligodendrocytes occurs in a variety of disorders, including immune mediated (multiple sclerosis), viral (papova virus of progressive multifocal leukoencephalopathy), and toxic (e.g. psychosine).

4. **Viral inclusions** form in oligodendrocytes in progressive multifocal leukoencephalopathy.
5. **Neoplasia:** Oligodendrogliomas represent another common primary CNS neoplasm (see notes on neoplasia).

EPENDYMAL CELLS

Ependyma line the ventricular surfaces.

1. **Cell loss:** Many noxious stimuli (e.g. increased intraventricular pressure, intraventricular blood, infectious organisms) can destroy ependyma with resultant loss of ependymal lining and proliferation of subependymal astrocytes (granular ependymitis).

2. **Neoplasia:** Ependymomas (see notes on neoplasia).

MICROGLIA

Microglial cells are bone marrow derived, and enter the CNS during embryonic development. The nature and functions of microglia in the normal CNS are not clear, but in pathological states, microglia turn into **macrophages** [CN-9] (eg. infarcts, trauma, hemorrhages, demyelinating diseases, necrosis accompanying tumors). Lesions in which the blood-brain-barrier is disrupted seem to induce the transit of monocyte-macrophage cells from the circulation into the CNS to participate in phagocytic activity. Microglia are also the most effective **antigen-presenting** cells in the CNS.

ENDOTHELIAL CELLS

Tight junctions between cerebral endothelial cells are the major determinants of the blood-brain-barrier.

1. **Hypertrophy and hyperplasia** of endothelial cells is commonly seen in ischemia and in the vicinity of primary and metastatic neoplasms.

2. Changes in the vessel wall accompany a large number of disorders (eg. **fibrotic and hyalin thickening** in hypertension, radiation damage, and atherosclerosis).

3. **Cell loss** is seen in radiation damage, ischemia, lead, rickettsiae and viruses [CN-10].

SCHWANN CELL

Schwann cells are the myelinating cells of the peripheral nervous system. (good regenerative potential; loss of myelin sheath accompanies loss of Schwann cell or axon)

1. Schwann cells are lost in **demyelinating** peripheral neuropathies. Non-myelinating Schwann cells are able to **remyelinate** demyelinated internodes.
2. **Storage:** see above. of abnormal
3. Schwann cells are also lost in certain **toxic** (eg. lead) and **infectious** (eg. leprosy) peripheral neuropathies.
4. **Schwannomas** are common, usually benign, neoplasms of peripheral nerves (see notes on neoplasia).

SUPPLEMENTARY READING:

1. "Cellular Pathology of the Central Nervous System" by G.W. Kreutzberg, W.F. Blakemore, and M.B. Graeber, pp. 85-156, Vol. 1; in Greenfield's Neuropathology, 6th ed., D.I. Graham and P.L. Lantos, eds.; Arnold, London, 1997.
2. "Diseases of the Peripheral Nerve" by P.K. Thomas, D.N. Landon, and R.H.M. King, pp367-487, Vol. 2; in Greenfield's Neuropathology, 6th ed., D.I. Graham and P.L. Lantos, eds.; Arnold, London, 1997.
3. "Textbook of Neuropathology" by R.L. Davis and D.M. Robertson, 3rd ed. pp. 1-205, Williams and Wilkins, Baltimore, 1997.

CEREBRAL EDEMA, INTRACRANIAL SHIFTS, AND HERNIATIONS

James E. Goldman, M.D., Ph.D.

I. ANATOMIC CONSIDERATIONS

1. It is important to review gross neuroanatomy and appreciate the anatomic relationships among the medial temporal lobe, tentorium cerebelli, the brain stem and upper cranial nerves, and the vertebro-basilar artery system (posterior circulation).
2. The brain is restricted by the skull and by two dural reflections. **The falx cerebri** acts as an incomplete partition separating the hemispheres in the sagittal plane, stopping just above the corpus callosum. The **tentorium cerebelli**, a horizontal reflection, which lies on the superior surface of the cerebellum, separates supra- from infra-tentorial spaces. The tentorium is open in the ventral midline to allow the midbrain to pass through (tentorial notch). Thus, each free edge of the tentorium lies adjacent to either side of the midbrain.
3. The brain itself, is not readily compressible. Small increases in volume of the brain may be tolerated, since there is some room for expansion (compression of ventricles and subarachnoid space). Large increases in volume cannot be tolerated, as they may be in visceral organs, without serious consequences. Should rapid expansion occur in one part of the brain, there will be **compromise of adjacent tissue**. Local expansion leads to local increase in pressure, and consequently to pressure gradients within the brain. These gradients result in shifts of tissue (deformation of brain substance). Thus, **structures at a distance from the main focus of a lesion can also be compromised**. Some of the important types of shifts, their pathological consequences, and clinical manifestations will be outlined below.
4. The blood-brain barrier (BBB): CNS capillaries differ from those in other organs, in that endothelial cells are linked by tight junctions. Furthermore, CNS capillaries are not fenestrated, and endothelial pinocytotic activity is limited, under normal conditions. Thus, most substances do not pass readily from blood vessels into the brain parenchyma.

II. BRAIN EDEMA

1. This is defined as an increase in volume and weight of the brain due to fluid accumulation. Edema is a common complication of many kinds of intracranial lesions, and a serious one because it produces an additional increase in volume over and above that resulting from the lesion itself. It is useful to divide cerebral edema into two categories - **vasogenic** and **cytotoxic**.
2. Vasogenic edema results from increased **vascular-permeability**. This may be due to several alterations:
 - a) destruction of vessels (e.g. trauma, hemorrhage),
 - b) increased pinocytotic activity,

c) the growth of capillaries that do not have a competent BBB (e.g.: vessels in tumors, either CNS or metastatic, or in granulation tissue).

The extent of edema is influenced by

- a) the mean systemic blood pressure and
- b) the duration of incompetence of the BBB.

Edema arising focally (e.g.: tumor, infarct, local infection) can spread through the CNS. Movement through white matter occurs more easily than through gray matter, since in the former, the extracellular space is irregular and wider (up to 800Å). Fluid spread through gray matter is restricted, because extracellular space is narrower (100-200Å) and there are many synaptic junctions.

Vasogenic edema fluid is a plasma filtrate, containing variable amounts of plasma proteins.

3. Cytotoxic edema refers to **swelling of cellular elements in the presence of an intact BBB**. Two examples of this are the consequences of triethyl tin and hexachlorophene toxicity (the former was used in cosmetics, the latter is a disinfectant). Both compounds cause an accumulation of fluid within the lamellae of myelin sheaths, inducing splits and blebs in the myelin. The fluid is an ultrafiltrate, and does not contain plasma proteins.
4. Edema accompanies ischemic infarcts. A characteristic pattern of edema formation has been observed in animal models of ischemic brain damage. Early changes include an increase in water content, then swelling of astrocyte processes. After several hours breakdown of the BBB occurs. Thus, the early edema after ischemic injury is cytotoxic, whereas the later edema has a vasogenic component.

III. HYDROCEPHALUS

A number of the lesions discussed in this lecture are associated with **hydrocephalus**. This term refers to the enlargement of ventricles, produced by (1) most commonly, an imbalance between the production of CSF and its resorption, or (2) atrophy of the brain (hydrocephalus ex vacuo). Usually, production of CSF by choroid plexus and at extra-choroidal sites is balanced by resorption from the subarachnoid space through arachnoid villi into dural sinuses. There are several general causes of hydrocephalus.

- A. Rarely, overproduction of CSF by choroid plexus papillomas.
- B. Obstruction within the ventricular system leads to **obstructive or non-communicating** hydrocephalus. Many lesions can cause this. **Stenosis** of the **aqueduct of Sylvius** is produced by infection or inflammation of the ependymal lining, by masses in the brain stem or posterior fossa that compress the aqueduct, or by hemorrhage and consequent scarring (as in intraventricular

bleeds). **Arnold-Chiari** malformations are a common cause of childhood hydrocephalus. The **Dandy-Walker** Syndrome is one in which the midline cerebellum does not form properly and the IVth ventricle enlarges to form a posterior fossa cyst. Occlusion of the IVth ventricular foramina leads to hydrocephalus.

- C. A block of CSF resorption is a communicating hydrocephalus, so-called because there is free flow of CSF from the ventricles into the subarachnoid space. Causes include meningitis, diffuse meningeal tumors, (such as lymphomas), subarachnoid hemorrhage, (leading to **fibrosis**), and dural sinus thrombosis.

Chronic hydrocephalus is usually progressive, leading to developmental failure in children. The treatment is either to remove the obstruction (if that can be done) or to place a shunt from the ventricles into some other body site where absorption of the extra fluid is relatively efficient. This site is often the pleural or peritoneal cavity. If the elevation in pressure is not relieved, CSF may breach the ependyma and extend into the extracellular space of the periventricular white matter (**interstitial edema**).

IV. INCREASED INTRACRANIAL PRESSURE

Intracranial pressure (ICP) is normally maintained by maintaining intracranial volume, through cerebral blood flow regulation and by a balance of cerebrospinal fluid production and resorption. Normal ICP limit falls below 15 mmHg. Increases in ICP can result from mass lesions, edema, or changes in the volume of intracranial blood or cerebrospinal fluid.

1. **Mass lesions:** Increased ICP is a major, serious complication of a variety of mass lesions - tumors, hematomas, abscesses, or granulomas, for e.g. Brain edema, due to incompetence of the BBB in these lesions, may further increase ICP.
2. **Edema:** Most commonly, edema is **focal**, occurring about lesions where there is BBB breakdown. **Generalized cerebral edema**, although rare, is observed in several settings: **Pseudotumor cerebri**, a condition seen largely in young woman, associated with obesity and endocrine dysfunction, produces headache and papilledema. The latter, if untreated, may result in visual field defects and even blindness. Generalized edema can also be seen in **Reye's syndrome**, viral encephalitis, and rarely, in diabetic ketoacidosis.
3. **Vascular changes:**
 - a) Compression of jugular veins leads to increased intracranial blood volume and increased ICP. Compression of abdominal veins by the Valsalva maneuver increases intraspinal pressure. This can be used in testing patency of the subarachnoid space, since, with a cervical or thoracic mass lesion, Valsalva produces a quick rise in lumbar pressure,

measured at lumbar puncture, but jugular compression will not. If the block is partial, a slow rise after jugular compression may be seen.

b) Hypercapnea causes intracranial vasodilatation. The increased ICP seen in some patients with pulmonary disease may be due in part to vasodilatation from CO₂ retention.

c) Head trauma is sometimes accompanied by a loss of the normal vasoregulation of the intracranial circulation, leading to uncontrolled vasodilatation. This complication, which appears to be more prevalent in children, leads to increased ICP. The loss of vasoregulation is usually transient, but requires treatment to prevent irreversible brain damage.

4. **Cerebrospinal fluid:** Blockage of CSF pathways can lead to increased ICP. Removal of CSF by lumbar puncture will transiently decrease ICP.
5. **Serum osmolality:** The brain, like other tissues, is in osmotic equilibrium with blood. Hypo-osmolal states, such as water intoxication, will lead to an increase in brain water, and brain volume. Symptoms of headache, seizures, and eventually even coma can occur with a fall from the normal 310 milliosmoles (mosm) of serum to 260 mosm. Hyper-osmolal states produce CNS dehydration. When serum osmolality rises to about 380 mosm, dehydration and brain shrinkage may produce mechanical distortion, with tearing of blood vessels. This complication is more important in dehydrated infants, or those fed inadvertently with too much salt in the formula. In adults, in whom it is rare, it is seen only in severe dehydration or uremia.

Continuous pressure measurements in patients with increased ICP have demonstrated that ICP does not remain constant, but that there are episodic increases reaching over 50 mmHg and lasting 5 to 20 minutes. These elevations, called **plateau waves**, apparently reflect hyperemia. An increase in cerebral blood volume accompanies plateau waves. Plateau waves may be associated with transient worsening of neurologic deterioration.

It is important to realize that the brain is **intolerant of rapid volume changes** but can adjust to slow changes. Slowly growing lesions (eg: meningiomas), may reach substantial size without producing an increased ICP. The brain adjacent to such a lesion will be compressed and gliotic, however.

V. PATHOLOGIC CONSEQUENCES OF INCREASED ICP.

- A. **Generalized increase in intracranial volume leading to increased ICP** (for eg: pseudotumor cerebri): signs and symptoms include headache, nausea, vomiting, papilledema, and, rarely, a sixth nerve palsy (false localizing sign). In pseudotumor cerebri, there is no obstruction to CSF flow nor is regulation of cerebral blood flow disturbed. Brain volume is increased diffusely. Consequently, shifts in brain substance usually do not occur.

- B. Shifts occur when pressure gradients develop within the CNS.** Local increases in pressure, due to the increase in volume of mass lesions, cause shifts away from the lesion. Areas remote from the lesion as well as areas adjacent to the lesion may therefore suffer distortion. If the distortion is severe enough to interfere with blood flow, tear vessels, or compress CNS fiber pathways or cranial nerves, then clinically significant effects occur.

The most serious CNS distortions are the **herniations**.

- 1. Cingulate herniation:** A lateral hemispheric lesion will shift that hemisphere medially, pushing the ipsilateral cingulate gyrus under the free edge of the falx cerebri. This may compress the internal cerebral vein and the ipsilateral anterior cerebral artery.
- 2. Uncal herniation:** With supratentorial lesions, particularly those in the temporal and lateral parietal lobes, the increased pressure is directed medially and downward, forcing the most medial part of the temporal lobe - the uncus and hippocampal gyrus - over the free edge of the tentorium cerebelli. Several important consequences ensue. The ipsilateral IIIrd nerve is compressed by the uncus against the tentorial edge or, anteriorly, against the supraclinoid ligament, leading to **ipsilateral pupillary dilatation**, one of the earliest signs of uncal herniation, and eventually to ipsilateral oculomotor palsy. The herniating uncus will push against the midbrain, compressing the ipsilateral cerebral peduncle or forcing the contralateral cerebral peduncle against the contralateral free edge of the tentorium and resulting in hemorrhage and pressure necrosis of the peduncle. **Ipsilateral peduncular compression leads to hemiparesis or hemiplegia on the side opposite the lesion, while contralateral peduncular compression leads to hemiparesis or hemiplegia, ipsilateral to the original lesion** (contralateral compression is known as Waltman-Kernohan's notch). The **ipsilateral posterior cerebral artery may be compressed**, leading to ischemic necrosis in its arterial supply: infarcts of the calcarine cortex produce a hemianopsia; infarcts of the posterior thalamus may also occur.

With increasing ICP and further herniation, pressure is transmitted to middle and lower brain stem levels, causing the stem to buckle. Pathophysiology of stem dysfunction includes ischemic changes, due to vascular compression, and hemorrhages (**Duret hemorrhage**). The latter are often multiple, appear in the lower midbrain and pons, and predominate in the midsagittal region. Duret hemorrhages are arterial, resulting from stretching of perforating vessels of the stem.

Clinical signs referable to brain stem compromise during herniation progress in a rostral to caudal fashion. Ipsilateral pupillary dilatation

usually occurs first (midbrain). **Disappearance of oculocephalic and oculo-vestibular reflexes** indicates pontine dysfunction. **Coma** develops as midbrain and pontine reticular formation is compromised. In late stages, the eye signs and pyramidal tract signs may become bilateral.

- 3. Central herniation:** Supratentorial lesions produce a downward shift of the hemisphere, first compressing the diencephalon, then forcing the midbrain down through the tentorial notch, and eventually distorting pons and medulla. Mass lesions of the frontal, parietal, or occipital lobes, or extracerebral lesions at the vertex may cause this. Also, in diseases such as Reye's syndrome or in trauma with loss of vasoregulation, the hemispheric white matter may swell diffusely, faster than the brain stem, producing a downward pressure gradient. **Progression of signs reflects a rostral-to-caudal progression of the herniation.** Signs of diencephalic dysfunction include **decreasing alertness progressing to stupor or coma** (upper reticular formation), **small pupils, Babinski reflexes, Cheyne-Stokes breathing, and decorticate posturing.** Midbrain signs include moderate **pupillary dilatation, dysconjugate eye movements, hyperventilation, and decerebration.** Pontine and upper medullary signs include **loss of oculocephalic and oculo-vestibular reflexes, shallow, irregular breathing, and flaccidity of limbs.** Pupils are in midposition and unresponsive. Medullary involvement produces **irregular respiration, apneic periods, tachy- or bradycardia, and hypotension.** This is a **terminal** stage.
- 4. Cerebellar tonsillar herniation:** The cerebellar tonsils are displaced downward through the foramen magnum. This can be seen as a late stage of uncal or central herniation, or may result from rapidly expanding cerebellar lesions. The tonsils are compressed against the margins of the foramen magnum, causing tonsillar necrosis. More importantly, the herniating tonsils squeeze the medulla, producing medullary paralysis and death (**loss of consciousness, bradycardia, irregular respirations or apneic periods, and hypotension**). **Cerebellar masses may produce signs of lower midbrain and of pontine compression also.**

VI. TREATMENT

Brain herniations are medical emergencies. The most appropriate treatment is removal of the mass lesion, but there are many instances when, because of the location of lesions, the rapidity with which brain swelling occurs or because of the presence of hemorrhages, such intervention is not feasible. In critical situations, the use of osmotically active substances is often life saving. Brain capillaries are impermeable to most substances, the exceptions being gases (O₂, CO₂, N₂O, anesthetics, etc.), glucose, H₂O, and lipid soluble substances (such as many drugs). Hence, an osmotic gradient is easily established between brain and plasma water. **Urea, mannitol, and glycerol** are the osmotic agents

used. These agents dehydrate the brain; areas of cerebral edema are less easily dehydrated than normal brain tissue, but the net effect in reducing intracranial pressure is, nevertheless, beneficial.

The diuretic furosemide is also found to be of use in reducing cerebral edema. This agent acts not only by increasing serum osmolality, but it also acts specifically on the choroid plexus to reduce the rate of formation of CSF, thereby lowering intracranial pressure.

Corticosteroids are most important in treating cerebral edema, especially the synthetic steroids prednisolone and dexamethasone. The beneficial effects of steroid therapy in patients with cerebral edema secondary to tumors and in pseudotumor cerebri are well established. There is controversy as to whether steroids are effective in ischemic edema associated with strokes, but their use in patients with stroke is widespread. Steroids are very effective in reducing the edema secondary to abscesses or tuberculous meningitis, but they must be used with special caution, since they may depress the host's resistance to the primary infections. Improvement becomes evident within 24 hours after initiation of treatment and can be maintained for prolonged periods of time. Steroids may exert their beneficial effects by more than one mechanism: for example, they may also affect cerebral function directly or decrease the size of the primary lesion, such as a tumor. The mechanisms of action of steroids on cerebral edema are not fully understood. It has been demonstrated that steroids suppress activation of lysosomal hydrolyzing enzymes. They reduce disruption of brain capillaries in areas adjacent to lesions and restrict the spread of cerebral edema from a site of injury.

In certain settings, direct measurement of ICP has been used. This is performed by insertion of a catheter into a lateral ventricle or into the subdural or epidural space; the catheter is then attached to a pressure transducer. This technique is advocated for children with Reye's syndrome and head trauma patients with severe neurological deficits. ICP monitoring allows the detection of increases in pressure before clinical manifestations occur.

Coma induced by phenobarbital is accompanied by a decrease in ICP. This has been used in patients with Reye's syndrome, when ICP remains too high even after other treatments. The patient must receive artificial ventilation, of course, and be very closely monitored.

CEREBROVASCULAR DISEASES

Kurenai Tanji, M.D.

CEREBROVASCULAR DISEASES

INTRODUCTION

Anatomic Review
Physiologic Considerations

INFARCTION

Atherosclerosis
Arteriolar Sclerosis
Embolism
Vasculitis
Hematologic

HEMORRHAGE

Intracerebral
Subarachnoid
Aneurysms
Arteriovenous Malformations

I. INTRODUCTION

Cerebrovascular disease, commonly referred to as “**stroke**” or “**brain attack**”, kills approximately 160,000 individuals in the US every year. This makes cerebrovascular disease the third most common cause of death in the US, after heart disease and cancer. Every year approximately 730,000 Americans have a new or recurrent stroke. There are about 4 million stroke survivors in the US. About one-third are mildly impaired, another third are moderately impaired and the remainder are severely impaired. Approximately one-third of these survivors will have another stroke within 5 years. It has been estimated that stroke costs the US \$30 billion annually with direct costs, such as hospitals, physicians and rehabilitation, adding up to \$17 billion and indirect costs, such as lost productivity, costing up to \$13 billion.

Cerebrovascular disease is any abnormality of the brain parenchyma caused by pathologic alterations of blood vessels that supply and drain the CNS. From a pathophysiologic and anatomic standpoint, it is convenient to consider cerebrovascular disease as processes that lead to **infarction (encephalomalacia)** or **hemorrhage**. These are the most prevalent cause of neurologic disease. The two most important predisposing conditions are atherosclerosis and systemic hypertension.

A. Anatomic Review

The right and left internal carotid and vertebral arteries supply the brain. The carotid and vertebral arteries feed, respectively, the anterior and posterior circulation systems of the

brain. They come together to form the circle of Willis around the pituitary stalk. From the circle, three pairs of branches emerge to supply the two cerebral hemispheres *in toto*. The vertebrbasilar arterial trunks give off branches to supply the cerebellum and the brain stem.

Anterior circulation: Each **internal carotid** artery enters the floor of the middle cranial fossa and makes a cephalad and caudad hairpin turn as it passes through the cavernous sinus in the lateral margin of the sella turcica. The postcavernous or **suprasellar** segment divides into the large **middle** and **anterior cerebral** arteries that, together with the short anterior communicating artery and the two posterior communicating arteries, form the anterior portion of the circle of Willis. The middle cerebral artery enters the Sylvian fissure and divides in the fissure. Its branches emerge laterally to fan out over virtually the entire convexity of the hemisphere. The anterior cerebral artery enters the interhemispheric fissure to supply all of the medial and apical convolutions of the frontal and parietal lobes, as well as the corpus callosum. The **anterior cerebral artery supplies the motor cortex responsible for voluntary movement of the leg**, while the **middle cerebral artery feeds the arm and face**. The basal ganglia are supplied by the **lenticulostriate arteries**, which arise from the first segment of the middle cerebral artery.

Posterior circulation: The **vertebral** arteries enter the foramen magnum, run anteriorly on the ventral surface of the medulla, and come together at the junction with the pons to become the **basilar** artery. At the pontomesencephalic junction, the **basilar** bifurcates terminally into the right and left **posterior cerebral** arteries. These two arteries arch around the cerebral peduncles and pass through the incisura of the tentorium to enter the supratentorial compartment, where further branchings supply the medial aspect of the **occipital lobe** (visual cortex), the **hippocampus**, the **thalamus**, and most of the ventral surface of the hemispheres. As they round the peduncles, each posterior cerebral joins a posterior communicating artery, which together compose the posterior half of the circle of Willis.

The three major cerebral arteries are **terminal arteries**. Regional neurologic deficits can be expected whenever occlusion of any of them is sudden and complete, as in thromboembolization from the left chambers of the heart. On the other hand, especially when the underlying obstruction develops slowly other anatomic factors – more or less variable from individual to individual – modify the consequences of the basic design outlined. **Variations** in the configuration of the circle of Willis and in the relative caliber of the arteries affect the amount of cross flow between the anterior and posterior circulation and between the two sides. Ten percent of individuals with total atherosclerotic occlusion of one internal carotid artery in the neck are asymptomatic. There are other sites of **intracranial** collateral circulation. Anastomoses in the subarachnoid space between terminal branches of the major cerebral arteries provide blood flow in one territory to an adjacent arterial field. A few communications between intracranial and extracranial vessels are of little or no consequence, with the exception of connections between the ophthalmic artery and branches of the external carotid artery in the orbit.

Most of the brain is fed by vessels of arteriolar caliber piercing the pia mater. However, penetrating small arteries and a few muscular arteries that run deep into the parenchyma supply much of the central gray masses of the cerebrum as well as the brain stem.

Intracranial blood vessels are structurally different from their systemic counterparts. The elastic fibers of intracranial arterial walls are limited to a single layer between the endothelium and the media, the internal elastica lamina. Intracerebral veins are almost devoid of smooth muscle. The distal branches of the arterial tree in the brain receive no autonomic innervation. Ultrastructurally, tight junctions between the endothelial cell membranes seal the lining of brain capillaries – a major facet of the relatively impermeable blood-brain barrier.

Circulatory disorders of the venous system account for a small fraction of cerebrovascular disease and time does not permit a review of the superficial and deep draining pathways of intracranial blood.

B. Physiologic Considerations

Hemodynamic as well as anatomic factors play an important role in the vulnerability of brain to disorders of the circulation.

The brain comprises only two percent body weight, but it receives **fifteen percent** of the **cardiac output**. Blood flow is a function of perfusion pressure (the gradient between mean arterial pressure and venous pressure) and the resistance of the vascular bed (determined mainly at the arteriolar level). Increased intracranial pressure (see the section on Intracranial Hypertension in this syllabus) raises venous pressure and, unless compensated for, lowers the perfusion gradient and the flow of blood.

Normally, only a fraction of the total vascular bed is in use. Overall cerebral blood flow is relatively constant over a broad range of arterial pressure. Autoregulatory mechanisms of blood flow are also finely tuned locally.

Positron emission tomography (PET) demonstrates that regional fluctuations in blood flow are frequent and that they occur instantly in response to alterations in local neuronal activity.

Arteriolar tone is not mediated by the autonomic nervous system or endocrine influences. Cerebral blood flow is clearly affected by oxygen tension, pH, and carbon dioxide tension. But many observations suggest that additional factors, possibly oligopeptide neurotransmitters among them, are important determinants of blood flow in the brain. Lack of information in this area is one of the impediments to major advances in cerebrovascular disease.

The nerve cell is dependent on oxidative metabolism and a continuous supply of glucose and oxygen for survival. Neuronal function ceases seconds after circulatory arrest; irreversible structural damage follows a few minutes later. Recent work proposes that an excess of excitatory amino acid transmitters and an abnormal influx of calcium into the cell play a decisive role in the death of the nerve cell. Pyramidal neurons in the hippocampus [CN-1] and the Purkinje neurons of the cerebellum are particularly vulnerable to ischemia. Glial cells, especially astroglial and microglia, are more resistant to impaired circulation than nerve cells.

II. INFARCTION

After a significant hypoxic or ischemic event, brain tissue undergoes a series of characteristic changes. The amount of damage and the survival of tissue at risk depends on a number of modifying factors, which include the duration of ischemia, availability of collateral circulation, and the magnitude and rapidity of the reduction of blood flow. Acute ischemic injury is of two general types – **global cerebral ischemia** and **focal cerebral ischemia** [CVD-1,2]. Global cerebral ischemia occurs when there is a generalized reduction of cerebral perfusion, such as in cardiac arrest and severe hypotension. Focal cerebral ischemia occurs when there is a reduction or stoppage of blood flow to a localized area of the brain. The resultant localized lesion is referred to as an “**infarct**” and the pathological process as “**infarction.**”

Within hours of irreversible injury, brain tissue becomes softer than normal – hence the term **encephalomalacia**. Whenever all parenchymal elements die, **liquifaction** necrosis ensues. Dissolution of cell structures, however, is a gradual process. Dead tissue is autolyzed, debris is ingested and digested by **phagocytes**. These **macrophages** slowly leave the field – over a period of weeks and months – and vacated spaces (microcysts) gradually grow larger. Months later, nothing remains of the infarcted region but a gross cavity (old, cystic encephalomalacia) [CVD-3]. The wall of the cavity, where nerve cells and oligodendrocytes may have succumbed but astrocytes survived the acute infarction, includes a network of elaborated astroglial cell processes (glial fibers) that make up the brain’s puny version of scar formation. This is the classical picture of total infarction of brain tissue, but encephalomalacia often stops short of cavitating necrosis. If only the most susceptible members of the neuronal population die while the majority of them survive, little more than a partial loss of nerve cells and astrocytosis may be detectable on microscopic examination.

Bear in mind that in the nervous system there is always **secondary degeneration** of neuronal processes at a distance from the site of injury. If the nerve cell dies, its dendritic arbor and its axon disintegrate. If the axon dies, the myelin sheath breaks down in short order. Destruction of the motor cortex in the frontal lobe, therefore, leads to secondary degeneration of nerve fibers along the entire length of the lateral and ventral funiculi of the spinal cord (“Wallerian” or “secondary tract degeneration”). In addition, in a number of heavily interconnected neuronal systems of the brain, secondary degeneration occurs transynaptically, orthogradely in some systems and retrogradely in others.

A. Atherosclerosis

The most common cause of infarction is atherosclerosis. Sometimes atherosclerotic plaque formation in major arteries is generalized and sometimes the cerebral arteries are affected – or spared – well out of proportion to the degree of involvement of the aortic or coronary systems. The internal carotid arteries at the **bifurcation** of the **common carotid** in the neck, the vertebral and basilar arteries, the supraclinoid segment of the internal carotid artery, and the middle and posterior cerebral arteries are all frequently affected in the usual segmental and eccentric fashion. Involvement of the anterior cerebral artery beyond the anterior communicating artery is distinctly unusual. Otherwise, proximal segments of major branches from the **circle of Willis** are also affected, but once the arteries reach the cerebral convexities

they develop thickening of the intimal layer only in the most advanced cases of atherosclerosis.

When stenosis of an internal carotid reaches a certain point, circulation through the ipsilateral middle and anterior cerebral arteries is critically compromised. In this situation, the overlapping areas of the brain bathed by the terminals of both arteries (a "**watershed**" or arterial border zone) are most vulnerable, e.g., the junction of the superior and middle frontal gyri along the convexity. However, occlusion affects one of the cerebral arteries only, the watershed zones may be spared as circulation from the neighboring artery is extended through the terminal anastomoses in the subarachnoid space.

Once a major artery is severely stenosed by an atherosclerotic plaque, other hemodynamic events are usually required to trigger infarction. Hemorrhage into the plaque itself and thrombus formation on the surface of the plaque are known to occur, but systemic factors affecting cardiac rhythm and output, blood pressure, and regional cerebral blood flow are probably also important.

Gray matter is usually more sensitive to ischemia than white matter. "**Laminar**" necrosis of the cerebral cortex is one recognized pattern of infarction in which some horizontal layers of the cortex, usually the middle or deeper ones, are severely affected while the other layers are relatively spared. The layer of predominantly astroglial tissue immediately beneath the pia and the ependyma (the subpial and subependymal glial "membranes") usually resists destruction, undergoes florid hyperplasia, and walls off an area of cavitory necrosis from the subarachnoid and ventricular spaces. The depths of cortical convolutions are often more severely damaged than the crests; this is especially true when brain swelling (with narrowing of sulci) contributes to impaired perfusion.

Transient ischemic attacks (TIA's) are **brief**, recurrent episodes of focal neurological dysfunction, often remarkably repetitive in each patient. Like angina pectoris, they are a prelude to infarction. Whether they are caused by embolizing material dislodged from atheromatous plaques or triggered by hemodynamic factors or both is not settled.

B. Arteriolar sclerosis

Cerebral arteriolar sclerosis is about as common as its counterpart in the kidney, arteriolar nephrosclerosis. Hyaline thickening of small vessels in the brain and leptomeninges is not unusual in advanced age, but it is particularly associated with sustained systemic **hypertension** at any age and with **diabetes mellitus**. It leads to small foci of infarction called, in their cystic end-stage, lacunes [CVD-4]). These lacunar infarcts are most common in the basal ganglia, but they may be widely distributed in the brain. **Lacunar infarcts** are often hemorrhagic [CVD-5]. A "multilacunar state" is one of the causes of progressive dementia.

Since the studies of **Charcot and Bouchard** in the 19th century, histopathologic evidence has accumulated pointing to the development of microscopic **aneurysms** in the thickened walls of small **intracerebral** arteries in **hypertensive** individuals - and their rupture - as the pathogenesis of hemorrhagic **lacunar infarcts**. It may well be that similar aneurysms, when

they occur in larger arteries that penetrate the basal ganglia and a few other sites, are also responsible for the major intracerebral **hemorrhages** [CVD-5] of hypertensive disease (see below).

C. Embolism

Arterial embolization, as a sudden occlusive event, leads to neurologic symptoms that begin **abruptly** and are maximal almost immediately. Small emboli lodge in small arteries in the subarachnoid space and their branches and produce small **infarcts** in the **cortex and subcortical white matter** - not unlike blood-borne metastatic tumors in the cerebral hemispheres, which are usually located superficially.

Embolic infarction is frequently, but by no means always, **hemorrhagic**. (A **hemorrhage** is a sizable extravasation of blood under pressure that replaces parenchymal tissue and produces a **hematoma**. In contrast, a hemorrhagic infarct is infarcted tissue peppered by tiny hemorrhages). A fresh infarct probably becomes hemorrhagic when blood flow is re-established through dilated and damaged blood vessels, attributed to the propensity of embolic material to lyse or fragment and move downstream hours or days after occluding a vessel. Pure thromboemboli tend to be reabsorbed completely. Mixed ones and other types, mainly atheromatous, tend to be organized by infiltrating fibroblasts from the wall of the blood vessel and a new lumen is gradually formed (recanalization).

Most cerebral **thromboemboli** come from the **heart**. Thrombi in the left atrium in association with **atrial fibrillation** and thrombi on the damaged endocardial surface of the left ventricle after acute myocardial infarction are the most common sources, but **vegetations** on the mitral and aortic valves in rheumatic, bacterial, and non-bacterial ("marantic") endocarditis also embolize the brain. An infected embolus causes an inflammatory reaction in the wall of the occluded artery ("**mycotic aneurysm**") and the infection can spill into the subarachnoid space. Showers of emboli, notably from the very soft and friable vegetations of marantic endocarditis, produce multiple infarcts and a confusing array of neurologic symptoms. Cardiopulmonary **by-pass surgery** introduced a major source of thrombotic and gaseous cerebral embolization. Hypercoagulable states from whatever cause may contribute to thromboembolic disease in the brain.

Ulceration and **dissection** of atherosclerotic plaques can give rise to emboli of mixed composition. Small thrombi also, particularly aggregates of platelets, may break loose from the turbulent surface of atherosclerotic plaques.

Fat emboli and **gaseous** emboli tend to produce global cerebral dysfunction rather than typical stroke because they are copious; and numerous small intraparenchymal blood vessels become occluded. Fat emboli arise from the marrow of fractured long bones, enter the venous system, and filter through the lung into the systemic circulation. Air emboli are caused by injury to the lungs or by rapid ascent in aviation and deep sea diving (Caisson's disease).

D. Vasculitis

An inflammatory process in blood vessel walls can produce infarction by swelling the wall and narrowing the lumen, by damaging the endothelial lining and inducing thrombosis, or by destroying the vessel wall (necrotizing vasculitis) giving rise to hemorrhage.

Cerebral vasculitis can occur as a result of an autoimmune disorder, e.g. **polyarteritis nodosa**. It also may be incidental to an intracranial infection. Bacteria that cause acute suppurative meningitis do not involve blood vessels directly, but those responsible for subacute or chronic meningitis (TB meningitis, meningovascular tertiary syphilis), often do. Among the fungi that invade the central nervous system opportunistically, *Aspergillus*, *Phycomyces* and *Candida* commonly infiltrate the blood vessels; *Cryptococcus* does not.

E. Hematologic

Hematologic disorders affecting the coagulability, viscosity, or oxygen-carrying capacity of blood can cause, or more likely contribute to, infarction in the brain - among them the **leukemias, sickle cell disease, thrombotic thrombocytopenic purpura, polycythemia, disseminated intravascular coagulation, and anticoagulant therapy**.

III. HEMORRHAGE

Primary subdural and epidural hemorrhages are typically related to traumatic lesions and are discussed in the section on Head Trauma. Spontaneous hemorrhages in the brain parenchyma and subarachnoid space are often a result of underlying cerebrovascular disease, although trauma can also result in hemorrhages in these sites.

A. Intracerebral

Often massive and fatal, **intracerebral** hemorrhage [CVD-5] is a dismal consequence of chronic **hypertension**. The most common site of rupture is one of the sizable arteries that run deep in the basal ganglia as the **lenticulostriate** branches of the middle cerebral artery. Less common sites of hypertensive hemorrhages are the corpus medullaris of the **cerebellum** and the brain stem, almost always the **pons**.

Massive hemorrhage in the basal ganglia is attended by immediate loss of consciousness - which would be unusual in the more common stroke on the basis of infarction. The mass effect is immediate and surrounding brain swelling and pressure are more marked than with infarction. Even with optimal medical management, the most important prognostic factor remains the size of the hemorrhage. Dissection of the hemorrhage into the ventricle is incompatible with life for more than a few hours. With hypertensive hemorrhage in the cerebellum, secondary compression of vital centers in the brain stem is the main threat to survival and timely removal of the hematoma may prove effective.

Pathologically, the damage from intracerebral hemorrhage is compounded by foci of hemorrhagic infarction surrounding the hematoma. Slowly the blood is resorbed and survivors end up with a cavity outlined by ragged walls stained by blood pigments.

Sizeable hemorrhages in the brain can be caused by an arteriovenous malformation (see below), amyloid (conophilic) angiopathy of the brain and others, but these disorders are less common.

B. Subarachnoid

1. Saccular aneurysms:

Rupture of a **saccular** (or "berry") **aneurysm** [CVD-6] at or near the circle of Willis is the major cause of arterial subarachnoid hemorrhage [CVD-7] at the base of the brain or in the Sylvian fissure. The initial symptoms are head pain, typically explosive, promptly followed by depression of consciousness of variable degree. The presence of a focal neurologic deficit soon after the bleed often reflects compression of a neural structure, sometimes in the tentorial notch, but may indicate instead that the blow-out under arterial pressure has dissected into the substance of the brain [CVD-8]

The morbidity of acute subarachnoid hemorrhage is related to the hemorrhage itself and to the high incidence of **segmental spasm of the parent artery** at and beyond the site of the aneurysmal rupture and not infrequently of nearby arteries as well. It is a delayed effect, not usually seen during the first 48 hours after rupture, and it persists for days before it resolves spontaneously. The spasm produces ischemia and may result in infarction. The behavior of arterial spasm is unpredictable, a second bleed in short order at the site of rupture is frequent, and the ideal time at which the defect should be repaired is not an easy surgical judgment. The mechanism for the arterial spasm remains unknown and the search for pharmacologic measures that will prevent or correct it continues.

Saccular aneurysms are called congenital, but they rarely occur in young children. Whether an embryologic maldevelopment underlies their appearance in later life is moot. They are located at or near arterial junctions, particularly between the posterior communicating artery and the internal carotid or the posterior cerebral artery, at the short anterior communicating artery, and at the first branching of the middle cerebral artery in the Sylvian fissure. They have a fairly broad base of origin from the parent artery and a short neck. They usually rupture near the dome, where the wall of the aneurysm is likely to be thinnest. Devoid of elastica and smooth muscle [CVD-9], they are composed entirely of poorly cellular collagen. One out of five individuals who bleeds from an aneurysm harbors another one.

Giant aneurysms are probably saccular aneurysms that enlarge slowly by repeated internal thrombosis and repair without hemorrhaging. Their wall becomes fairly thick, although not uniformly so, they attain a diameter of a few centimeters, and they become symptomatic as a tumor mass compressing adjacent structures. Fusiform aneurysms are segmental distensions of severely atherosclerotic arteries, notably the basilar or a vertebral artery, and are also called atherosclerotic aneurysms.

2. Arteriovenous malformation

The second major cause of spontaneous subarachnoid hemorrhage is rupture of a congenital vascular malformation of the arteriovenous type. As the name suggests, arteriovenous malformations are congeries of abnormally large arteries and veins [CVD-10]. These vessels are interconnected and shunt arterial blood directly into venous channels. The vessel walls are of uneven thickness and composition, often of ambiguous denomination, and not proportional to the caliber of the lumen.

They are located mainly in the subarachnoid space, but they always extend into the cortex and sometimes into the white matter also. They undergo sclerosing changes at an accelerated pace. Blood flow through the malformation is hemodynamically abnormal, they thrombose, they leak or hemorrhage, and neuronal degeneration, foci of encephalomalacia, and astroglial reaction and fibrosis in the intervening parenchyma are the rule.

Seizures, especially focal fits, and less commonly headaches, usually do not appear until adolescence or early maturity, but the lesion may be silent for decades. Small episodes of hemorrhage or ischemic parenchymal injury, as well as aging vascular changes in the malformation, are probably responsible, cumulatively, for the belated onset of symptoms. When the malformations finally hemorrhage in the subarachnoid space, the hemorrhage tends to be smaller than from a ruptured aneurysm, but malformations that are large and fed by more than one major artery are not easily corrected surgically.

SUPPLEMENTARY READING:

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INFECTIOUS DISEASES OF THE CENTRAL NERVOUS SYSTEM

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CENTRAL NERVOUS SYTEM INFECTION-- BACTERIAL, FUNGAL, PARASITIC, VIRAL and PRION

I. CNS BACTERIAL INFEECTIONS

Anatomical Localization of CNS Infections

The bones of the skull and spine, the dura, the pia and arachnoid each are physical barriers shielding the central nervous system (CNS) from the spread of infection. Therefore, infections are often contained in spaces between these anatomic structures. For example, infections occur between the bone and the dura (epidural abscess), between the dura and arachnoid (subdural abscess - empyema), in the CSF between the pia-arachnoid (leptomeningitis or just meningitis) and in the brain parenchyma beneath the pia (encephalitis and cerebral abscess).

A. EPIDURAL INFECTION: Infection between bone and dura.

1. Intracranial epidural abscess: Relatively frequent and associated with overlying infection of cranial bones. Commonly due to direct extension from infected frontal or mastoid sinuses or osteomyelitis of skull
2. Spinal epidural abscess: Usually from direct extension from overlying skin infections, osteomyelitis of spinal vertebrae, pleural empyema, subphrenic or perinephric abscess. Staphylococcus is usually the offending organism (60% of cases). Severe back pain is the presenting symptom as well as malaise, fever, neck stiffness and headache. Complications can include spinal cord compression as a result of vascular thrombosis, infarction and irreversible paraplegia. Regarded as acute emergency and requires decompression

B. SUBDURAL INFECTION (EMPHYEMA): Accumulation of pus within a potential space between dura and arachnoid. This is relatively rare and due to direct extension from infections of paranasal sinuses or skull and fractures of skull. Symptoms include local pain and tenderness, fever, chills, headache, neck stiffness. The infecting organism is usually Streptococcus. Complications include thrombophlebitis that may lead to superficial cerebral infarction and seizures. Difficult to treat and there is a high mortality.

C. LEPTOMENINGITIS (MENINGITIS): Infection in the subarachnoid space due to hematogenous or direct invasion by organisms resulting from surgery, trauma or CNS malformation. Most often due to bacteria or viruses, but fungi, or parasites may also cause disease [ID-1])

Bacteria love CSF - with its physiologic salt concentrations, protein for growth and glucose for energy. And, CSF is woefully inadequate in fighting infection. Levels of immunoglobulins in CSF rise only late in meningitis when antibody synthesis may be produced locally or pass blood-brain barrier. Polymorphonuclear neutrophils are

inefficient at phagocytosis as a result of lack of opsonic and bactericidal activity in CSF early in disease.

Patient age is most important factor in absolute attack rate and host susceptibility to bacterial meningitis. Over 70% of bacterial cases occur in children under 5 years; about 20% of cases occur in people over 70 years old.

Most commonly encountered causative organisms according to patient age

Neonates – Group B streptococci; *E. coli*

Infants and children – *Haemophilus influenzae*

Adolescents and young adults – *Neisseria meningitidis*

Elderly – *Streptococcus pneumoniae*; *Listeria monocytogenes*

General pathologic features of bacterial meningitis

- Early: Leptomeningeal congestion; abundant neutrophils; intracellular bacteria [ID-2]
- Few days: Purulent material, first cuffing blood vessels in cerebral sulci, later covering cortex; increasing proportion of mononuclear chronic inflammatory cells; fibrin exudate; ventricular dilatation as CSF outflow obstructed; cerebral swelling as a result of edema
- Later: Purulent ventricular exudate; vascular thrombosis with focal cerebral infarction.
- Final: Thickening of leptomeninges; chronic hydrocephalus.

Complications: Hydrocephalus; subdural effusion; cystic loculation of subarachnoid fluid; cranial nerve damage, especially deafness; focal neurological deficits; psychomotor retardation

D. BACTERIAL BRAIN ABSCESS

Osler said over 100 years ago "Suppuration of the brain substance is rarely if ever primary, but results as a rule, from extension of inflammation from neighboring parts or infection from a distance through the blood". Brain abscesses are rare and are due to contiguous spread (most commonly from sinusitis, otitis, mastoiditis) or from blood-borne infection (vegetative endocarditis, pulmonary disease, especially bronchiectasis, intravenous drug abuse, congenital heart disease). Abscesses are often multiple; often in middle cerebral artery territory and have a predilection for the gray/white junction. Streptococci and staphylococci are the most common causative organisms.

Stages in cerebral abscess formation

EARLY CEREBRITIS (1-3 days):

Acute inflammation and edema

LATE CEREBRITIS (4-9 days):

Central necrosis with peripheral invasion of macrophages and fibroblasts

EARLY CAPSULE FORMATION (10-13 days):

Proliferation of capillaries and, fibroblasts and laying down of collagen fibrils;
brain has poor supply of fibroblasts, derived from blood vessel adventitia
[ID-7]

LATE CAPSULE FORMATION (14 days and later):

Fibrotic capsule surrounded by edematous gliotic brain tissue.

Symptoms and Signs: More common in 1st - 3rd decades of life; related to mass size and location and to degree of edema, not infection -- fever uncommon, headache, nausea, vomiting and seizures common; sudden deterioration suggests internal herniation or rupture into ventricle

Treatment:

Surgical drainage or excision

Systemic and sometimes local antibiotics

II. CEREBRAL FUNGAL INFECTIONS

Fungal infection may occur in previously healthy individuals, but more often develops as opportunistic infections in patients with lowered resistance. Examples are diabetes, keto-acidosis; leukemia, lymphoma, and other malignant processes; prolonged use of antibiotics, corticosteroids, cytotoxic and immunosuppressive drugs; AIDS.

May produce meningitis, cerebritis and cerebral abscess, or stroke-like syndromes

COMMON CEREBRAL MYCOSES

<u>Genus</u>	<u>Morphology</u>	<u>Patient Status</u>
<i>Aspergillus</i> [ID-3]	Septate hyphae	Opportunistic
<i>Rhizopus</i> (zygomycosis - mucormycosis [ID-4])	Nonseptate hyphae	Opportunistic
<i>Candida</i>	Budding yeast; pseudohyphae	Opportunistic
<i>Cryptococcus</i> [ID-5,6]	Budding yeast; encapsulated	Opportunistic or previously healthy

UNUSUAL CEREBRAL MYCOSES

<u>Genus</u>	<u>Morphology</u>	<u>Patient Status</u>
<i>Coccidioides</i>	Large yeast with endospores	Previously healthy Southwestern USA
<i>Histoplasma</i>	Budding yeast	Previously healthy Ohio and Central Mississippi River Valleys
<i>Blastomyces</i>	Budding yeast	Previously healthy

III. CNS PARASITIC INFECTIONS

Parasitic infections of the CNS are relatively uncommon in USA; probability of exposure increases with travel to endemic areas. Thus, a good clinical history is essential.

Acanthamoeba, *Naegleria*, *Trypanosoma* and *Toxoplasma* cause diffuse meningoencephalitis; cerebral malaria (*Plasmodium falciparum*) lodges in capillaries resulting in petechial hemorrhages and angiitis

Larger parasites obstruct larger blood vessels and/or migrate into cerebral parenchyma.

PARASITES THAT CAUSE NEUROLOGIC INFECTIONS

Protozoa

Toxoplasma
Acanthamoeba
Naegleria
Plasmodium
Trypanosoma

Metazoa

Cysticercus (Taenia)
Echinococcus
Sparganum
Paragonimus
Schistosoma
Trichinella
Strongyloides
Toxocara
Angiostrongylus

A. TOXOPLASMOSIS

Toxoplasmosis is caused by an intracellular organism, *Toxoplasma gondii*, which gains access to the human host when it is ingested with raw or poorly cooked meats.

Worldwide, about 25-50% of adults have been infected. Infected immuno-competent hosts may experience a transient parasitemia and lymphadenopathy, or may be entirely symptom free. In its life cycle within the human host, *T. gondii* can become dormant and exist in an encysted form, called a bradycyst, in the muscles and the CNS. It is felt that in immunocompromised patients, reactivation of the encysted organisms in the brain gives rise to toxoplasma encephalitis. Toxoplasma encephalitis is the only protozoal parasitic

nervous system infection that is seen with any significant frequency in patients with AIDS. In New York over one-third of AIDS patients with opportunistic infections have toxoplasma encephalitis.

Gross pathology: Toxoplasma infection tends to localize around ventricles in the basal ganglia and thalamus and at the junction of gray and white matter where it may cause focal abscesses.

Microscopic pathology: The encephalitis is initially characterized by scattered microglial nodules within which toxoplasma cysts [ID-13] are frequently found. These small foci of infection will eventually evolve into abscesses with a central necrotic zone containing few identifiable organisms; and intermediate zone with vascular congestion, neutrophilic infiltration and numerous tachyzoites; and peripherally, a zone with relatively little inflammation but numerous encysted organisms.

CONGENITAL TOXOPLASMOSIS: Affects 1/1,000 births in the U.S. The fetus is infected via the placenta during maternal infection, and consequences are worst if the infection occurs during the latter part of the 1st or entire 2nd trimester. Affected infants are often premature with jaundice, enlarged spleen and liver, chorioretinitis, microphthalmus. Microscopically there is necrotizing cerebritis, diffusely scattered foci of coagulative necrosis followed by calcification, meningeal inflammatory exudate. Hydrocephaly may occur as a result of periaqueductal inflammation, repair and aqueductal stenosis.

IV. CNS VIRAL INFECTIONS

Inflammation of the CNS caused by viruses may manifest itself as aseptic meningitis if the leptomeninges are the only structures involved and no bacteria are found, encephalitis if the brain parenchyma is the main target or myelitis if the parenchyma of the spinal cord is involved. Frequently both parenchyma and meninges are affected, and the condition is often referred to as meningoencephalitis.

GENERAL PATHOLOGIC CHANGES IN VIRAL ENCEPHALITIS

All the acute encephalitides present essentially similar microscopic changes, but they often differ in the distribution of the more severe lesions in the CNS--some regions or some cell groups being more susceptible than others, depending on the type of virus. The ultimate diagnosis, however, depends on the isolation of the virus and/or correlation with positive serological tests. Most viruses that attack the CNS do so after they have multiplied in other organs.

The following stereotyped reactions are often encountered in viral encephalitides.

1. **Infiltration by Inflammatory Cells**: This is usually the most conspicuous histologic abnormality. Perivascular and parenchymal mononuclear cell infiltrates, including lymphocytes, plasma cells, and macrophages, is the most characteristic feature of viral infections [ID-8].
2. **Hyperplasia and Proliferation of Microglia**: Seen throughout the brain and particularly in the cortex and basal ganglia. The microglia hypertrophy to form "rod cells" and these subsequently acquire long and slightly convoluted nuclei. They are most active in and around destroyed tissue where many become converted to lipid phagocytes (foam cells).
3. **Neuronophagia**: This refers to phagocytosis of an injured neuron by a dense mass of hypertrophied microglia often obscuring the dead cell. However, in acute infections such as in polio, polymorphonuclear leukocytes are the cells involved in neuronophagia.
4. **Microglial Nodules and Gliomesenchymal nodules**: Are often used synonymously to describe clusters of hypertrophied microglia admixed with other mononuclear cells not specifically related to nerve cells and occurring mainly in the white matter. Some of these clusters may contain as many as one hundred nuclei. It should be remembered that both neuronophagia and the microglial nodules, although frequently observed in viral encephalitides, are by no means specific since both phenomena can occur in hypoxic brain damage.
5. **Astrocytic Proliferation**: In acute encephalitis, enlarged astrocytes with plump cytoplasm are usually restricted to regions of tissue destruction. However, in certain subacute forms, there may be considerable astrocytosis.
6. **Intracellular inclusion bodies**: These are important and may be diagnostic of a specific viral infection. However, not all intracellular inclusions are caused by viruses. They may be found in neurons or/and glial cells. They may be intranuclear or intracytoplasmic or both. Intranuclear inclusions known as Cowdry type A [ID-9] are frequently seen in herpes encephalitis, cytomegalovirus infection and subacute sclerosing panencephalitis. The Cowdry type A inclusion is an eosinophilic oval or spherical mass with a clear halo surrounding it. Intracytoplasmic inclusions are characteristically seen in rabies, especially in Purkinje cells and pyramidal cells of the hippocampus. Both intracytoplasmic and intranuclear inclusions are seen in SSPE and CMV.
7. **Neuronal Changes**: Acute degeneration of neurons such as chromatolysis, eosinophilia of cytoplasm, and pyknosis of nuclei can occur but are by no means characteristic unless there is actual necrosis of the nerve cells associated with neuronophagia.

8. **Necrosis:** This may range from selective necrosis of one neuronal cell element (e.g. motor nerve cells in polio) to frank hemorrhagic infarctions of one or more lobes (e.g. herpes simplex encephalitis). Sometimes necrosis is scattered throughout the brain and forms cavities (e.g. equine encephalitis).

SPECIFIC CNS VIRAL INFECTIONS

A. POLIOMYELITIS:

Used to be the leading epidemic form of viral infection of CNS. With the polio vaccination programs, acute polio has been practically eradicated in the Western Hemisphere. The polio virus selectively destroys the motor neurons of the spinal cord and brain stem to cause flaccid, asymmetric weakness of the muscles innervated by the affected motor units.

B. RABIES:

The great majority of human cases in the U.S. are caused by bites of dogs, the virus being transmitted by the saliva. The major reservoir host, however, is not the dog but the skunk in the Midwest and the fox in the Eastern Seaboard. Increasing numbers of raccoons and skunks have become infected in the New York metropolitan area over the last few years. Bats seem to be important in maintaining the circulation of virus in some regions.

The incubation period is variable and is dependent on retrograde axonal transport of the virus from the site of the bite wound along peripheral nerves into the CNS (usually one to three months). The pathognomonic pathologic finding is the Negri body [ID-10]. In both dog and man, Negri bodies are most numerous in the pyramidal layer of hippocampus and Purkinje cells. Negri bodies are well-defined, rounded, acidophilic, intracytoplasmic inclusions about 5-10 nm. Rabies virus antigen has been identified in them by the immunoperoxidase technique.

C. ARBOVIRUS INFECTIONS

Most of the viral epidemics in recent years are caused by arboviruses (arthropod-borne) of which there are at least 200. Their only shared attributes are that they are RNA viruses and are transmitted from host to host by blood-sucking insects (vectors). After an incubation period in the arthropod vector, the virus reaches the salivary glands, and is inoculated into a new host where it proliferates. A period of viremia follows during which period a further arthropod may become infected. Man is not a natural host of any of the arboviruses but becomes infected accidentally during periods of epizootic spread among the natural hosts.

The important thing to remember about arbovirus infections is that they occur as seasonal epidemics since climate exerts a strong influence in maintaining the vector-host cycle. In this country, mosquitoes are the principal vectors of arboencephalitides while in the Far East and Central and Eastern Europe, tickborne encephalitides are far more common.

Western equine encephalitis occurs over most of the U.S. to the West of the Appalachian Mountains and in Southern Canada.

Eastern equine encephalitis is predominantly seen along the Eastern Seaboard. Eastern equine encephalitis has a high mortality rate that can attain 75% while the Western the rate is about 10%.

California encephalitis: Almost entirely affects children who usually have a history of recreational exposure in the woods prior to the onset of the disease. Woodland mosquitoes are probably the vectors and small animals and birds do not appear to be involved. Although the disease may be quite severe, death is rare, and sequelae occur in only 15% of the children.

D. HERPESVIRUS INFECTIONS

1. HERPES SIMPLEX ENCEPHALITIS

The most important cause of fatal sporadic viral disease. There are two herpes simplex viruses, type 1 and type 2. Type 1 is usually associated with primary oropharyngeal lesions and causes acute encephalitis in adults. Type 2 is associated with genital lesions and causes disseminated infection in neonates and an aseptic meningitis in adults.

Clinical symptoms and signs:

- Starts with fever and headaches
- Seizures are common
- Nuchal rigidity may be present
- Progressive mental deficits, confusion and personality changes

Pathological findings:

- Intense meningitis
- Necrotic, inflammatory, or hemorrhagic lesions
- Predilection for frontal and temporal lobes.
- Intranuclear inclusions, Cowdry type A
- Perivascular inflammation

Though treatable, the mortality rate is high (around 70%). Many survivors are left with permanent neurologic or intellectual debilities. The diagnosis of Herpes can be made rapidly by brain biopsy using an immunoperoxidase test.

2. VARICELLA-ZOSTER

Zoster (shingles) is a viral disease that produces inflammatory lesions in the dorsal root ganglia clinically associated with pain and a skin eruption in the distribution of the ganglia.

The infection is thought to be due to reactivation of latent varicella-zoster originally acquired as childhood chicken pox. Pathologically there is a lymphocytic infiltrate in the ganglia of the spinal cranial nerve roots. Rarely, varicella-zoster may cause an acute encephalitis, particularly after involvement of cranial nerve roots.

3. CYTOMEGALOVIRUS

CMV is by far the leading opportunistic viral pathogen in AIDS and in the general population. Up to one-third of AIDS patients have evidence of CMV involvement in the CNS at autopsy.

Pathologic features: Except for the unusual case in which there may be small focal areas of necrosis in the periventricular region, the gross appearance of the brain may be deceptively normal. The microscopic features are likewise subtle but include the presence of scattered microglial nodules and large CMV-infected cells containing both intranuclear and cytoplasmic inclusion bodies [ID-11]. The most common sites of infection appear to be the basal ganglia, diencephalon, and brain stem--possibly reflecting adjacent spread from ependyma that is particularly susceptible to CMV infection. Rarely, a fulminating case will show necrotizing lesions with parenchymal destruction.

CONGENITAL CMV: Fetal infections occur via transplacental transmission and results in stillbirth or prematurity. The cerebrum is affected by a granulomatous encephalitis with extensive subependymal calcification. Hydrocephalus, hydranencephaly, microcephaly, cerebellar hypoplasia, or other developmental defects may be found. Subclinical infections can result in deafness.

E. HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Neurological complications are frequent in patients with AIDS. Clinical evidence of nervous system dysfunction has been reported to occur in approximately 30 - 40% of patients. Neuropathologic studies indicate that an even larger proportion (75 - 90%) of AIDS patients exhibit nervous system pathology at autopsy. In general, the neuropathologic findings in AIDS can best be examined by separating them into three categories:

1. Primary effects of HIV
2. Opportunistic infections, and
3. Neoplasms

1. PRIMARY EFFECT OF HIV-- HIV encephalitis or AIDS dementia complex is one of the most interesting complications of AIDS and affects approximately 30% of patients with AIDS. Many patients with AIDS gradually develop mental deterioration and variable degrees of motor debilities that culminate in dementia, mutism and quadriparesis. Experimental evidence indicates that HIV encephalopathy results from primary HIV infection of brain rather than from opportunistic infections.

This notion is also supported by the experience in children with AIDS in whom HIV encephalopathy is quite common but in whom opportunistic infections are much rarer than in adults. The cells containing the majority of this virus appears to be of macrophage origin. However, the mechanism by which HIV infection of brain macrophages/microglia results in dementia has not been determined.

Gross pathology:

In the early stages of HIV encephalopathy, the brain may appear grossly unremarkable. However, as the disease progresses, atrophy develop as evidenced by a decrease in brain weight, prominent gaping of the cerebral sulci and dilatation of the ventricular system. There may be some attenuation of the white matter, particularly of the cerebral hemisphere. No focal lesions are seen.

Microscopic pathology:

Reactive microglial cells are present throughout the gray and white matter. Occasionally, they aggregate into cellular clusters with reactive astrocytes to form microglial nodules. Peculiar multinucleate cells [ID-12] with numerous small, dark nuclei and granular eosinophilic cytoplasm is a hallmark of HIV infection. These cells can be found in microglial nodules, perivascularly, or scattered through the brain parenchyma. A diffuse, mild gliosis is also seen. Nonspecific white matter changes include foci of demyelination and vacuolar change. Cerebral calcification is a frequent complication in pediatric AIDS patients but rare in adults. The calcification often involves the basal ganglia, but may spill into the centrum semiovale.

2. OPPORTUNISTIC INFECTIONS IN AIDS

Opportunistic infections are responsible for most of the neuropathology of AIDS and account for about 60% of neurological disabilities. More than one organism may be present in the inflammatory lesions.

A. VIRAL INFECTION

The main viral infections commonly encountered in AIDS include CMV and PML. Others are rare.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

PML is a progressive neurologic illness first described in 1958 and is caused by infection of a papovavirus, the JC virus. Prior to the AIDS epidemic, PML had been sporadically reported in individuals with a variety of immunodeficiencies. In AIDS patients, it is the second most frequent viral infection seen, after CMV.

GROSS PATHOLOGY:

There are multiple areas of gray discoloration of white matter that consists of lesions measuring several millimeters to lesions that coalesce to form large zones of softening. These lesions are found throughout the CNS wherever white matter is represented. In addition, they also may be found in the lower layers of the cortex and in the basal ganglia.

MICROSCOPIC PATHOLOGY:

There are three cardinal features of the white matter lesions:

- 1) Abnormal oligodendrocytes with glassy, purple intranuclear inclusions found predominantly at the periphery of the lesions,
- 2) Bizarre astrocytes with large, hyperchromatic, irregular nuclei, and
- 3) Demyelination associated with a variable degree of inflammatory infiltration made up predominantly of macrophages. Immunocytochemical and ultrastructural demonstration of the presence of papovavirus confirms the diagnosis of PML.

B. BACTERIAL INFECTIONS

Not notably increased from the general population

C. FUNGAL INFECTIONS

Not notably increased from the general population

D. PARASITIC INFECTIONS

The main parasitic infection seen in AIDS is toxoplasmosis [ID-13]. Others are much less common.

3. NEOPLASMS

PRIMARY CNS LYMPHOMA.

Previously a rare disease accounting for 1 - 1.5% of all primary brain tumors, primary CNS lymphoma has been projected to become one of the most common primary brain tumors as a result of the AIDS epidemic. This entity is the second most frequent CNS mass lesion in adults with AIDS and the most frequent in children with AIDS.

V. TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY

The transmissible spongiform encephalopathies are a group of rare diseases that occur in humans and animals and are associated with an abnormal form of a specific protein, termed prion protein, which is the presumed etiologic agent that causes these diseases. These disorders are quite unusual and have been classified in the past as 'infectious', but more appropriately 'transmissible' disorders. This group of disorders is also widely classified as neurodegenerative disorders because the clinical and pathological features are more characteristic of neurodegenerative disorders rather than infectious disorders.

Scrapie, the prototypic prion disease of sheep, bears a remarkable resemblance biologically and pathologically to an exotic disease of man known as Kuru that affected certain tribes in New Guinea and to an uncommon sporadic disease of man known as "Creutzfeldt-Jakob" disease (CJD), and a rare familial condition, Gerstmann-Straussler-Scheinker syndrome (GSS). The putative transmissible agent has been called a Prion (proteinaceous infectious particle). This agent differs radically from conventional infectious agents in that it appears to

be composed of protein only. No DNA or RNA has been found in the prion. It is insensitive to physical or chemical treatments that inactivate all known viruses. Formalin fixation does not destroy infectivity, but exposure to Clorox, formic acid or stringent autoclaving does. Two isoforms of the Prion protein (PrP) have been hypothesized: a normal, cellular form (PrP-C) and a modified infectious form (PrP-Sc). Recent experiments show that mice devoid of PrP-C are resistant to disease expression and that lack of homology between species from which the prion originates and the species of the host (a lack of homology between the prion and the host's PrP-C gene) retards disease.

The pathological changes in Scrapie, Kuru and CJD disease are limited to the CNS and characterized by cytoplasmic vacuolization (status spongiosis), astrocytosis and neuronal loss. The mode of natural transmission of scrapie and CJD is not known. The incidence of Kuru has dropped precipitously since the suppression of ritual cannibalism. All three diseases are transmissible by intracerebral injection of infected nervous tissue into experimental animals.

A. KURU: Endemic to New Guinea, thought to be transmitted by ritualistic cannibalism of deceased family members. Cerebellar ataxia and later dementia predominate the clinical picture.

GROSS PATHOLOGY [ID-16]

- closely resembles CJD "acute spongiform encephalopathy"
- atrophy of the vermis and flocculonodular lobe of cerebellum

MICROSCOPY

- loss of Purkinje and granular cells
- the presence of many "kuru" amyloid plaques

B. CREUTZFELDT-JAKOB DISEASE (CJD): Rare, subacute disease of late adulthood

CLINICAL

- progressive dementia (55 - 70 years, typical age of onset)
- focal neurologic deficits (e.g. cortical blindness, aphasia)
- evidence of cerebellar, pyramidal, extrapyramidal and gray matter involvement.

By six months dementia is profound and myoclonic jerking is evident as the individual becomes vegetative, mute and bedfast. Accidental transmission of the disease with corneal graft and with intracerebral electrode implantation has been reported. It is also important to remember that the tissues remain 'infective' after formalin fixation for a year or two.

PATHOLOGY

- widespread microcystic appearance of the gray matter (status spongiosis)
- eventual neuronal loss
- astrocytosis out of proportion to neuronal loss
- absence of inflammatory infiltrates

C. GERSTMANN-STRAUSSLER (-SCHEINKER) SYNDROME

- familial disorder characterized by slowly progressive cerebellar ataxia
- spinal tract signs, later dementia
- Kuru-like plaques and spongy changes.

D. "NEW VARIANT" CJD

CLINICAL

- mainly affects young people (19-39, median 28 years) in the United Kingdom
- presenting symptoms include behavioral changes, ataxia, dysesthesias
- insidious onset, prolonged course

PATHOLOGY

- prominent 'florid' plaques
- distinguishing PrP-Sc protein banding pattern on Western blot analysis which resembles that seen in bovine spongiform encephalopathy--suggesting possible link

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NEURORADIOLOGY

Angela Lignelli, M.D.

NEURORADIOLOGY

Computerized axial tomography (CT) and magnetic resonance imaging (MRI) are the major imaging techniques in neurodiagnosis. CT is quicker and less expensive, but MRI is now the “gold standard” for detecting and delineating intracranial and spinal lesions.

Computerized Axial Tomography (CT)

CT images are reconstructed from sets of quantitative x-ray measurements obtained through the head from multiple angles. The x-ray source rotates around the patient’s head and divides the x-ray attenuation into compartments called pixels. From about 800,000 measurements, the computer assigns a number to each pixel and, by using a gray scale, reconstructs an image. The major advantage of CT is that it is quicker and less expensive than MRI. Scan times can be shortened to less than 1 second to minimize motion artifact when the patient is restless. However, the major limitation of CT is in imaging the posterior fossa, where lucent linear artifacts (caused by x-ray attenuation by thick osseous structures at the skull base) project across the brainstem and cerebellum, and may obscure underlying lesions. CT allows differentiation of gray matter from white matter, and shows the main divisions of the basal ganglia and thalamus. Infusion of iodinated contrast allows the major arteries to be depicted.

CT is still widely used in the initial evaluation of **stroke, head injury** or **acute infection**. CT is especially useful for patients who are neurologically or medically unstable, uncooperative, or claustrophobic, as well as for patients with pacemakers or other metallic implants (cochlear implants, old aneurysm clips, metallic foreign bodies in the eye, and implanted neurostimulators). For these reasons, CT is generally preferred in the early detection of acute intracranial hemorrhage, especially **subarachnoid hemorrhage**. CT is also superior in evaluating cortical bone structures of the skull and spine, while MRI is superior in studying the bone marrow. Thus, the major uses of CT are in the evaluation of patients with acute stroke and head trauma, and in the demonstration of hemorrhage, calcification and skull fracture.

For acute infarcts, CT is less sensitive than MRI in showing nonhemorrhagic infarction during the first 48 hours after the ictus. Also, infarcts within the brainstem and cerebellum are usually better demonstrated on MRI (due to the aforementioned imaging artifacts in the posterior fossa found on CT). About 58% of acute infarcts can be identified within the first 24 hours with CT, versus ~82% with conventional MRI. The relatively recent development of diffusion-weighted MRI now allows acute infarcts to be detected in well over 95% of cases.

Iodinated water-soluble contrast agents can be given intravenously to enhance differences in tissue density. **Contrast enhanced CT (CECT)** is used to detect lesions that involve breakdown of the blood brain barrier, such as brain or spinal tumors, infections, or other inflammatory conditions. CECT is often used to rule out cerebral metastases, but is considered less sensitive than gadolinium enhanced MRI, especially in the detection of certain intracranial tumors, infections, and other inflammatory lesions that are associated with lesser degrees of blood-barrier breakdown.

Intravenous CT contrast agents are based on iodine. The older and cheaper iodinated agents are classified as **high-osmolar contrast media (HOCM)**. Newer nonionic agents, called **low-osmolar contrast media (LOCM)** are considerably more expensive. The new agents are less allergenic and are associated with less morbidity than HOCM. At some institutions, LOCM are given only to patients at high risk for adverse reaction, namely those with severe heart disease, renal insufficiency, asthma, prior allergic reaction to HOCM or

severe debilitation. However, reimbursement for use of LOCM varies from one third-party carrier to another.

Magnetic Resonance Imaging (MRI)

A magnetic field causes alignment of atomic nuclei into one of two (or more) magnetic states. In proton-based MRI, application of radiowaves of the hydrogen-specific resonance frequency to biologic tissue excites some protons into a higher energy state. Following the pulse, the relaxation of these protons back to their original energy state is accompanied by emission of radiowaves that are characteristic of the particular tissue. Two tissue-specific relaxation constants, known as T_1 and T_2 , as well as **proton density** can be measured. The differences in proton density, T_1 relaxation, and T_2 relaxation enable MRI to distinguish fat, muscle, bone marrow and gray or white matter of the brain.

MRI images can be modified to allow differential weighting of T_1 , T_2 , or proton-density relaxation characteristics. These different weightings are produced by varying 1) the imaging techniques (spin-echo, fast spin-echo, gradient-echo, inversion-recovery or echo-planar), 2) the repetition time (interval between repetitions of the pulse sequence), and 3) the echo time (the interval between radiofrequency excitation and measurement of the radiowave emission or signal). The time required for obtaining conventional spin-echo images ranges from 4 to 7 minutes for T_1 -weighted images to 8 to 12 minutes for both proton density and T_2 -weighted images. Fast spin-echo images allow similar images to be obtained in as little as 2 to 3 minutes. A relatively new technique known as fluid-attenuated inversion recovery (FLAIR) imaging (which suppresses signal from normal cerebrospinal fluid) allows many lesions to be more easily detected. An even newer technique known as echo-planar imaging allows images to be obtained in a matter of seconds; these include “fast T_2 -weighted images” and diffusion-weighted images.

MRI is the neuroimaging method of choice for intracranial and intraspinal lesions, except for those already listed as specific indications for CT. Major advantages of MRI are 1) **greater soft tissue contrast**, provides better definition of both normal anatomic structures and pathologic lesions, 2) **multiplanar capability** (i.e. axial, coronal and sagittal) and 3) **visualization of blood flow or cerebrospinal fluid flow**. Other advantages include better visualization of the posterior fossa and spinal cord, and the lack of ionizing radiation.

Indications for Gadolinium-enhanced MRI

Intravenous contrast agents for MRI are based on **chelates of gadolinium** (Gd), a rare heavy metal. Unlike iodinated contrast agents for CT, there are few adverse reactions with Gd-contrast media. The accumulation of Gd-media within a specific region of the brain shortens both T_1 and T_2 relaxation times, and appears as an area of increased signal intensity on T_1 -weighted images, even when precontrast images show no evidence of abnormal signal.

In the first evaluation of patients with **stroke**, either CT or MRI can be used. Where MRI is available for acute studies, infarcts can be readily identified within the first 24 hours in over 95% of patients. The earliest changes of cerebral infarction may be seen within the first three hours after the onset of stroke on diffusion-weighted images; this is related to the visualization of cytotoxic edema within affected cells in the zone of acute infarction. On FLAIR and proton-density-weighted images, hyperintensity may be identified later than 3 hours after onset within the affected cortical gray matter. During the first 5 days after stroke onset, Gd-enhancement may be seen within the small arteries of the ischemic cerebral territory, with gyral enhancement present 5 days to several months after onset. The focal reversible lesions of transient ischemic attacks are also seen more frequently on MRI than on CT.

Gadolinium enhanced MRI (Gd-MRI) has greater sensitivity than CECT in detecting **neoplastic and inflammatory lesions**. Gd-MRI is known to have high sensitivity in detecting certain primary brain tumors that are often difficult to detect on CT, such as small schwannomas, optic nerve and hypothalamic gliomas, meningeal carcinomatosis and cerebral metastases. The multiplanar capability of MRI delineates the extent of neoplastic lesions and is used to directly plan neurosurgery and radiation therapy.

MRI is the imaging method of choice in detecting the demyelinating plaques associated with **multiple sclerosis (MS)**. MS plaques are characteristically seen on T₂-weighted images as multifocal hyperintense lesions within the periventricular white matter and corpus callosum. Additional lesions within the optic nerves, brainstem, and spinal cord may also be detected. Gd-MRI may also help to distinguish acute demyelinating plaques from more chronic lesions.

Gd-MRI is vastly superior to CECT in the detection of **meningitis, encephalitis and myelitis**. Epidural abscess of empyema may be better delineated on Gd-MRI. In AIDS, many kinds of lesions show increased signal intensity within the cerebral white matter on non-contrast T₂-weighted images; these lesions can be further characterized by Gd-MRI. For example, if a single large enhancing mass is seen on Gd-MRI, the diagnosis of cerebral lymphoma is favored. If multiple small enhancing nodules were found, the diagnosis of cerebral toxoplasmosis or other granulomatous infection would be favored. When no enhancement is present, the white matter lesions may be secondary to HIV encephalitis (if symmetric) or progressive multifocal leukoencephalopathy (if asymmetric).

Gd-MRI is also useful for evaluation of the spine. **Herniated discs and degenerative spondylosis** can be evaluated well on noncontrast MRI in unoperated patients. However, in patients who have undergone spine surgery, Gd-MRI is needed to separate recurrent disc herniation from postsurgical scarring or fibrosis. Identification and delineation of **spinal tumors and infections** are also improved with Gd-MRI.

There are some clinical situations in which Gd-MRI is not so useful because relatively few contrast-enhancing lesions are found. These include patients with complex partial seizures, headache, dementia, head trauma, psychosis and congenital craniospinal anomalies. Discussion with radiologists may help to ensure optimization of the MR imaging protocols for such patients.

Magnetic resonance angiography (MRA)

On standard spin-echo images, the major arteries and veins of the neck and brain are usually seen as areas of signal void due to relatively fast blood flow through the vessels. A gradient-echo pulse sequence enables visualization of flowing blood as areas of increased signal intensity. After obtaining a series of contiguous thin sections with gradient-echo techniques, a map of the blood vessels is reconstructed as a set of projection angiograms that can be viewed in any orientation. These MRA images can show the vascular anatomy like a conventional angiogram, but have the advantage of providing views in nonstandard angiographic orientations and avoid the hazards of intra-arterial injection. Conventional angiography is still the “gold standard” for cerebrovascular imaging, as the resolution currently exceeds that of MRA, but is associated with a 0.5% to 3% risk of neurologic complications. With further technical improvements in MRA, the use of conventional carotid angiography is likely to decline.

Indications for MRA include stroke, transient ischemic attack, possible venous sinus thrombosis, arteriovenous malformation, and vascular tumors. MRA can also detect cerebral aneurysms as small as 3 mm. In patients with acute stroke, MRA of the brain is useful in determining the patency of the arteries of the circle of Willis. Other MR angiographic techniques allow venous blood flow to be depicted separately from arterial blood flow. MR

venography of the brain is used to visualize the cerebral venous sinuses and other major cerebral veins; this is particularly useful in diagnosis of venous sinus thrombosis. MRA of the extracranial carotid arteries is used to detect carotid artery stenosis and compares favorably with conventional angiography. However, it should be noted that MRA may occasionally overestimate the degree of carotid stenosis. Also, MRA does not clearly demonstrate areas of ulceration within atherosclerotic plaques.

DEGENERATIVE DISEASES AND DEMENTIA

Jean Paul Vonsattel, M.D.

Degenerative Diseases and Dementia
Jean Paul G. Vonsattel, M.D.

- A. General considerations**
- B. Usual aging**
- C. Mild cognitive impairment**
- D. Alzheimer disease**
- E. Frontotemporal Dementia**
- F. Parkinson disease**
- G. Huntington Disease**

A. GENERAL CONSIDERATIONS

Key concepts:

- 1. The relative regional selective vulnerability within the brain causes atrophy, which can be detected intra vitam using neuroimaging techniques (radiologic evaluation).*
- 2. The selective vulnerability of one or more systems may cause specific symptoms such as dementia or movement disorder or both (clinical evaluation).*
- 3. The neuropathological examination determines the type, distribution and extent of the abnormal changes involving the brain (biopsy or postmortem evaluation).*
- 4. The integration of the neuroimaging, clinical, and pathologic findings leads to a definitive diagnosis of neurodegenerative diseases.*

Neurodegenerative diseases encompass a group of chronic, progressive disorders usually involving the elderly. Neurodegenerative disorders of childhood are generally considered in separate categories. The common link uniting these entities is a slowly progressive loss of neurons, the symptoms of which are dependent on the region of the brain affected. The psychological and financial burdens of neurodegenerative diseases increasingly strain the familial and social framework of our societies. This trend is linked to the gradual lengthening of life expectancy and is therefore worsening. Many neurodegenerative diseases occur exclusively in humans. The pathogenesis of neurodegeneration is only partially understood and there are no cures currently available. They are sporadic except in about 10 percent of instances in which they are either autosomal dominant or recessive.

While brain atrophy may be diffuse, it often involves specific regions differentially. This phenomenon is known as *selective vulnerability*. The anatomical substrate of neurodegeneration includes a gradual shrinkage of the brain (atrophy) with loss of neurons and reactive gliosis, with or without the formation of pathologic proteinaceous aggregates. These aggregates occur both within cells and in the extracellular space. The atrophy may be strikingly circumscribed and confined to certain regions of the brain. Neuroimaging is used to assess the distribution of the cerebral atrophy, which may provide important diagnostic clues.

Often a correlation exists between the sites prone to lose neurons prematurely and the clinical phenotype. This selective regional vulnerability in the brain varies according to the type of the disease and contributes to the differential diagnosis. Indeed, the pattern of the cerebral atrophy due to the degenerative process may translate into specific symptoms.

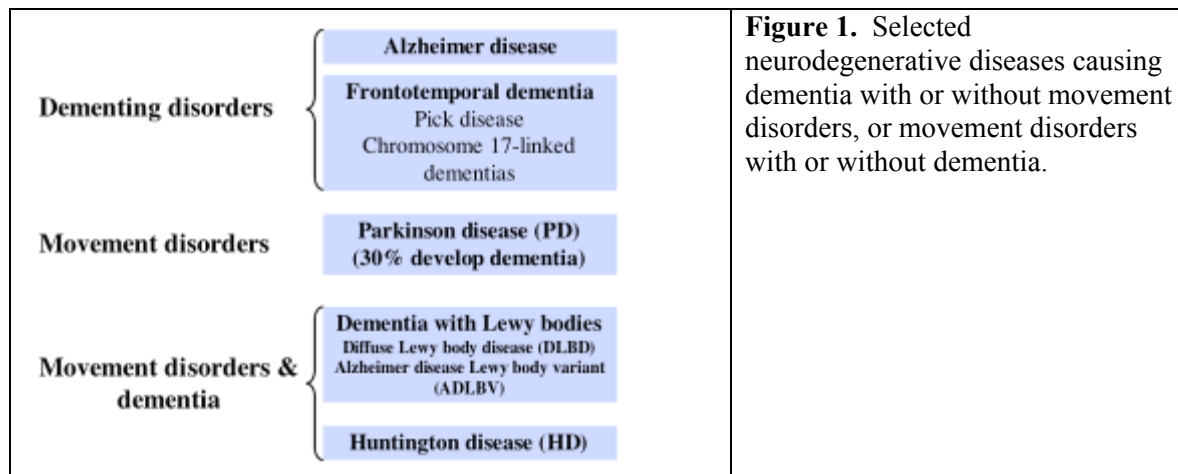
The onset of symptoms is often insidious. In early disease stages, symptoms may initially fluctuate and hinder diagnosis. The definitive diagnosis depends on clinical and pathological data with or without molecular techniques. In addition to the occurrence of relatively specific clinical symptoms and neuroimaging data, the categorization of neurodegenerative diseases also depends on the availability of biopsy specimens, molecular data, or on the postmortem examination of the brain. These methods assess:

- (i) The **class** of neurons that are especially vulnerable (e.g., dopaminergic neurons in parkinsonisms);
- (ii) The presence of abnormal **aggregates** of protein involving either the nucleus, cytoplasm or both of neurons (e.g., polyglutaminopathies), or that of glial cells (e.g., α -synucleinopathies), or extracellular space (e.g., amyloid);
- (iii) The **region(s) or system(s)** of the central nervous system (CNS), which bears the brunt of the degenerative process (e.g., striatum in chorea), and when appropriate
- (iv) **Genetic testing** (e.g., polyglutaminopathies including Huntington disease [HD]).

The focus in this course is on three groups of neurodegenerative diseases with the following distinctive, predominant, clinical phenotypes or symptoms:

- 1) Dementing disorders
- 2) Movement disorders
- 3) Movement disorders with dementia.

One should keep in mind that overlaps occur between these groups. Figure 1 lists the seven, representative diseases selected for the course.



B. USUAL AGING, MILD COGNITIVE IMPAIRMENT (MCI) AND DEMENTIA

“If we live long enough, will we all become demented? With our present lack of means to prevent the most common dementia, AD, more and more of us will decline cognitively as life expectancy increases, evidently with an age-related acceleration of incidence.¹”

Mild cognitive impairment (MCI) is a condition in which a person has problems with memory, language, or another cognitive function severe enough to be noticeable to other people and to show up on neuropsychological testing, but not severe enough to interfere with daily life. Because the problems do not interfere with daily activities, the person does not meet criteria for a diagnosis of dementia. Indeed the conversion MCI to Alzheimer disease (AD) may reach a rate of 15 percent per year². Thus, MCI may be a transition phase between usual aging process and AD. However, not all individuals with MCI go on to develop AD. In such instances, MCI may represent age-associated memory impairment.

On postmortem examination, the brains of elderly individuals without a clinically recognized neurological or psychiatric disorder usually show changes that are similar to those observed in brains from patients with AD but to a far lesser extent (Figure 2)³. Hence the question is raised as to whether a continuum exists between age-related changes and AD.

PATHOLOGICAL CHANGES IN USUAL AGING

a) Macroscopically:

- Atrophy of the brain evidenced by
 - Weight loss (up to 200 grams [normal: women 1,260 g; men 1,360 g]);
 - Narrowing of gyri and widening of sulci;
 - Ventricular dilatation (termed “hydrocephalus ex vacuo”);

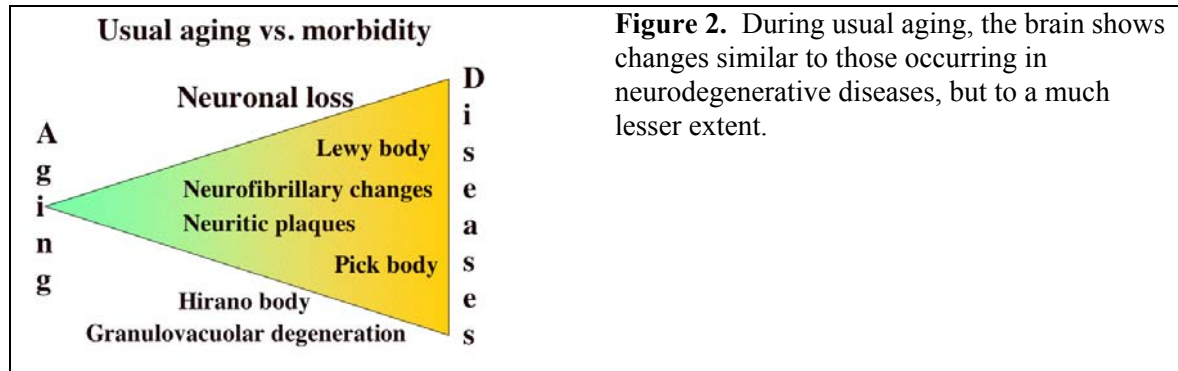
b) Microscopically:

- Neuronal loss (neuronal density decreases);
- Occurrence of
 - Neurofibrillary tangles of Alzheimer;
 - Neuritic plaques;
 - Granulovacuolar degeneration;
 - Hirano bodies;
 - Marinesco bodies; and
 - Vasculopathies (e.g., hypertensive or cerebral amyloid angiopathy [CAA]).

¹ Neurology 1994;44:1563-1565.

² The Lancet Neurology 2003;2:15-21.

³ Journal of the Neurological Sciences 1968;7:331-356.

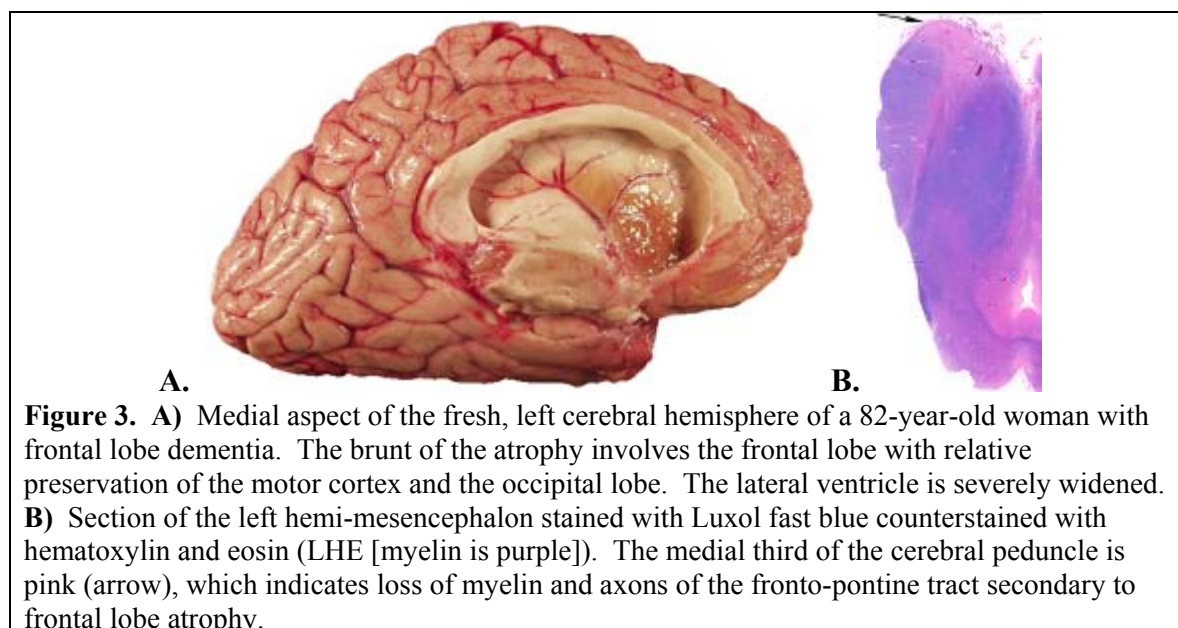


The pathological substratum of primary degeneration of the brain consists of the premature loss of neurons within areas of variable vulnerability. Usually this process occurs without acute or chronic inflammatory infiltrates, although microglial cells contribute to the pathogenesis.

The hallmarks of neurodegeneration include diffuse and/or regionally accentuated volume loss of the brain associated with neuronal loss, myelin loss, reactive astrocytosis, formation of neurofibrillary tangles of Alzheimer, neuropil threads and neuronal and glial inclusions.

An essential step in reaching a diagnosis for a specific neurodegenerative disease consists of assessing where the atrophy predominates, and which type of inclusions or abnormal aggregates are present.

By the time the patient dies, the changes are usually widespread, but they tend to predominate in one or more areas from which they appear to have spread. The primary site of degeneration, which is the most involved region of the brain, may in turn trigger remote secondary changes. For example, severe atrophy of the hippocampal formation causes myelin and fiber loss of the fornix and mammillothalamic tract; the enucleation of one eye causes anterograde transneuronal atrophy of the lateral geniculate bodies. Likewise, severe atrophy of the frontal lobe may cause shrinkage of the medial third of the cerebral peduncle, which includes the fronto-pontine tracts (Fig. 3).



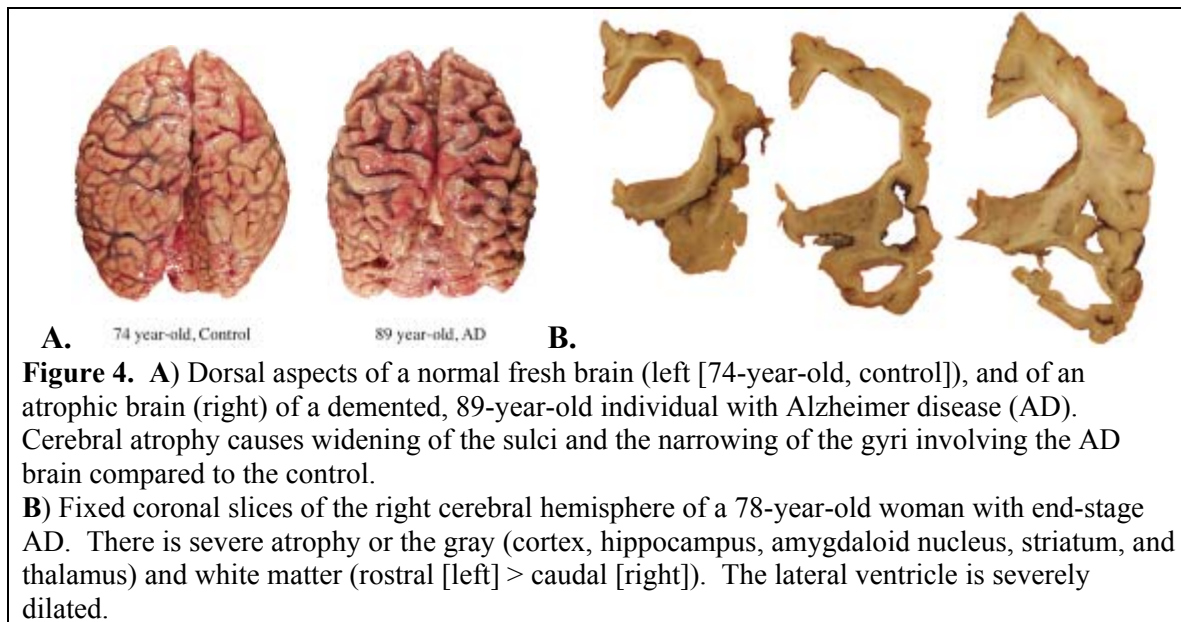
The symptoms may reflect the relative, selective topography of the degenerative process. Dementia may result from the degeneration of many structures with variable severity of involvement. The structures may include predominantly:

- The cerebral cortex, as in AD for example;
- The cerebral white matter, as in multiple sclerosis or in Binswanger disease;
- The hippocampal formation, entorhinal region, amygdala, nucleus basalis of Meynert, as in AD;
- The striatum, as in Huntington disease; and
- The mesencephalon especially the substantia nigra, as in Parkinson disease or Lewy body diseases (including Diffuse Lewy body disease [DLBD] and Alzheimer disease Lewy body variant [ADLBV]).

PATHOLOGICAL HALLMARKS OF DEMENTING DISEASES AND USUAL AGING

Cerebral atrophy

Cerebral atrophy results in the narrowing of the gyri and widening of the sulci including up to 20 to 30% weight loss. The atrophy results in apparent enlargement of the ventricular system, termed *hydrocephalus ex vacuo*. The volume of each lateral ventricle is about 7.0 - 10.0 cc in individuals without neurological or psychiatric diseases. The ventricular volume may reach up to 50 cc or more in demented people (Fig. 4). The severity and topography of the ventricular widening tend to match that of the parenchymal atrophy.



Cerebral atrophy may occur in cognitively normal subjects as an expression of usual aging. Atrophy may be lacking or may be subtle early during any neurodegenerative process. Atrophy is often conspicuous in advanced dementia (Fig. 4). Typical examples of dementia with prominent circumscribed atrophy are Pick disease (Fig. 5) with or without amyotrophic lateral sclerosis, and hippocampal sclerosis. Severe dementia with little or no atrophy

usually occurs in DLBD or in occasional patients with AD especially those who are older than 80 at death. Severe dementia without or with mild cerebral atrophy on neuroimaging or postmortem gross examination of the brain may occur in the following conditions:

- Dementia lacking distinctive histology,
- Creutzfeldt Jakob disease or prion diseases, and
- Acquired immune deficiency syndrome encephalopathy (AIDS).



Figure 5. Formalin fixed, lateral aspect of the left cerebral hemisphere of a 71-year-old-man with Pick disease. Note the prominent circumscribed atrophy involving the frontal lobe, rostral temporal lobe, and the inferior parietal lobule. Although atrophic, the pre-and post central gyri are relatively preserved, as are the superior parietal lobule and the occipital lobe.

The degeneration of the cerebral cortex is a major cause of dementia. While the vulnerability of the cortex varies anatomically there is often a remarkable reproducibility within a group of patients with the same disease. This relative selective vulnerability of the cerebral cortex may be governed by its regional nature determined phylogenetically.

The cerebral cortex is composed of the allocortex, and the phylogenetically more recent, neocortex. This phylogenetic subdivision includes the following regions, which are useful in assessing the topographic characteristics associated with the dementia:

Allocortex **Archicortex:** Hippocampal formation (presubiculum, subiculum, prosubiculum, cornu ammonis, dentate fascia)
Paleocortex: Pyriform cortex (entorhinal area)

Neocortex **Homotypical:** Cortex with six distinct layers (e.g., parietal lobe)
Heterotypical: Agranular (motor) cortex; granular (visual) cortex.

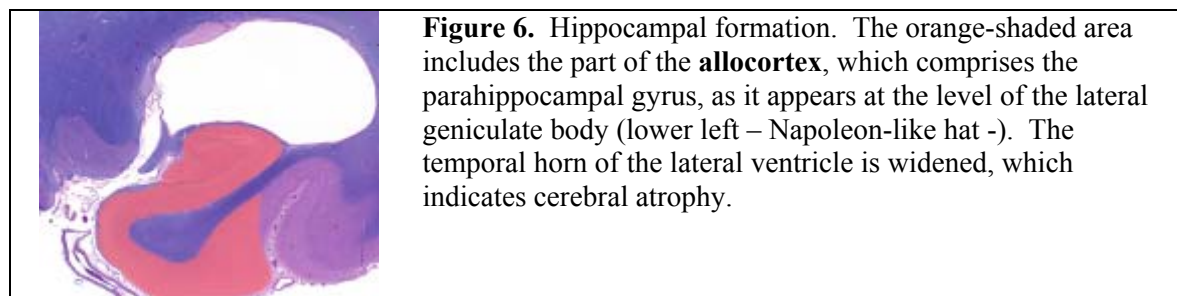


Figure 6. Hippocampal formation. The orange-shaded area includes the part of the **allocortex**, which comprises the parahippocampal gyrus, as it appears at the level of the lateral geniculate body (lower left – Napoleon-like hat -). The temporal horn of the lateral ventricle is widened, which indicates cerebral atrophy.

The allocortical regions (hippocampus, parahippocampal gyrus) are particularly prone to degeneration in usual aging and, more extensively, in dementing illnesses (e.g., AD, frontotemporal lobar degeneration [FTLD]). The large pyramidal neurons, especially those of the Sommer sector of the hippocampal formation, are susceptible to neurofibrillary tangle formation, granulovacuolar degeneration, and Hirano body formation in usual aging. The stellate neurons of layer 2 of the entorhinal cortex are highly susceptible to neurofibrillary tangle formation. These changes are conspicuous in AD (Fig. 7) or in Alzheimer disease Lewy body variant (ADLBV). The large and small

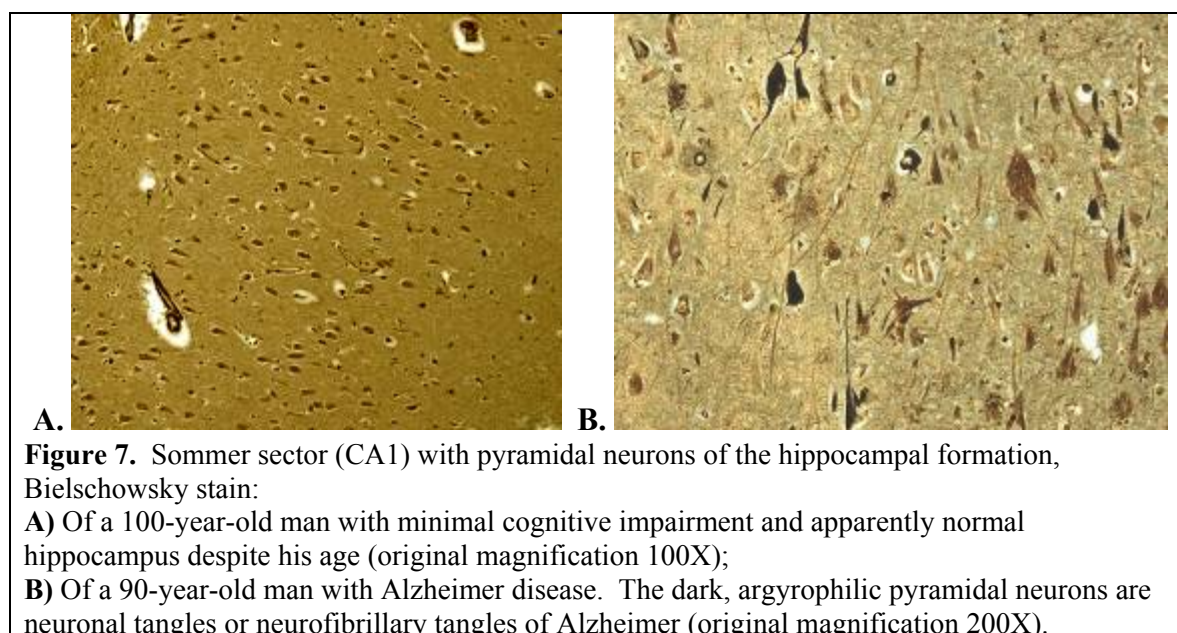


Figure 7. Sommer sector (CA1) with pyramidal neurons of the hippocampal formation, Bielschowsky stain:
A) Of a 100-year-old man with minimal cognitive impairment and apparently normal hippocampus despite his age (original magnification 100X);
B) Of a 90-year-old man with Alzheimer disease. The dark, argyrophilic pyramidal neurons are neuronal tangles or neurofibrillary tangles of Alzheimer (original magnification 200X).

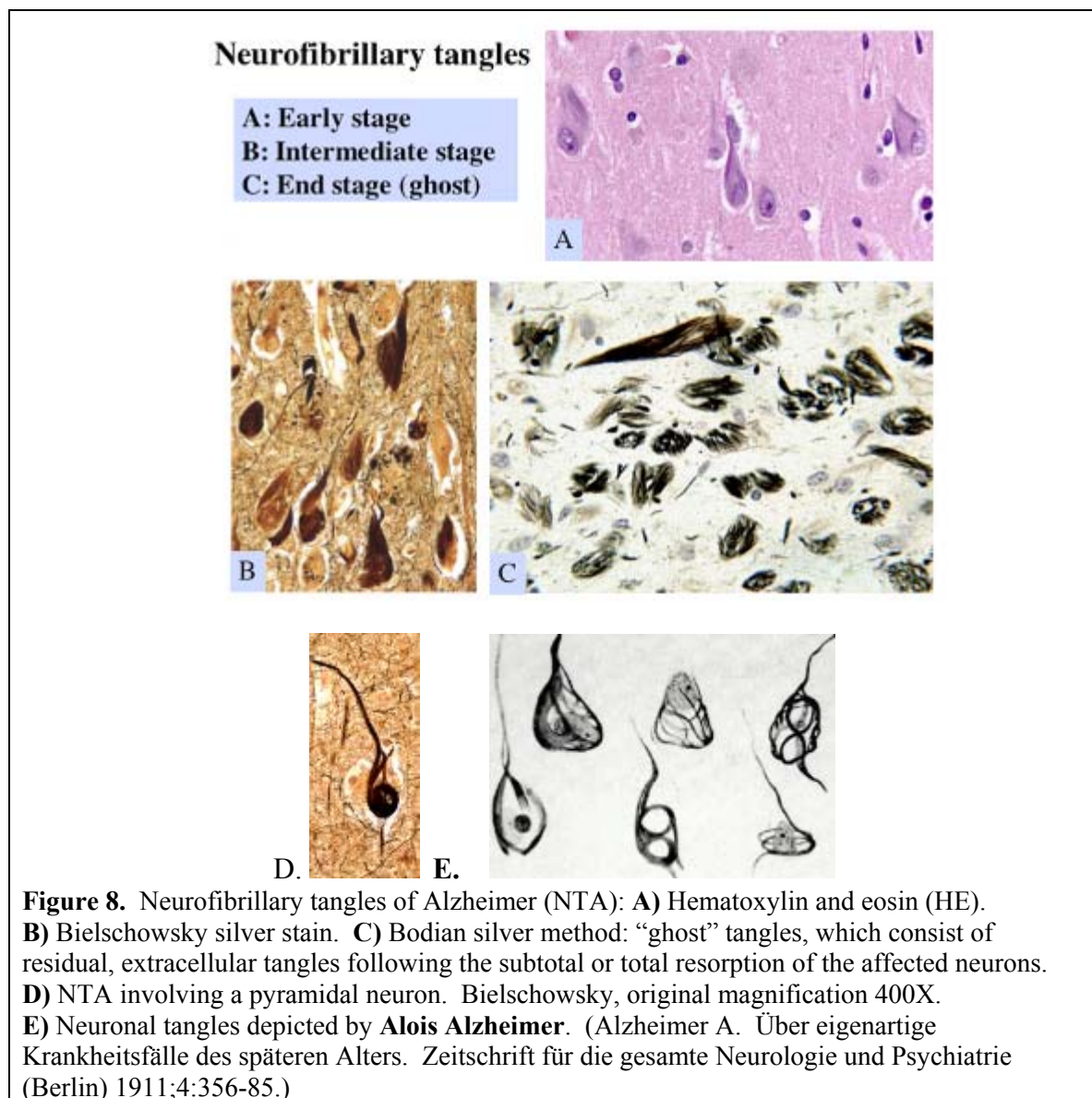
pyramidal neurons and the granule neurons of the fascia dentata are susceptible to Pick body formation in Pick disease (PcD).

Within the neocortex, the homotypical cortex is usually more vulnerable than the heterotypical cortex (motor cortex where the pyramidal neurons including with Betz cells predominate, or visual cortex where the granular neurons prevail). Neocortical neurons can be categorized as pyramidal, and non-pyramidal. The pyramidal neurons have extensive intracortical and extracortical connections; and it is these neurons that are most affected in dementing, degenerative diseases.

Neurofibrillary changes

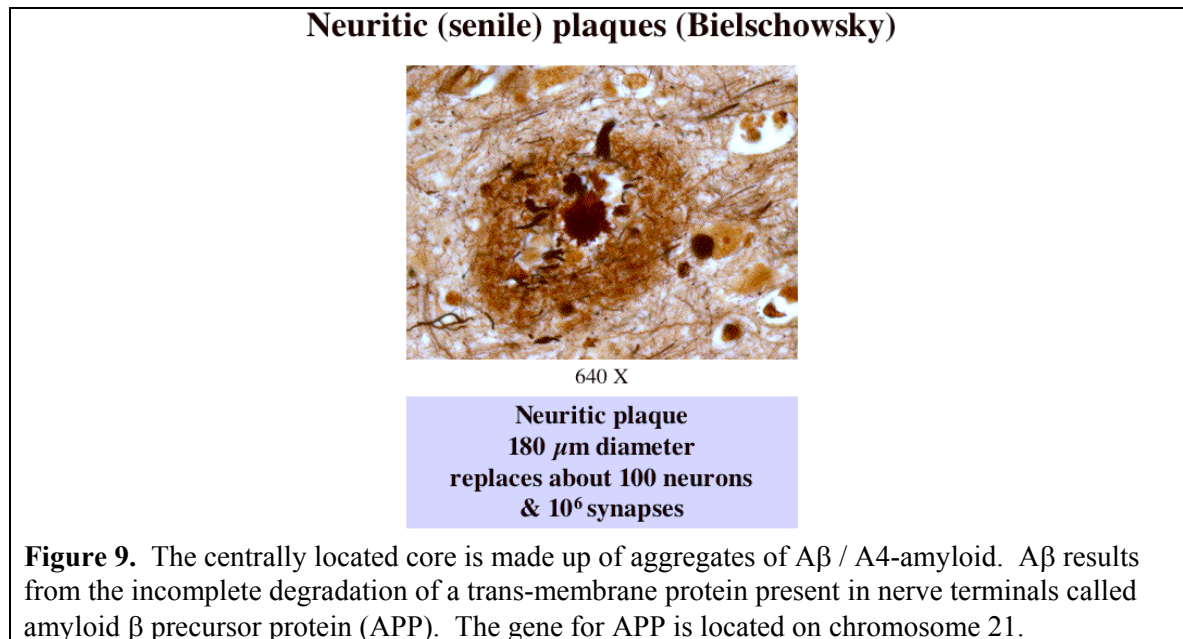
Neurofibrillary changes (Fig. 8) are due to the cytoplasmic, intracellular accumulation of paired helical filaments whose formation is mainly secondary to the hyperphosphorylation of tau. Tau is a microtubule-associated protein that promotes tubulin assembly and stabilizes microtubules.

Neurofibrillary changes consist of tortuous, argyrophilic (stain with silver dyes), tau positive fibrils found in the neuropil (neuropil threads), in the halo of neuritic plaques (dystrophic neurites), in the cytoplasm of pyramidal neurons (flame shaped neurofibrillary tangles) or oval neurons (globose tangles) and in the cytoplasm of oligodendrocytes or astrocytes (glial cytoplasmic tangles). Tau labeled glial cytoplasmic inclusions are observed in certain forms of familial frontotemporal dementia associated with parkinsonism due to a mutation involving the tau gene on chromosome 17.



Neuritic plaques

Neuritic plaques (or senile plaques, amyloid argyrophilic plaques) are extracellular, pathologic changes that are abundant in AD; and, to a much lesser extent, in individuals with MCI, or in many intellectually normal, older subjects. Neuritic plaques develop in the cerebral cortex, amygdala, hippocampal formation, and in the striatum especially in the nucleus accumbens. They may occur in the thalamus particularly within the dorsomedian and anterior nuclei; and in the cerebellar cortex. The ‘classical’ or ‘neuritic plaques’ are a spherical lesion, the diameter of which measures 50 to 180 μm (Fig. 9). They are composed of a centrally located Congo red positive amyloid core (β -amyloid). This core is surrounded by a halo of distorted neurites containing argyrophilic, paired helical filaments (PHF [dystrophic neurites]). Microglial cells, and macrophages can be seen within the plaques. Reactive astrocytes tend to be at the periphery of the plaques and in the parenchyma surrounding the plaques.



Hirano bodies

Hirano bodies are ovoid, or rod-shaped, 10-30 μm in length, eosinophilic, amorphous structures found adjacent to or within the cytoplasm of hippocampal pyramidal neurons, especially in CA-1 (Fig. 10). They can be found from youth to old age in both normal and demented subjects. Their number increases with age. They are more frequent in people with dementia than in intellectually normal subjects. They may derive from an age-related alteration of the microfilamentous actin system.

Hirano body

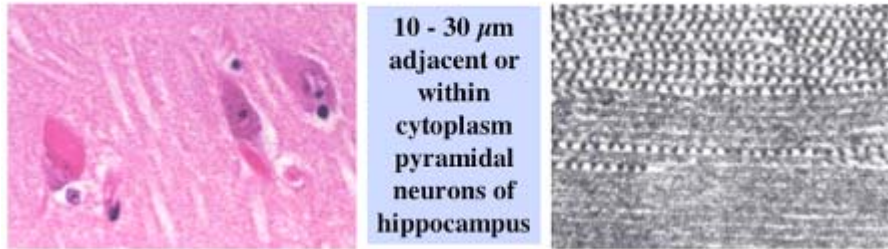


Figure 10. Hirano body. **Left:** Hematoxylin & eosin, original magnification 400X. **Right:** Electron microscopy of a Hirano body in Sommer sector (CA1) of hippocampus showing arrays of interlacing filaments that display either a lattice-like or “herringbone” configuration, original magnification 65,000. (From Hirano et al. *J Neuropathol Exp Neurol* 27:167, 1968).

Granulovacuolar degeneration (GVD)

GVD consists of the presence of one or more cytoplasmic granules, 1-2 μm across, surrounded by an optically empty rim, or vacuole measuring 3-5 μm in diameter (Fig. 11). These changes most frequently involve the pyramidal neurons of the Sommer sector (CA1) and subiculum of the hippocampus. They may be seen in cortical and subcortical neurons. GVD can occur in elderly individuals with normal cognition, although, to a lesser extent than in patients with AD. Tomlinson et al. reported severe involvement of the pyramidal cells of Sommer sector in every demented patient and that “some degree” of this change was found in 70 percent of their control brains⁴.

Granulovacuolar degeneration

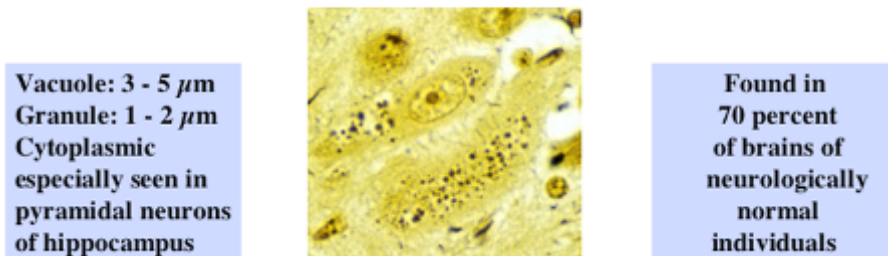


Figure 11. Granulovacuolar degeneration, Bielschowsky, original magnification 630X.

CEREBRAL WHITE MATTER

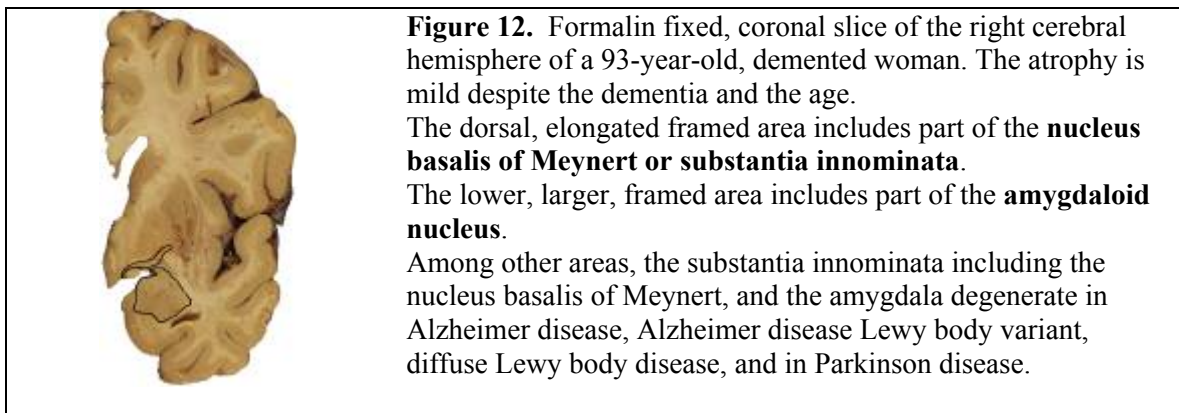
The cerebral white matter, or “centrum semi-ovale,” occupies much of each cerebral hemisphere. Age related volume loss of the brain involves the white matter more than the gray matter. Extensive loss of the cerebral white matter with subsequent dementia may be caused by vasculopathies. Hypertensive vascular changes (fibrosis of the walls of the vessels) cause hypoperfusion of the centrum semi-ovale. A gradual loss of oligodendrocytes, myelin and neuronal processes occurs with a reactive gliosis and widening of the perivascular spaces. Prominent involvement of the subcortical white matter is termed Binswanger disease.

⁴ *Journal of the Neurological Science* 1970;11:205-242.

Nearly 30% of individuals with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) develop dementia. Dementing illnesses with a destructive or demyelinating process include progressive multifocal leukoencephalopathy, the encephalopathy of the acquired immune deficiency syndrome, and multiple sclerosis.

SUBCORTICAL NUCLEI AND DEMENTING ILLNESSES

The amygdala (Fig. 12) often shows severe pathological changes in dementing diseases, e.g., AD (neuronal loss, neurofibrillary tangles, neuritic plaques, and gliosis); diffuse Lewy body disease (DLBD) (neuronal loss, neurons with Lewy body, spongiform changes); and Pick disease (neuronal loss, gliosis, ballooned neurons, and Pick bodies). The nucleus basalis of Meynert (substantia innominata) is the site of degeneration in AD, LBD including ADLBV and DLBD, Parkinson disease, and progressive supranuclear palsy.



The large neurons of the neostriatum⁵ (caudate nucleus, nucleus accumbens and putamen) undergo neurofibrillary degeneration in AD. The striatum⁶ bears the brunt of the cerebral atrophy in Huntington disease (HD), which is characterized by movement disorder (chorea) and dementia.

The dorsomedian and the anterior nuclei of the thalamus (Fig. 13), which are the limbic nuclei, are especially prone to neuronal loss with or without the formation of neuritic plaques, or neurofibrillary tangles, or both especially in AD. The centrum medianum is gliotic in the late stage of HD. The rostral half of the thalamus may be atrophic (usually medial > lateral) in Pick disease. These thalamic changes are almost always encountered in the context of dementia. In addition, unilateral thalamic infarct or hemorrhage may cause dementia.

⁵ **Neostriatum:** Is made up of the caudate nucleus and putamen.

⁶ **Striatum:** Includes the neostriatum and the globus pallidus (or paleostriatum).



Figure 13. Formalin fixed, coronal slice of the left cerebral hemisphere of a 83-year-old demented man. The cut passes through the mammillothalamic tract. The size of the head of the hippocampus is severely reduced. The dorsomedian nucleus and the anterior nucleus of the thalamus, which are the limbic nuclei, are severely atrophic. The lateral ventricle is widened, as is the sylvian fissure reflecting the loss of parenchyma.

BRAINSTEM AND DEMENTING ILLNESSES

The brainstem (Fig. 14) often shows degenerative changes in dementing illnesses. Neuronal loss involves the:

- Substantia nigra pars compacta (mainly dopaminergic) in LBD including DLBD and ADLBD, PcD (in up to 70% of cases), Parkinson disease, and progressive supranuclear palsy;
- Nucleus coeruleus (norepinephrine – catecholamine) in AD, DLB, and Parkinson disease;
- Dorsal and median raphe nuclei (serotonergic) in AD, LBD, Parkinson disease, and progressive supranuclear palsy.
- Dorsal nucleus of vagus (cholinergic) in LBD, and Parkinson disease.



Figure 14. Medial aspect of the hemi brainstem including the lower edge of the mesencephalon, which contains a portion of the substantia nigra, especially the pars compacta. The short (blue) bar within the fourth ventricle indicates the site of the locus coeruleus. The long bar (green) indicates the site of the dorsal nucleus of the vagus. Resting on the ventral aspect of the pons is the longitudinally sectioned, normal basilar artery.

In summary, the areas that are vulnerable to degeneration causing dementing illnesses with or without movement disorders are amygdala; allocortex: entorhinal and pyriform cortices, hippocampal formation; mammillary bodies, anterior and dorsomedian nuclei of thalamus; neocortex (homotypical > heterotypical); neostriatum, nucleus coeruleus, and raphe nuclei.

D. ALZHEIMER DISEASE (AD)

EPIDEMIOLOGY - AD is the most common cause of dementia. The growing awareness of the early signs of mental decline caused by neurodegeneration has increased the **incidence**⁷ of the diagnosis of **dementia**⁸. Likewise, the increasing life expectancy with the growing number of elderly individuals raises the **prevalance**⁹ of dementing illnesses since dementia or neurodegeneration occurs primarily late in life. The prevalence of AD is age dependent, and is estimated to be between three and 11 per 100 persons older than 65 years. Dementia including AD is a growing problem facing modern society and care providers (Fig. 15-17).

Estimated cost of AD \$100 billion / year (1993)	Figure 15. (*) In the US: Archives of Neurology, 2003. 60:1119-1122.
4 th or 5 th leading cause of death	
n AD patients will continue to increase unless discoveries contribute prevention of the disease (*)	

In 2000, there were 4.5 million persons with AD (*)	Figure 16. (*) In the US: Neurology, 2005 (Suppl 3). 65:S31-S32.
By 2050 -> 13.2 million AD patients (*)	

<p>Predicted percent increase in Alzheimer disease by 2050</p> <p>Based on estimated data for 2006 and 2050 Alzheimer's and Dementia 2007:3:S168-9</p>	Figure 17. Predicted world-wide increase in Alzheimer disease
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⁷ **Incidence:** Number of patients that are NEWLY DIAGNOSED with dementia in a defined population and time frame. Incidence is preferable to prevalence.

⁸ **Dementia:** Is characterized by acquired cognitive impairments with intact arousal causing disruption of independent life. Memory, language and judgment fail.

⁹ **Prevalence:** Number of patients ALIVE with dementia in a defined population and time frame. Prevalence is biased by differences in SURVIVAL.

PATHOLOGICAL CHANGES IN AD

1. Gross appearance. On external examination of the brain the hallmarks of atrophy are the narrowing of the gyri and widening of the sulci (Fig. 4). The atrophy is diffuse with a predilection for the prefrontal, parietal, and temporal regions. The atrophy may be circumscribed or minimal in 10 percent of the cases. On examination of the cut sections, the brunt of the atrophy involves the white matter and cortex notably in the areas mentioned above; the amygdaloid nucleus, hippocampal formation, and the anterior part of the thalamus. The ventricular system is widened proportionally to the volume loss of the parenchyma. The nucleus coeruleus is pale in contrast to the usually well-pigmented pars compacta of the substantia nigra.

2. Microscopic changes. The microscopic changes are found almost throughout the brain; however, their severity varies according to the regions. Especially involved are the areas exhibiting the most prominent atrophy including the amygdaloid nucleus, hippocampal formation, and the following regions of the cerebral cortex: temporal, prefrontal, and parietal. The motor and visual cortices are relatively preserved although not spared.

The pathologic changes include:

- 1) A decrease of neuronal density the severity of which varies according to region
- 2) Neurofibrillary tangles of Alzheimer (**Figure 8**).
- 3) Neuritic plaques (**Figure 9**).
- 4) Cerebral amyloid angiopathy (CAA) (**Figure 18**).

Neuritic plaques tend to predominate in cortical layers II and III. Neurofibrillary tangles usually predominate in layer III and V of the neocortex. In advanced stages of the disease they may be found within the motor or visual cortices or both. Neuronal tangles occur within the amygdaloid nucleus, hippocampus, substantia innominata (nucleus of Meynert), hypothalamus, thalamus, raphe nuclei, nucleus coeruleus, and reticular formation.

Amyloid may gradually accumulate within the walls of medium size leptomenigeal or cortical vessels (Fig. 18). This accumulation causes compression

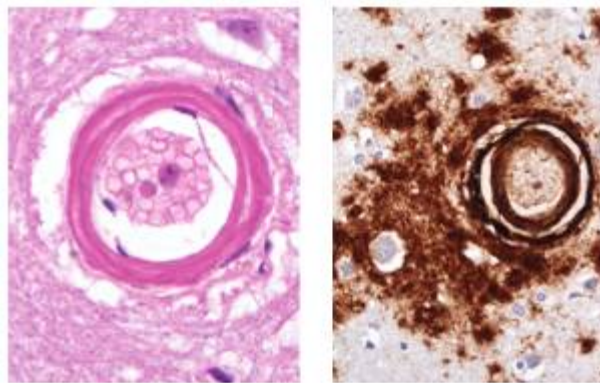


Figure 18. Amyloid angiopathy (or cerebral amyloid angiopathy [CAA]) involving cortical vessel, original magnification 400X. The vessels are patent in part because of the presence of amyloid.

Left: The wall is eosinophilic and smudgy. Amyloid replaced the smooth muscle fibers as inferred by the absence of their nuclei within the media (Hematoxylin and eosin).

Right: Section subjected to antibodies directed against β -amyloid, which labeled the abnormal deposits present within the wall of the vessel and within the surrounding parenchyma.

atrophy of the smooth muscle of the media with subsequent loss of the flexibility and contractibility of the vessel, which predisposes to blood leakage. The frequency of this vasculopathy increases with age and occurs often in elderly people including those without cognitive impairment. The frequency and severity of CAA is enhanced in individuals with Alzheimer disease. Severe CAA may cause recurrent, lobar cerebral hemorrhages.

PATHOGENESIS OF ALZHEIMER DISEASE

The causes are probably multifactorial; among them, the most important is aging. Familial AD accounts for ~10 percent of the patients. Genes linked with AD are found on chromosome 21 (amyloid precursor protein); on chromosome 14 (presenilin-1); and on chromosome 1 (presenilin-2). These mutations are associated with early onset of symptoms (< 65 years). The Apolipoprotein E gene on chromosome 19 is an important genetic factor for both the familial and sporadic form of AD. Carriers of the variant $\epsilon 4$ gene have an increased risk of developing AD.

Genetic and biological studies provide strong evidence that the deposition of amyloid- β peptide ($A\beta$) contributes to the etiology of AD. **$A\beta$ is generated from amyloid- β precursor protein (APP) by β - and γ -secretases.** Both secretases are transmembrane proteases: β -site APP cleaving enzyme 1, the main neuronal β -secretase, is a single span transmembrane aspartyl protease; γ -secretase is a multiprotein complex comprising four core subunits that are all transmembrane proteins: presenilin, nicastrin, anterior pharynx-defective 1 and presenilin enhancer 2.

1. Genetic. Epidemiological studies have shown that an individual with first-degree relatives with AD has an increased risk of developing AD themselves. In addition, there are forms of AD that are clearly inherited in an autosomal dominant pattern (approximately 10% of all cases).

Studies have revealed several **point mutations in the APP gene on chromosome 21** in a few families with inherited AD. The mutations lie either within the amyloid peptide region itself or adjacent to it. Most families that have been examined do not show these APP mutations, however. Interestingly, patients with **Down's Syndrome (chromosome 21 trisomy)** develop the pathological changes of AD after the age of 35-40. The reason for this is unclear, but perhaps over production of APP and thus amyloid (a "gene-dosage" effect) plays a critical role.

AD is a genetically heterogeneous disorder. Recent studies have shown familial AD loci on **chromosomes 19, 14, and 1**. Thus, familial AD has several different genetic bases, all of which must in some way result in a common set of pathological changes and clinical features.

Genetic studies of families with **early-onset**, or 'presenile' (onset age < 65 years), AD have identified mutations in two genes, the **presenilin** genes. **Presenilin-1 (PS-1)**, located on **chromosome 14**, is the major gene affected in familial early-onset AD. **Presenilin-2 (PS-2)** mutations, located on **chromosome 1**, account for a much smaller number of affected families. These genes are highly homologous and encode for a transmembrane protein that is

part of the γ -secretase protein complex. Recent studies of the mutant presenilin proteins of AD have shown that their expression is strongly associated with an increased production of the highly amyloidogenic 42-residue form of β -amyloid, which is deposited early and selectively in senile plaques. γ -secretase is also involved in proteolysis of the Notch protein transmembrane domain, required for Notch signaling.

γ -secretase has been a target for Alzheimer therapeutics, but it will be necessary to develop compounds that can modulate the enzyme to alter or block A β production with little or no effect on Notch processing and signaling.

The **chromosome 19 linkage** site is near the locus of **apolipoprotein E (APO-E)** (19q13.2). APO-E, a 34 kDa glycoprotein, is the major apolipoprotein in the CNS and plays an important role in triglyceride-rich lipoprotein metabolism and cholesterol homeostasis. It is synthesized in CNS glia, is found in amyloid plaques and in fact binds tightly to amyloid *in vitro*. Studies have shown that the **e4 allele of APO-E** is significantly associated with AD, both in **late-onset familial and sporadic cases**. Thus, the APO-E e4 frequency in AD patients is many times that of the frequency of the more common e3 allele. The highest association is seen with e4 homozygous individuals, with a lesser association with e4 heterozygotes. The strong association suggests that Apo-E e4 is involved in the pathogenesis of AD, in some way conferring genetic susceptibility or "risk", or that APO-E is in linkage disequilibrium with another nearby locus that confers susceptibility. How Apo-E e4 acts in the pathogenesis of AD is unknown, but perhaps its association with amyloid alters amyloid processing or toxicity, and that the association is a function of the allelic form of Apo-E. It should be kept in mind that 50-60% of all AD patients do not have an e4 allele.

Table 1. Genes linked with Alzheimer's disease

Chromosome	Gene	Protein	Clinical
21	APP	Amyloid precursor protein	Early onset familial AD
19	APO-E	Apolipoprotein E	Late onset sporadic AD
14	PS-1	Presenilin-1	Early onset familial AD
1	PS-2	Presenilin-2	Early onset familial AD

2. Immune. There is growing speculation and experimental evidence that cellular and soluble immune system mediators, **cytokines**, play roles in the pathogenesis of AD. Senile plaques typically exhibit varying degrees of reactive cellular response by microglia and astrocytes, both of which are known to produce cytokines.

3. Infectious. There is little evidence for an infectious etiology. The idea that AD is caused by a transmissible agent, like that which causes Creutzfeldt-Jacob disease (see Infectious Disease notes), is unlikely by the fact that AD has not been transmitted to animals and the typical brain spongiform changes of CJD have not been observed in patient's with AD. Nevertheless, some investigators are looking for specific viral genetic material in the brains of AD patients.

4. Toxic. In the recent past there was considerable interest in the effects of **aluminum**, because neurons that contain tangles also appeared to contain high levels of aluminum, and

because the injection of aluminum salts into brains of experimental animals produced accumulations of neurofilaments in neuronal cell bodies and axons. However, the paired helical filaments of AD are not generated and amyloid plaques are not found.

Age-related oxidative stress has been proposed in playing a role in the pathogenesis of Alzheimer's disease, as well as in other neurodegenerative diseases. The exact mechanisms have yet to be defined.

E. FRONTOTEMPORAL DEMENTIAS (PICK DISEASE AND CHROMOSOME 17-LINKED DEMENTIAS)

The denotation “Frontotemporal lobar degeneration (FTLD) “ or “Frontal lobe dementia (FLD)” emphasizes the clinical rather than the pathological aspect of this multifaceted condition. Indeed, many neuropathological abnormalities are associated with FTLD¹⁰.

The clinical distinction between patients with FTLD and those with AD may be challenging especially in non-academic settings. The main distinctive features are:

1) Clinically

1.1 Poor judgment, perseveration, aphasia, and altered executive functions (mainly due to dysfunction of the dorsolateral prefrontal cortex). Usually the onset of symptoms of FTLD is earlier than in AD.

1.2 Disinhibition including inappropriate behavior, impulsivity, euphoria (dysfunction of the orbitofrontal region);

1.3 Apathy or loss of motivation and interest (dysfunction of the anterior cingulate gyrus);

1.4 Hyperorality (weight gain), placidity and aspects of the Klüver-Bucy syndrome¹¹ (dysfunction of anterior temporal lobe);

1.5 **With or without motor neuron impairment** (amyotrophic lateral sclerosis – called FTD-ALS) (Fig. 19).

2) Genetics

FTLD may be familial in 60 percent of cases. Many kindreds have been linked to chromosome 17, with mutations identified in the tau gene and progranulin gene. Gene linkage to chromosome 3 and 9 has also been identified. The patients are phenotypically heterogeneous even within the same kindred, although consistent features occur.

¹⁰ Forman et al. Frontotemporal dementia: Clinicopathological correlations. *Annals of Neurology* 2006;59:952-962.

¹¹ Following removal of both temporal lobes including the uncus and greater part of the hippocampus macaques exhibited “psychic blindness”, strong oral tendencies [licking, biting gently, chewing], and a strong tendency to react to every visual stimulus. Klüver H, Bucy PC. Preliminary analysis of functions of the temporal lobes in monkeys. *Archives of Neurology and Psychiatry* 1939;42:979-1000.

3) Neuropathological abnormalities

Two broad subdivisions are currently used

3.1 Brains **with tau-protein changes** (tauopathies), e.g., Pick disease.

3.2 Brains **without tau-protein changes**, but **with or without ubiquitinated inclusions**, which are either nuclear or cytoplasmic.

The atrophy usually predominates within the frontal, or fronto-temporal, or fronto-temporal-parietal regions (Fig. 5, 19). Neuritic plaques are rare or absent. The neuronal tangles tend to be confined to the temporal region. Status spongiosus (Fig. 26) involves the upper cortical layers.

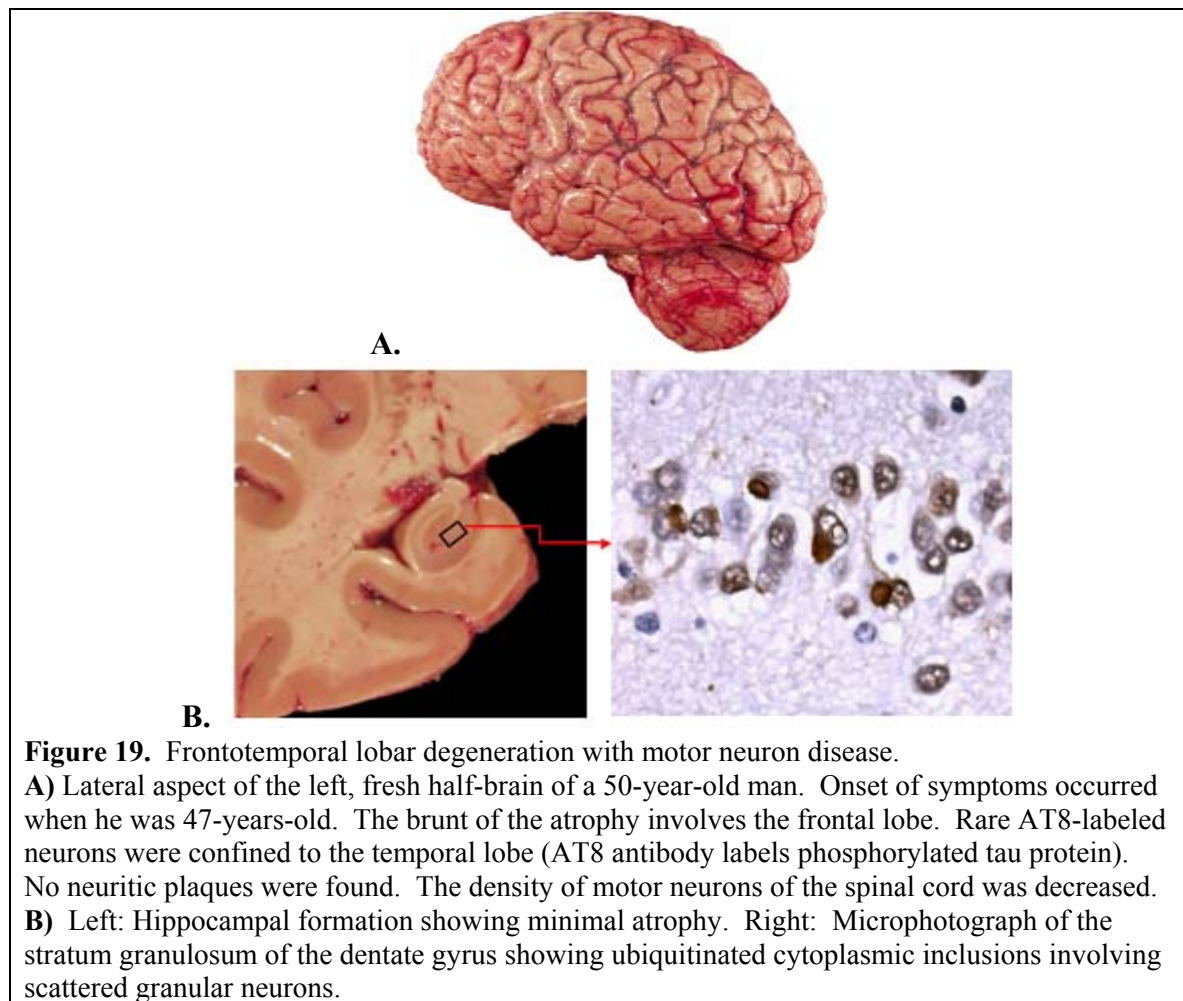


Figure 19. Frontotemporal lobar degeneration with motor neuron disease.

A) Lateral aspect of the left, fresh half-brain of a 50-year-old man. Onset of symptoms occurred when he was 47-years-old. The brunt of the atrophy involves the frontal lobe. Rare AT8-labeled neurons were confined to the temporal lobe (AT8 antibody labels phosphorylated tau protein). No neuritic plaques were found. The density of motor neurons of the spinal cord was decreased.

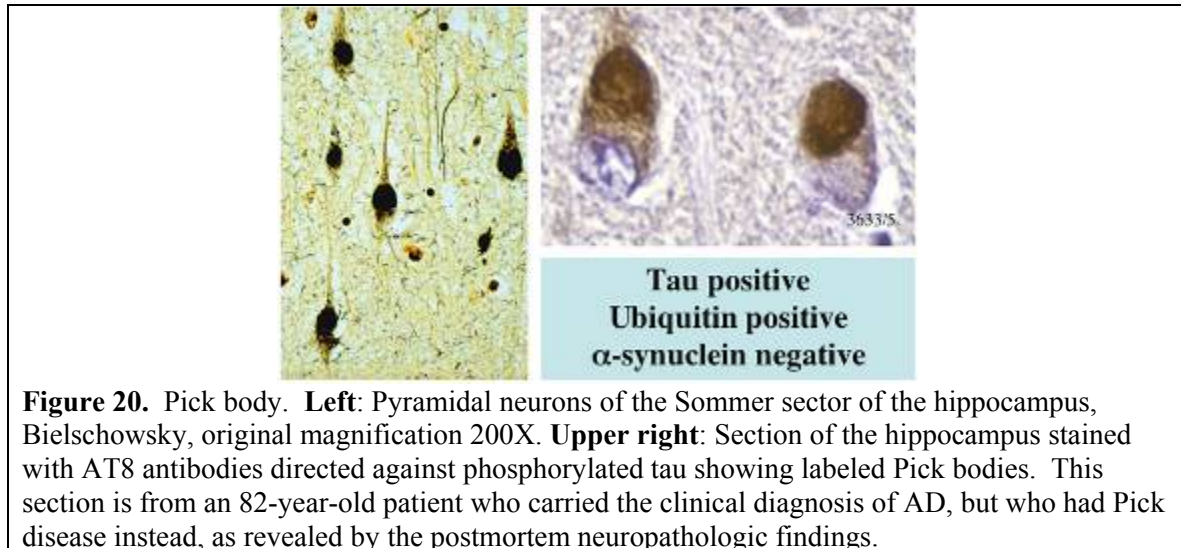
B) Left: Hippocampal formation showing minimal atrophy. Right: Microphotograph of the stratum granulosum of the dentate gyrus showing ubiquitinated cytoplasmic inclusions involving scattered granular neurons.

The hallmarks of Pick disease are:

- Diffuse atrophy with regional, circumscribed accentuation of the atrophy (Fig. 5)
- The presence of
 - Neurons containing Pick bodies (Fig. 20);
 - Ballooned neurons (Fig. 21), and
- Status spongiosus (Fig. 26).

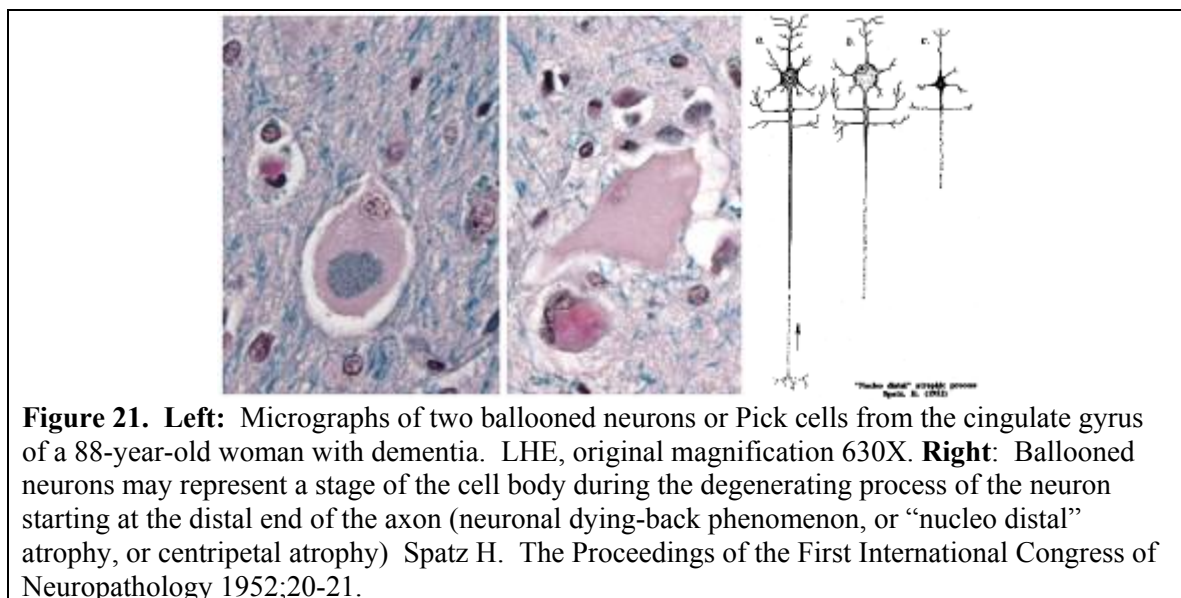
Pick bodies

Pick bodies (Fig. 20) are round, or oval, well-outlined, argyrophilic, tau positive, ubiquitin positive, synuclein negative, cytoplasmic bodies measuring 10-15 μm across. They are found in cortical pyramidal neurons and in the hippocampal formation; and in the amygdala, and occasionally within the striatum and brainstem. Pick bodies are found in about 30 to 50 percent of brains from demented patients with discrete, circumscribed atrophy.



Ballooned neurons (Pick cells)

Ballooned neurons (BN), also referred to as “Pick cells”, are swollen neurons with convex contours, homogeneous glassy, pale, eosinophilic cytoplasm, and eccentric nuclei (Fig. 21). The cytoplasm is diffusely argyrophilic with variable intensity. Ballooned neurons are found in a variety of neurodegenerative diseases included Pick disease and Alzheimer disease.



F. PARKINSON DISEASE (PD)

CLINICAL FEATURES

PD is a chronic neurodegenerative disease with insidious onset mainly involving the elderly. The disease is characterized by a constellation of neurological symptoms collectively termed *Parkinsonism*, including **resting tremor, bradykinesia, rigidity and postural instability (gait disturbance)**. Approximately one-third of Parkinson's disease patients also develop cognitive problems, such as memory dysfunction or dementia.

Elderly individuals are predominantly involved (the exception being the rare form of juvenile Parkinson disease). About 1% of the population over the age of 50 has some degree of Parkinson's disease. About 50,000 Americans are diagnosed with Parkinson's disease each year. It is estimated that more than half a million Americans are affected at any one time.

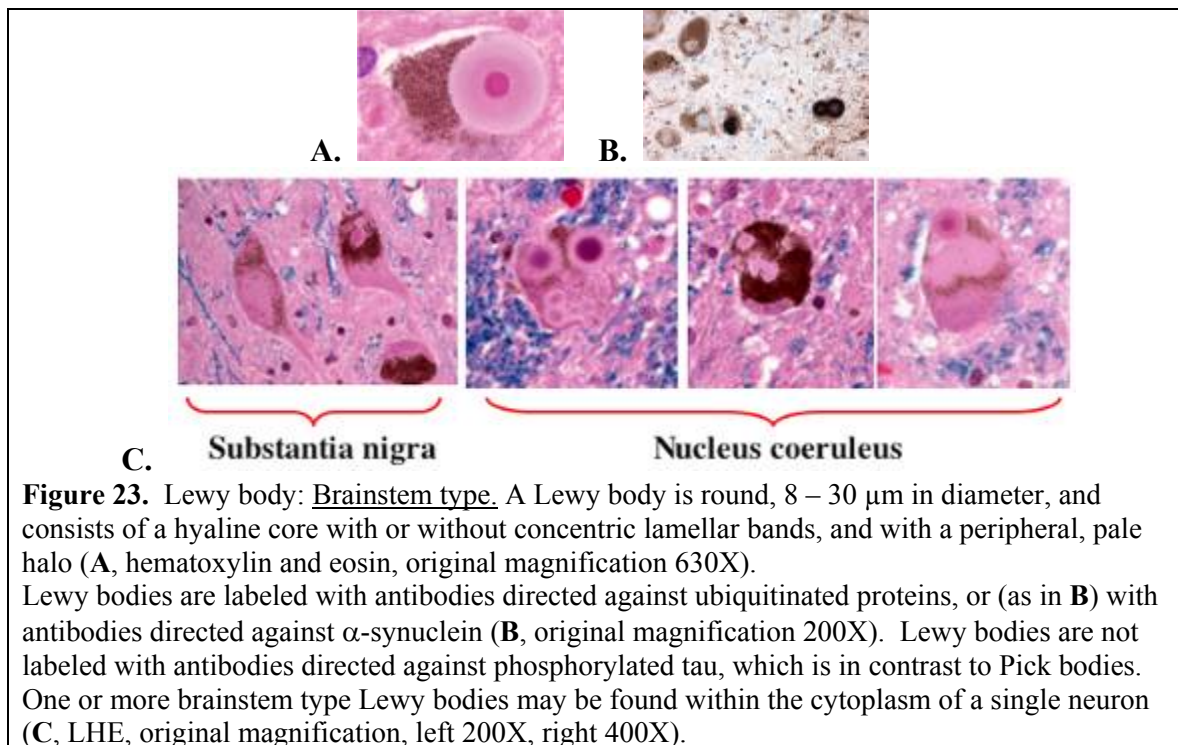
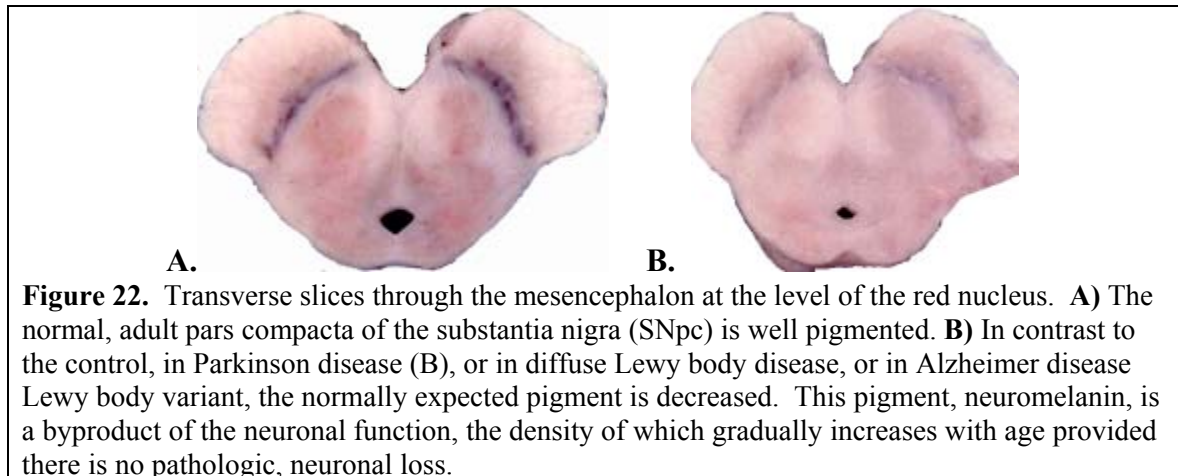
Strategies for treatment focus on replacement of dopaminergic functions, mainly by giving **L-DOPA**. This has been the mainstay of treatment for many years. More recently an inhibitor of MAO-B, **L-Deprenyl**, has proved to be efficacious. Recently, transplants of adrenal medullary tissue or fetal nigral tissue into the striatum has generated considerable interest and raised hopes for effective therapy; application of stem cell therapies to replace lost dopaminergic neurons are being actively researched. Surgical implantation of stimulatory generators is used in advanced stages.

PATHOLOGICAL FEATURES

Gross examination of the brain reveals *pallor of the substantia nigra* within the mesencephalon (principally in the pars compacta— Fig. 22) and of the nucleus coeruleus (metencephalon). There may be mild generalized atrophy of the brain.

The neuropathological hallmark of PD is the presence of cytoplasmic inclusions in neurons termed “Lewy bodies,” seen on microscopic examination. *Lewy bodies are principally composed of α -synuclein*; however there are other proteins contained within them (e.g., ubiquitin). α -synuclein is a protein found in presynaptic terminals. Two types of Lewy bodies can be distinguished by morphology and regional distribution: the brainstem or classical type (Fig. 23) and the cortical type (Fig. 24, see below). In addition to Lewy body-containing neurons, there is loss of neurons, which involves predominantly the following structures:

- **Substantia nigra (pars compacta)**
- Dorsal nucleus of vagus
- Nucleus coeruleus
- Substantia innominata including the nucleus of Meynert
- Hypothalamus



Brainstem type Lewy bodies are most commonly found in the pigmented neurons of the brainstem, including:

- 1) within the mesencephalon and metencephalon:
 - The pars compacta of the substantia nigra (Fig. 23C, left),
 - Nucleus coeruleus (Fig. 23C, right),
 - The Edinger-Westphal nucleus (cholinergic, preganglionic parasympathetic motor neurons that control lens accommodation and pupillary constriction, which lie near the midline, dorsal to the oculomotor nucleus [III cranial nerve nucleus]);

- 2) within the myelencephalon:
 - Dorsal motor nucleus of the vagus;
- 3) within the diencephalon:
 - Thalamus,
 - Hypothalamus,
 - Substantia innominata; and
- 4) within the peripheral nervous system: Olfactory bulb, autonomic ganglion, and myenteric plexus of the intestines.

DEMENTIA WITH LEWY BODIES

- Diffuse Lewy body Disease (DLBD)

- Alzheimer Disease Lewy body Variant (ADLBV)

Neocortical neurons can develop cortical type Lewy bodies, primarily those located in layers V (Fig. 24A) and VI. In general, affected cortical neurons have only one Lewy body. **In DLBD**, Lewy body-containing neurons occur in the same areas as those involved in PD (see above), but are additionally present within the cerebral cortex. The involvement of the cerebral cortex disrupts its function, and is associated with dementia. Thus, in diffuse Lewy body disease the main symptoms are parkinsonism and dementia. The sites of predilections for the occurrence of cortical type Lewy bodies are the cingulate gyrus, insula, entorhinal cortex, parahippocampal gyrus (Fig. 24B), occipitotemporalis gyrus, and amygdaloid nucleus. Possibly, DLBD represents the ultimate clinical and neuropathologic stages of PD especially in individuals with long course of the illness (Fig. 25).

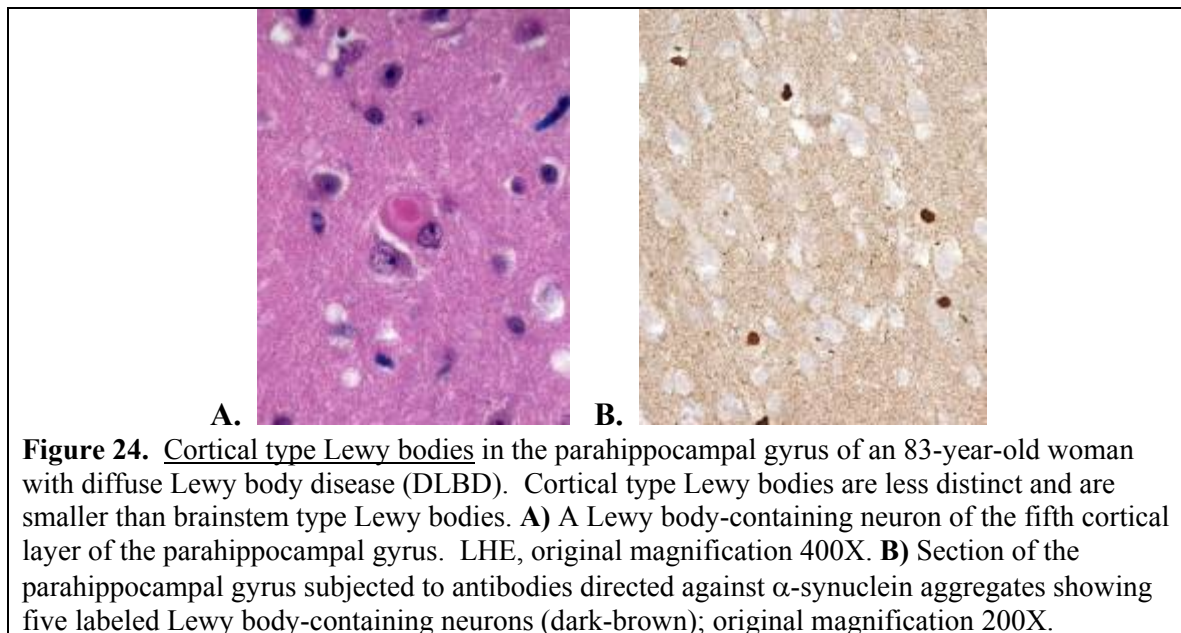


Figure 24. Cortical type Lewy bodies in the parahippocampal gyrus of an 83-year-old woman with diffuse Lewy body disease (DLBD). Cortical type Lewy bodies are less distinct and are smaller than brainstem type Lewy bodies. **A)** A Lewy body-containing neuron of the fifth cortical layer of the parahippocampal gyrus. LHE, original magnification 400X. **B)** Section of the parahippocampal gyrus subjected to antibodies directed against α -synuclein aggregates showing five labeled Lewy body-containing neurons (dark-brown); original magnification 200X.



Figure 25. The sequential occurrence of Lewy body-containing neurons is as follows:
- **In Parkinson disease:** Dorsal nucleus of vagus, nucleus coeruleus, pars compacta of the substantia nigra, substantia innominata (nucleus of Meynert), hypothalamus¹²;
- **In diffuse Lewy body disease:** As above, but, in addition within the cerebral cortex in the following sequence: - Entorhinal cortex, parahippocampal, and occipitotemporalis gyri, insular cortex, cingulate gyrus, homotypic neocortex, and heterotypic neocortex (motor or visual cortex). Dementia develops and worsens with the gradual involvement of the cerebral cortex.

Clinically, **Alzheimer disease Lewy body variant (ADLBV)** cannot be reliably distinguished from Alzheimer disease. Thus the definite diagnosis of Alzheimer disease Lewy body variant relies mainly on postmortem examination or occasionally on the availability of biopsy specimens. This diagnosis is made when the brain of a demented patient shows the changes of Alzheimer disease together with those of diffuse Lewy body disease. In ADLBV, in addition to the widespread presence of the Lewy body-containing neurons, the extent of the neuronal loss, the density of neuritic plaques and of neurofibrillary tangles of Alzheimer are such as to meet the current criteria applied to establish the diagnosis of Alzheimer disease.

Status spongiosus vs. spongiform changes

Status spongiosus consists of irregular cavitation of the neuropil in the presence of a dense glial meshwork (Fig. 26A). It is non-specific and characteristically is the manifestation of end-stage gliosis. *Spongiform changes* consist of the presence of small, round, or ovoid, optically empty vacuoles within the neuropil (Fig. 26B). Transcortical or deep cortical spongiform changes associated with gliosis are hallmarks of the spongiform encephalopathies including CJD. However, to some extent, spongiform changes (with mild, or without reactive astrocytosis) are observed in LBD, ADLBV, and occasionally in AD. Spongiform changes are seen in DLBD (Fig. 26B) and may or may not involve the entorhinal cortex, parahippocampal, and occipitotemporalis gyri, temporal pole, insular cortex, or cingulate gyrus. The spongiform changes in Creutzfeldt-Jakob disease (CJD) are different in that the spongiform changes in DLBD tend to involve the superficial, cortical layers, and are either without or with mild reactive gliosis. But, at times, the spongiform changes occurring in DLBD, ADLBV, or even in AD are indistinguishable from those observed in spongiform encephalopathies, which must be ruled out.

¹² Braak H, Del Tredici K, Rüb U, de Vos RAI, Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging* 2003;24:197-211.

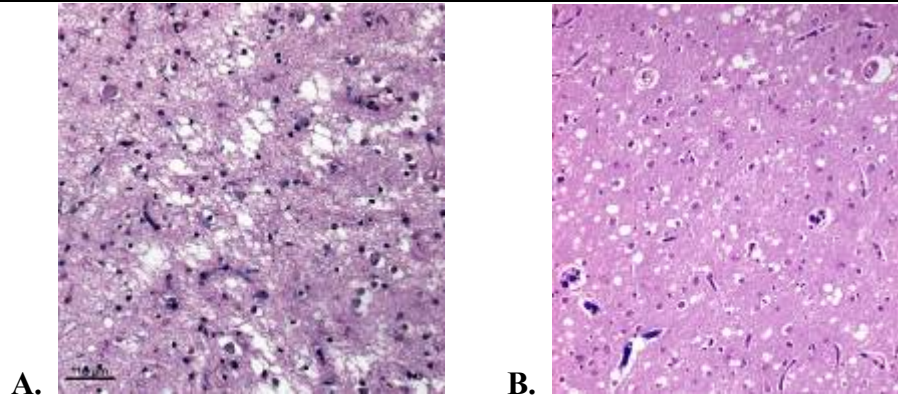


Figure 26. Optically empty vacuoles involving the neuropil in a variety of neurodegenerative diseases:

A) Status spongiosus involving the subpial layer of the frontal lobe of a 70-year-old man with Pick disease.

B) Spongiform changes involving the upper cortical layers of the temporal lobe of a 66-year-old woman with Alzheimer disease Lewy body variant. LHE, original magnification 200X.

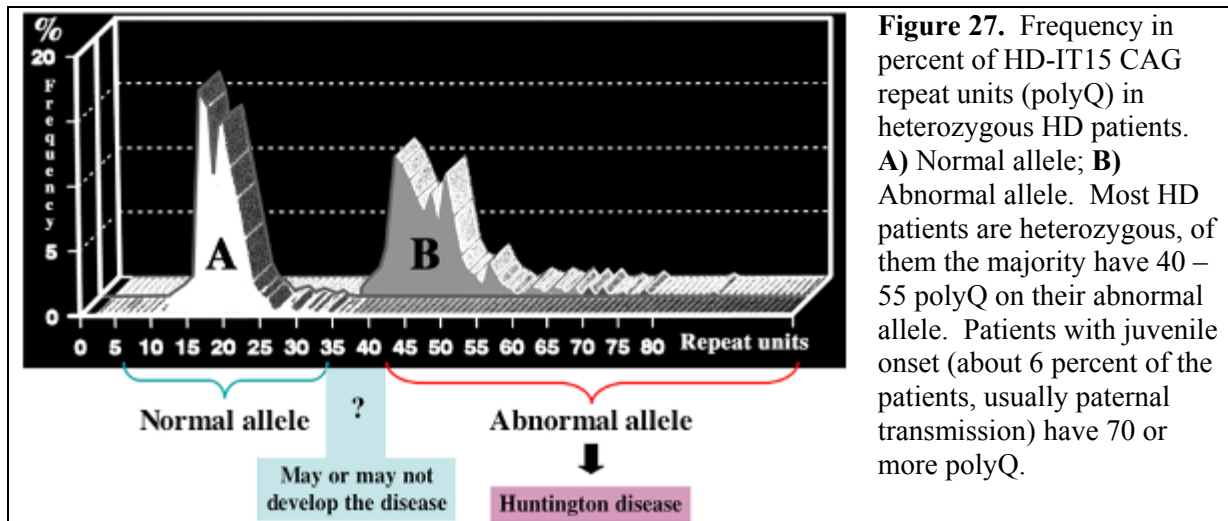
G. HUNTINGTON DISEASE (HD)

CLINICAL FEATURES - HD is an illness usually with midlife onset of motor, psychiatric and cognitive symptoms. The disease occurs approximately 1 in 10,000 people in most Western countries. HD is characterized clinically by abnormal, involuntary movements of a writhing, or choreiform nature, psychiatric abnormalities, and a loss of intellectual functions (dementia). Symptoms usually begin in the 4th or 5th decades of life, and progress slowly but inexorably. Forms that appear in childhood or older ages are rarer. Childhood patients tend to inherit the disease from their fathers and have an age of onset 8-10 years earlier than their fathers. Affected children of affected mothers have an onset age similar to their mothers. This is an example of what has been referred to as genetic 'anticipation,' in which the severity of the disorder increases and the age of onset decreases in successive generations of a pedigree.

Chorea is a key feature and defining symptom. ***Chorea is a rapid, involuntary, non-repetative or arrhythmic movement involving the face, trunk and limbs.*** Chorea may begin as “restlessness”, but invariably progresses to grossly evident choreaform movements. Symptoms begin insidiously, with death occurring 12-15 years from the time of symptomatic onset. The earliest cognitive changes often consist of irritability, moodiness, and antisocial behavior. ***Dementia subsequently develops***, with impairment of attention and executive function consistent with frontostriatal pathology. There is no cure for HD.

ETIOLOGY/GENETICS - HD is inherited in an autosomal dominant manner with a high degree of penetrance. The genetic defect that underlies Huntington's disease on **chromosome 4p** was identified in 1993. *The disease is caused by an unstable expansion of CAG (trinucleotide) repeats* within the coding region of the *IT15* gene (for “Interesting Transcript,” referred to as HD-IT15 CAG repeats). This gene, on chromosome 4 (4p16.3), encodes the 350 kDa protein huntingtin whose function is only partially known. An expanded polyglutamine residue (polyQ) distinguishes the mutated huntingtin (with about 37 to 250 polyQ [mhtt]) from the wild type (with 8 to about 34 – 36 polyQ [whtt]). The disease occurs when the critical threshold of about 37 polyQ is exceeded (Fig. 27). People with 30-36 CAG repeats are considered to be in a “grey zone” and it is presently difficult to predict whether they will become symptomatic. The lengths of the repeat correlates inversely with the age of onset, with younger affected patients bearing larger repeat lengths. How an increased repeat length causes the pathological changes of HD is as yet unknown. A **gain of function** mechanism has been proposed.

The phenomenon of polyQ extension is observed in other less common inherited neurodegenerative diseases, collectively referred to as polyglutaminopathies. Other diseases include the genes underlying fragile x- syndrome, spino-bulbar muscular atrophy, spinocerebellar ataxia, and myotonic dystrophy. Patients should be educated about the risk of transmitting the disease.



PATHOLOGICAL FEATURES - The mhtt is expressed in all organs, yet the brunt of the changes of HD identified so far occurs in the brain. Degeneration initially involves the striatum, then the cerebral cortex, and eventually may appear throughout the brain as a constellation of the toxic effect of the mutation and the ensuing secondary changes. The most striking feature is marked *atrophy of the caudate nucleus*. There is bilateral atrophy of the striatum in 95 percent of the HD brains. The striatal atrophy is prominent in 80 percent, mild in 15 percent, and subtle, if at all, in 5 percent of the brains. Non-striatal regions show atrophy of variable severity or have normal appearance. The HD brain is diffusely smaller than normal in the late stage of the disease (Fig. 28). The striatum is probably the only site where neuronal loss and “active” reactive, fibrillary astrocytosis coexist.

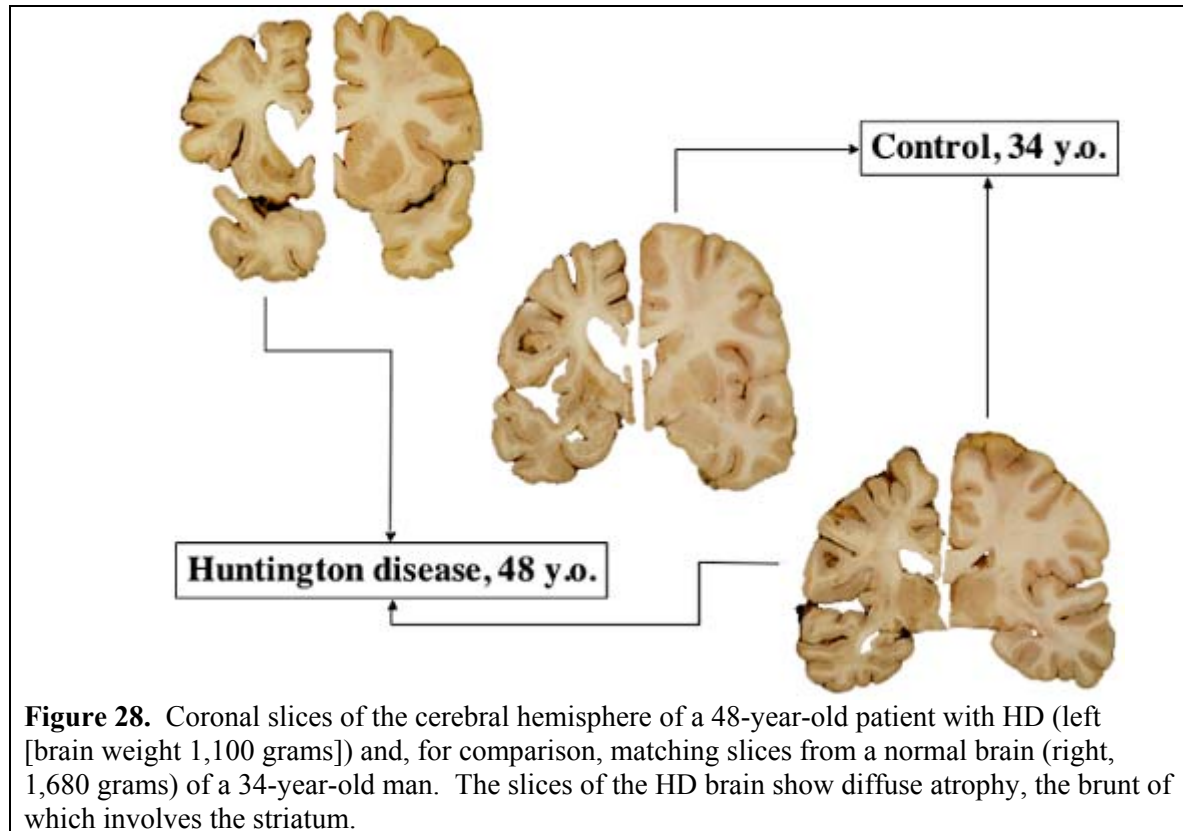


Figure 28. Coronal slices of the cerebral hemisphere of a 48-year-old patient with HD (left [brain weight 1,100 grams]) and, for comparison, matching slices from a normal brain (right, 1,680 grams) of a 34-year-old man. The slices of the HD brain show diffuse atrophy, the brunt of which involves the striatum.

The gradual atrophy of the striatum, which sequentially involves the neostriatum, external segment, then the internal segment of globus pallidus typifies HD. In turn, the neostriatal loss has an ordered, topographic distribution. The tail of the caudate nucleus shows more degeneration than the body, which is more involved than the head. Similarly, the caudal portion of the putamen is more degenerated than the rostral portion. Along the coronal (or dorsoventral) axis of the neostriatum, the dorsal neostriatal regions are more involved than the ventral ones (Fig. 29). Along the medio-lateral axis, the paraventricular half of the caudate nucleus is more involved than the paracapsular half. *In essence, the dorsal third of the rostral neostriatum is especially prone to degenerate in contrast to the relatively preserved ventral third, including the nucleus accumbens* (Fig. 29).

Microscopically, degeneration is manifested by *neuronal loss and reactive gliosis* (Figure 29). Fibrillary astroglia parallels the loss of neurons along the caudo-rostral and dorsoventral striatal gradients of decreasing severity.

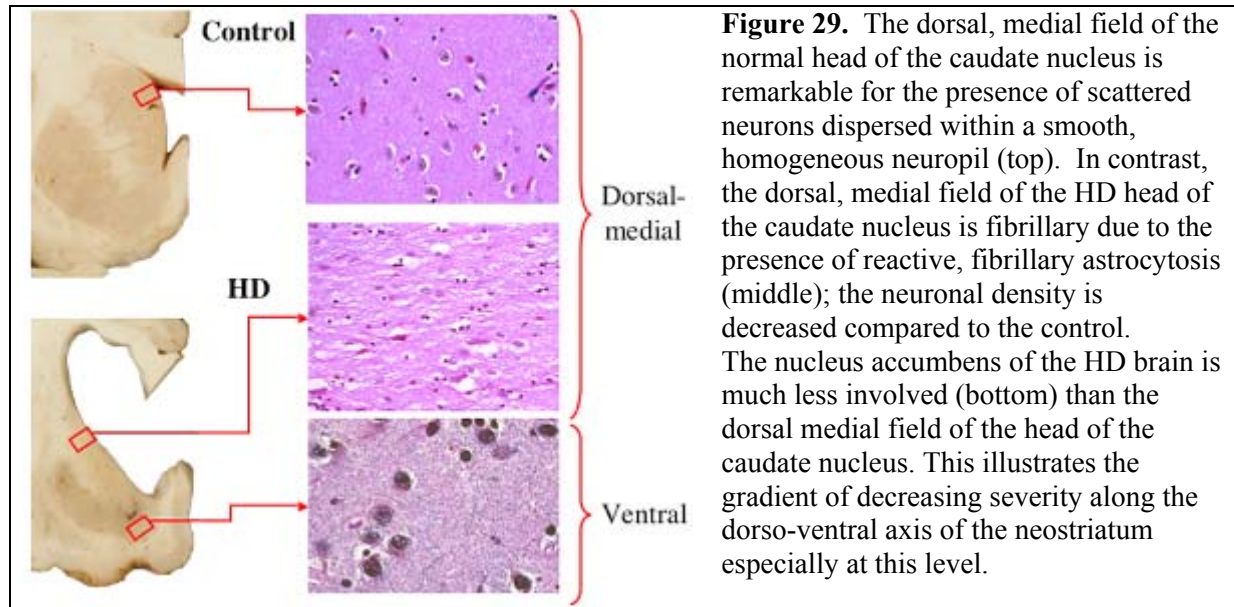


Figure 29. The dorsal, medial field of the normal head of the caudate nucleus is remarkable for the presence of scattered neurons dispersed within a smooth, homogeneous neuropil (top). In contrast, the dorsal, medial field of the HD head of the caudate nucleus is fibrillary due to the presence of reactive, fibrillary astrocytosis (middle); the neuronal density is decreased compared to the control. The nucleus accumbens of the HD brain is much less involved (bottom) than the dorsal medial field of the head of the caudate nucleus. This illustrates the gradient of decreasing severity along the dorso-ventral axis of the neostriatum especially at this level.

Features that HD shares with the other eight known polyglutaminopathies are **ubiquitinated, neuronal nuclear inclusions** involving scattered neurons (Fig. 27), and **dystrophic neurites**. The distribution of neuronal loss in particular brain regions is more or less distinctive for each disease of this group. The discovery of nuclear ubiquitinated aggregates in HD was first made in transgenic mice (R6/2) harboring exon 1 of the human gene (Fig. 30, left). This genetic insertion encodes htt with expanded CAG-repeats, which translate into a series of consecutive glutamine residues or polyQ.

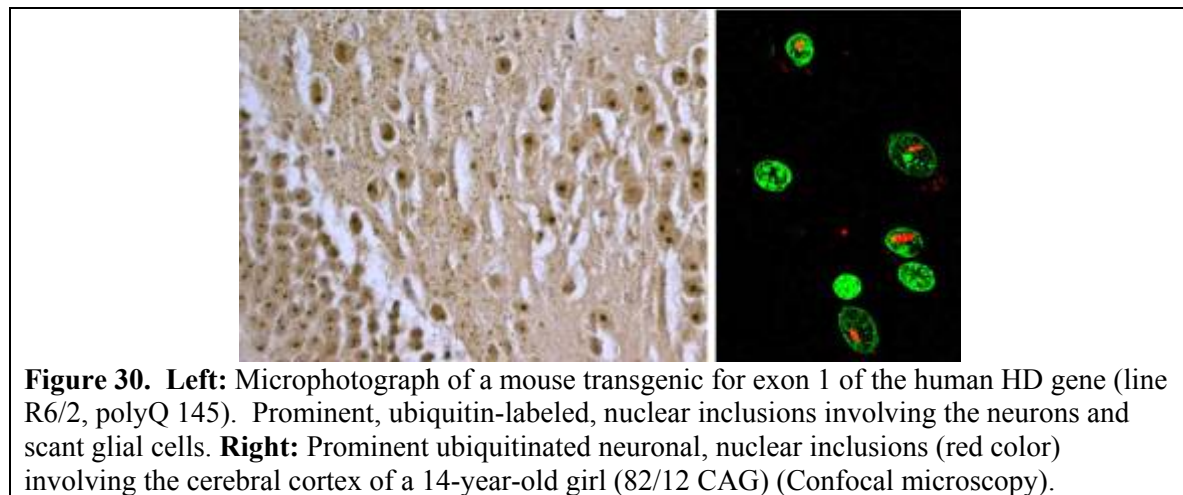


Figure 30. Left: Microphotograph of a mouse transgenic for exon 1 of the human HD gene (line R6/2, polyQ 145). Prominent, ubiquitin-labeled, nuclear inclusions involving the neurons and scant glial cells. **Right:** Prominent ubiquitinated neuronal, nuclear inclusions (red color) involving the cerebral cortex of a 14-year-old girl (82/12 CAG) (Confocal microscopy).

Selective vulnerability

Among the theories for the selective, cellular damage in HD, the most compelling involve impaired energy metabolism, excitotoxicity (Fig. 31), and relative, selective endotoxicity. The excitotoxicity theory proposes that subpopulations of striatal medium-sized spiny projection neurons are hypersensitive to corticostriatal and thalamostriatal

glutamate, or excessive glutamate is released by these afferents, while striatal interneurons are less affected. Mutated huntingtin causes neuronal dysfunction long before cell death¹³. Perhaps endotoxicity results from misfolding of mhtt. Wild type htt is soluble. In contrast, mhtt is insoluble and forms aggregates. Despite the tremendous amount of recent important data obtained on htt, or mhtt, the relative selective loss of striatal neurons seen in HD has remained mysterious.

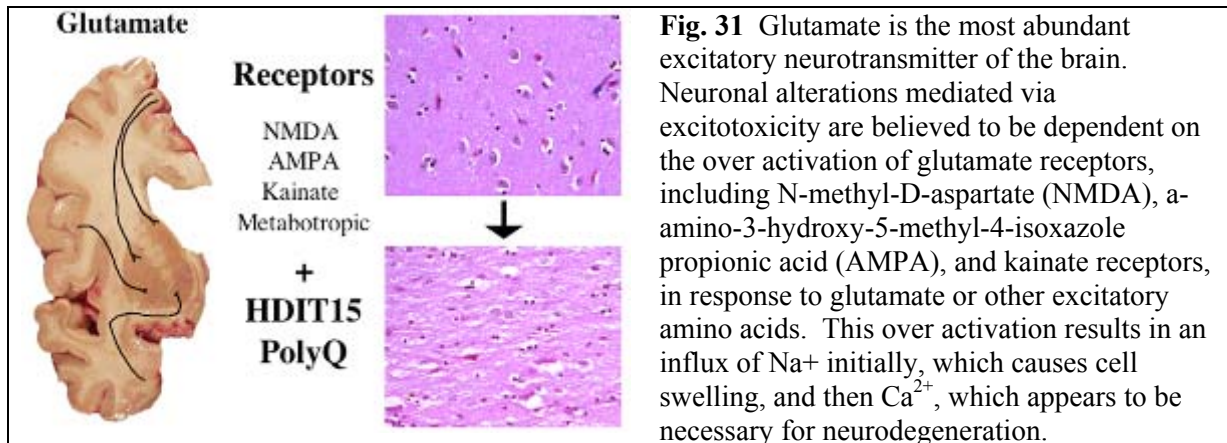


Table 2. Summary of neurodegenerative disease associated inclusions

Disease	Inclusion	Composition
Alzheimer's disease	Senile plaque	Beta-amyloid, apoE
	Neurofibrillary tangles	Tau, ubiquitin
	Hirano bodies	Actin, actin-binding proteins
Lewy body diseases	Lewy body	Alpha-synuclein, neurofilament, ubiquitin
Pick's disease	Pick body	Tau, ubiquitin
Chromosome 17-linked dementias	Neurofibrillary tangles	Tau
	Glial tangles	Tau
Huntington's disease	Intranuclear inclusions	Huntingtin, ubiquitin

¹³ M. DiFiglia, E. Sapp, K.O. Chase, S.W. Davies, G.P. Bates, J.P. Vonsattel and N. Aronin, Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain, Science 277 (1997) 1990-1993.

Abbreviations

AD:	Alzheimer disease
ADLBV:	Alzheimer disease Lewy body variant
AIDS:	Acquired immune deficiency syndrome
AMPA:	a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
BN:	Ballooned neuron
CA:	Cornu Ammoni
CAA:	Cerebral amyloid angiopathy
CADASIL:	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CJD:	Creutzfeldt-Jakob disease
CNS:	Central nervous system
DLBD:	Diffuse Lewy body disease
FTD:	Frontotemporal dementia
FTLD:	Frontotemporal lobar degeneration
HD:	Huntington disease
LBD:	Lewy body disease
LHE:	Luxol fast blue counterstained with hematoxylin and eosin
MCI:	Mild cognitive impairment
NMDA:	N-methyl-D-aspartate
NTA:	Neurofibrillary tangles of Alzheimer
PcD:	Pick disease
PD:	Parkinson disease
PHF:	Paired helical filaments
SNpc:	Pars compacta of the substantia nigra.

METABOLIC DISEASES

James E. Goldman, M.D., Ph.D.

METABOLIC DISEASES

There are many metabolic abnormalities that have an adverse impact on the nervous system. One way to approach and classify metabolic diseases is to divide them onto three broad groups: (I) deficiency of a necessary metabolic substrate or co-factor, (II) deficiency of an enzyme (usually lysosomal and almost always catabolic) with resultant excess (storage) of a normal or toxic substrate, and (III) excess of endogenous toxic metabolites. One principle that must be emphasized when one speaks of metabolic diseases of the nervous system is that of **selective vulnerability**. By this we mean that specific cell types or populations are more susceptible to a particular (metabolic) insult than others.

I. DEFICIENCY OF METABOLITE

Hypoxia and hypoglycemia [MBD-1]. It is best to consider these two conditions jointly, since their pathologic effects on the nervous system are almost identical. Neurons require both oxygen and glucose to fulfill their metabolic needs. If the central nervous system is deprived of either oxygen or glucose for even short periods of time, **neurons** are rendered incapable of functioning and may die. Oligodendrocytes are also sensitive to oxygen deprivation. The most common clinical setting for hypoxia is that of oligemic or **ischemic** hypoxia, produced by a reduction or absence of blood flow. There are infrequent instances, however, of hypoxic, anemic or histotoxic hypoxia in which blood flow is normal, but sufficient oxygen is not presented to neurons. The major acute change produced by hypoxia or hypoglycemia is that of individual neuronal necrosis, manifested histologically by **cytoplasmic eosinophilia** and nuclear pyknosis. If, as usually happens, blood flow is also compromised, then one may find evidence of both **cytotoxic** and even **vasogenic edema**. Specific neurons and regions of the central nervous system are more vulnerable to oxygen or glucose deprivation than others. Pyramidal neurons of **Sommer's sector** (also known as CA1) in the hippocampus, **Purkinje** cells of the cerebellum, neurons of the **globus pallidus** and mid-cortex (**layer III**), particularly in **border zone** (watershed) areas, are four highly vulnerable populations. Watershed zones are those areas between the terminations of the major cerebral arteries, and are typically parasagittal or lateral parieto-temporo-occipital in location. Permanent or residual clinical manifestations depend upon the extent and localization of the lesions.

Hypovitaminosis. For the sake of this course, we will restrict ourselves to deficiencies of **thiamine (vitamin B1)** and **cobalamin (vitamin B12)**. A deficiency of thiamine results in **Wernicke-Korsakoff disease** [MBD-2]. In the acute stage (**Wernicke's disease**), symptoms are characterized by confusion, ocular disturbances and ataxia. Its clinical recognition is important, since the prompt administration of thiamine will result in a dramatic reversal of the symptomatology. Histologically, acute Wernicke's encephalopathy consists of **vascular swelling** and proliferation, and sometimes hemorrhages. Neurons, however, remain viable, at least in the early stages. The preservation of neurons is the major reason for its reversibility. If thiamine deficiency persists, or if the patient has repeated bouts of thiamine deficiency, then **neuronal loss** may occur and the deficit will become **irreversible**. In this situation one usually finds

that patients also have defects in memory (**amnesic syndrome**), particularly in the retention of short-term memory, referred to as **Wernicke-Korsakoff** psychosis. The areas that are specifically affected in thiamine deficiency are the **mammillary bodies**, the **medial dorsal nucleus** of thalamus and other nuclei around the IIIrd and IVth ventricles and aqueduct of Sylvius. Although Wernicke-Korsakoff disease is the most frequent form of the Korsakoff syndrome, any destructive lesion that bilaterally interrupts the **limbic circuit** may produce the same amnesic syndrome.

Deficiency of vitamin B₁₂ is most commonly seen as a result of the malabsorption syndrome in **pernicious anemia**. Pathologic changes in the spinal cord, brain, optic nerves and peripheral nerves may occur. We will restrict ourselves to the classical **myelopathy** seen in this condition, **subacute combined degeneration** [MBD-3]. A variety of abnormalities of the motor and sensory systems occur. **Myelin sheaths** of spinal cord white matter, particularly at the **upper thoracic levels**, are most vulnerable. These lesions are asymmetrical and involve the **posterior** columns and the **postero-lateral** aspects of the lateral funiculi. They are not restricted to specific tracts and are characterized histologically by a dramatic **spongy change**. At the ultrastructural level, this spongy change represents **intramyelinic edema**; that is, excessive fluid between myelin lamellae. With time, axons degenerate, oligodendrocytes are lost, astrocytes proliferate and macrophages appear.

II ENZYME DEFICIENCIES/ENZYME OR MITOCHONDRIAL MUTATIONS

These are genetic diseases usually transmitted as autosomal recessive traits. Some of the mitochondrial diseases, the "ragged-red fiber" disorders, are caused by mitochondrial genomic mutations, and show a maternal inheritance pattern. Those diseases related to deficiency of lysosomal enzymes often display conspicuous morphologic and biochemical manifestations of "storage" of specific chemical substances. Before discussing these, we will mention those that involve two other organelles: mitochondria and peroxisomes; with the exception of adreno-leukodystrophy, these do not qualify as "storage" diseases.

MITOCHONDRIAL DISORDERS

- A. Subacute Necrotizing Encephalomyelopathy of Leigh (SNE)
- B. Pyruvate decarboxylase deficiency
- C. Pyruvate dehydrogenase complex deficiency
- D. Biotin dependent deficiency
- E. Glioneuronal dystrophy (Alpers Disease)?
- F. Respiratory chain enzyme deficiency
- G. Carnitine and carnitine palmityl transferase deficiency
- H. Ragged Red Fiber Related Disorders
 - 1. Kearns-Sayre Syndrome
 - 2. MERRF (myoclonic epilepsy, ragged red fibers)
 - 3. MELAS (mitochondrial encephalopathy, myopathy, lactic acidosis, strokes)

SNE (Leigh's disease) [MBD-4] usually presents within the first few years of life as **failure to thrive**, poor development, lethargy, hypotonia, nystagmus, deafness, and seizures. **Family** history is often positive, and juvenile and adult onsets have been well documented. At least four different metabolic defects have been offered to explain this disease: inhibition of thiamine pyrophosphate-ATP phosphoryl transferase, defective activation of pyruvate dehydrogenase complex, deficiency of pyruvate carboxylase and deficiency of **cytochrome c oxidase**. There may be several molecular etiologies underlying Leigh's disease.

Neuropathologic lesions in this disease are distinctive and involve all levels of the nervous system. Wernicke's disease (thiamine deficiency) needs to be ruled out clinically in juvenile or adult cases, since the fundamental histopathologic lesions and topographical distributions in both diseases are similar, except for **sparing of mammillary bodies and involvement of substantia nigra in SNE**. Classical SNE also has **bilaterally symmetrical softenings** of both gray and white matter of the **diencephalon** (especially putamen and thalamus) and **brain stem tegmentum** (especially periaqueductal and substantia nigra). Histopathologically, these lesions correspond to **rarefaction of neuropil with vascular hyperplasia and proliferation** to microcytic degeneration to frank cavitory necrosis [MBD-5]. Involvement of the optic system, cerebral and cerebellar white matter, dentate nucleus, and spinal gray is frequently noted. Lesions, primarily of demyelinating type, in spinal roots, dorsal root ganglia, and peripheral nerve also have been reported.

PEROXISOMAL DISORDERS

I. Reduced number of peroxisomes; deficiency of multiple enzymes

- A. Cerebro-hepato-renal (Zellweger) syndrome
- B. Neonatal adreno-leukodystrophy (autosomal recessive)
- C. Infantile Refsum's disease
- D. Hyperpipecolic acidemia

II Normal number of peroxisomes; deficiency of multiple enzymes

- A. Rhizomelic chondrodysplasia punctata

III. Normal number of peroxisomes; deficiency of a single enzyme or activity

- A. Adreno-leukodystrophy (X-linked)
- B. Thiolase deficiency (Pseudo-Zellweger)
- C. Adult Refsum's disease
- D. Hyperoxaluria I

Many of the above disorders have been known clinically and pathologically for years, but only recently have their etiologies been traced to peroxisomal abnormalities. Some (**Zellweger**) patients display an **absence of peroxisomes**, due to defects in peroxisome assembly; others (adreno-leukodystrophy) have normal appearing peroxisomes, but are deficient in certain specific peroxisomal functions. In adreno-leukodystrophy very long chain fatty acids are not admitted to the beta-oxidation system of the peroxisome, and demyelination occurs progressively as these fatty acids accumulate (see discussion above under Myelin Disorders).

Cerebro-Hepato-Renal (Zellweger) Syndrome is characterized by **dysmorphic** features and the **neonatal** onset of profound **hypotonia and seizures**. This disease is the prototype of a new class of inherited metabolic diseases in which there is an absence of, or severe reduction in, peroxisomes. This results in the dysfunction of multiple enzyme systems, particularly those that catabolize **very long chain fatty acids** and synthesize **ether lipids (plasmalogens)**. In Zellweger infants, centrosylvian **polymicrogyria** and **pachygyria**, other CNS migration defects, and abnormalities in CNS white matter are seen. These infants usually die within the first year of life.

LYSOSOMAL DISEASES

There are a large number of genetic diseases that result from enzymatic deficiencies in the catabolism of lipids or mucopolysaccharides (glycosaminoglycans). They are called "storage" diseases because catabolic enzyme mutations result in the build-up, or storage, of substrates proximal to the affected catabolic step. They have been generically called "neuronal storage diseases"; but, while many result in the storage of substrates in neurons, others affect white matter, and still others involve peripheral organs as well as CNS.

Many of these disorders are rare (although within some populations the carrier, or heterozygote, frequency, is high - e.g. the carrier rate for classical **Tay-Sachs disease** among the Ashkenazi Jewish population is about 1:30). Most of the disorders tragically affect children.

There are 4 major classes of lysosomal storage diseases: **gangliosidoses, mucopolysaccharidoses, ceroid storage disorders and leukodystrophies.**

Gangliosidoses: Gangliosides are acidic glycolipids that form prominent components of neuronal membranes. The brain is the richest source of gangliosides. These compounds have a lipid portion and an oligosaccharide chain. They are catabolized by sequential removal of sugars, performed in lysosomes. There are a large number of lysosomal enzymes, each specific for a catabolic step. There are known mutations in many of them, each leading to the accumulation of substrate. Most of the mutations are autosomal recessive.

Storage diseases are systemic diseases, even when clinical and pathological manifestations are limited to one organ system. This means that one can diagnose a specific disorder by assaying the appropriate **enzyme** in many tissues, including **blood cells and fibroblasts**. If genetic probes are available, then specific mutations can be assayed from genomic DNA.

Enzymatic activity in heterozygous carriers of **recessive** traits is **intermediate** between that of normal and homozygotes, enabling the detection of carriers. This is the basis for screening populations at high risk because of an elevated gene frequency and for genetic counseling of the relatives of affected probands.

Treatment by replacement of a mutant enzyme with a normal one is problematic. There has been some success in experimental models by **bone marrow transplantation** with normal cells or with bone marrow stem cells genetically engineered to produce the normal enzyme. Getting the enzyme into the CNS is a real problem, however.

One of the best studied of these disorders is **GM2 gangliosidosis**. The removal of the terminal N-acetyl-galactosamine is catalyzed by the enzyme **hexosaminidase A**. The enzyme is composed of two different subunits, alpha and beta, each the product of a different gene on different chromosomes. Hexosaminidase A, the enzyme in brain, is a heterodimer (**alpha/beta**). Hexosaminidase B, found in peripheral organs is a beta/beta dimer. Thus, mutations in either the alpha or the beta subunit can affect hexosaminidase A activity.

GM2 gangliosidosis was originally described as **Tay-Sachs disease**, a disorder that affects children in infancy and leads to death in a few years. The infants suffer from **severe retardation** and **myoclonic seizures**. There is a typical "**cherry-red**" **spot** [MDB-6] in the retina. The brain is enlarged. Neurons are filled with abnormal membranes formed from large amounts of GM2 ganglioside and other lipids [MBD-7]. Interestingly, neurons add dendritic membranes and spines to the axon hillock region, forming bulbous deformities called meganeurites [MBD-8]. These abnormally placed post-synaptic elements are innervated by axons, thus creating entirely new synaptic zones, which may bypass the normal dendritic tree and cell body.

Recent studies have determined that there are several forms of GM2 gangliosidosis. **Tay-Sachs** disease is an **alpha** subunit mutation, the gene for which is encoded on **chromosome 15**. A mutation in the **beta** subunit, encoded on **chromosome 5** creates a disorder that looks the same as Tay-Sachs disease. Thus, mutations in either of two different genes can produce **similar phenotypes**. The issue is complicated further because different allelic mutations in the same gene can produce different phenotypes. For example, different mutations in the alpha subunit can produce Tay-Sachs disease, a late infantile variant, a juvenile variant that clinically mimics spino-cerebellar degeneration, and an adult variant that looks like a motor neuron disease. The affected adults don't show dementia, myoclonus, or retinal cherry-red spots. Some patients may even be double heterozygotes (i.e. bearers of two different allelic mutations).

How these mutations in ganglioside hydrolases actually produce the pathological changes is not at all clear.

Mucopolysaccharidoses: These are caused by mutations in enzymes that catabolize mucopolysaccharides, large molecules that are components of **many organs**. Thus, the clinical and pathological manifestations of these diseases are far more widespread than those of the gangliosidoses. Typical manifestations include **hepato- and splenomegaly, joint and bone deformities, opacities of the lens** and cornea, connective tissue abnormalities, and **storage of mucopolysaccharides in neurons**. Many patients show intellectual retardation. Hydrocephalus is also common, due to mucopolysaccharide deposition in the meninges with resultant deficits in the circulation and resorption of cerebrospinal fluid.

Neuronal Ceroid-lipofuscinoses (NCL) [MBD-9,10]: This varied group of disorders is characterized by the accumulation of an **autofluorescent** pigment, called **ceroid**, within neurons. This material, which is highly insoluble, resembles lipofuscin. Three typical variants: **infantile (chromosome 1) late infantile, and juvenile (chromosome 16)** and an adult form are known. All but the latter produce **pigmentary degeneration** of the retina and blindness. They are all accompanied by intellectual deterioration. As in many of the storage diseases, the infantile form is the most severe and rapidly progressive. Mutations in a number of different genes cause diseases in the spectrum of NCL. Some of these genes encode proteolytic enzymes (cathepsins, for eg.), while others encode soluble or membrane proteins that preferentially locate to the endosome/lysosome or endoplasmic reticulum organelle systems. The diagnosis rests on clinical patterns and genetic testing, although the demonstration of typical intracellular inclusions by fluorescence and electron microscopy in neurons, skin, muscle, or white cells can be helpful in narrowing down the diagnosis.

Leukodystrophies: As the name indicates, these are disorders that preferentially affect white matter and may be included under Diseases of Myelin. Since oligodendrocytes or myelin sheaths are affected, patients display a loss of myelin or abnormal myelination. Typically, they show neurological signs referable to white matter destruction, such as spasticity. One example is **adreno-leukodystrophy**. Very long chain fatty acids, normally degraded in peroxisomes, are elevated or "stored" in brain and other organs, particularly the adrenal cortex.

III. EXCESS OF TOXIC METABOLITES

Kernicterus [MBD-11], also referred to as **nuclear jaundice** because of the yellow staining of specific neuronal groups, is an infantile disorder presenting clinically with **feeding** difficulties, a **high pitched cry** and **hypertonicity**. This disease was most commonly related to hemolysis from Rh incompatibilities but any source of hemolysis results in the presentation of excessive bilirubin to immature hepatic cells lacking sufficient glucuronyltransferase activity for conjugation. Therefore, large amounts of indirect or **unconjugated bilirubin** accumulate in blood. The incidence of kernicterus has been greatly reduced due to the decrease in hemolytic jaundice of the newborn. Gross

abnormalities in the CNS consist of yellow discoloration of specific nuclei: **globus pallidus, subthalamic nucleus, hippocampus**, superior and inferior colliculi, vestibular nuclei, interior olives and dentate nucleus. These infants also have superimposed anemic and oligemic hypoxia due to hemolysis and problems with cardiac function.

Consequently, the lesions are thought to result from both unconjugated hyperbilirubinemia and **hypoxic/ischemic damage to "old" neuronal groups**, which are active metabolically at birth. The pigment is **lethal to the neurons**. Children who survive the kernicteric episode develop the classical triad of opisthotonus, sensorineural deafness and defective ocular supraversion.

Acute Intermittent Porphyria. **Episodic** attacks (often following the use of barbiturates or sulfonamides) of emotional instability, sleeplessness, severe pains of abdomen, back, and limbs and vomiting commence in the postpubertal period. The genetic deficiency is of an anabolic enzyme: **hepatic uroporphyrinogen I synthetase**; the accumulated metabolites are **porphobilinogen (PBG)** and aminolevulinic acid (ALA). Histologic lesions in the CNS have included **neuronal loss**, mild gliosis, myelin pallor in deep cerebral and cerebellar white matter and central **chromatolysis of lower motor neurons**. All, except the chromatolytic lesions, are believed to be **hypoxic-ischemic** in origin. Chromatolysis of anterior horn motor and dorsal root ganglion neurons is secondary to a distal axonopathy of peripheral nerve.

Wilson's Disease [MBD-12]. This is a disease in which copper levels are elevated in organs, particularly liver and brain. Usually, young adults present with an extrapyramidal syndrome or hepatic failure. **Kayser-Fleischer corneal rings**, composed of copper granules in the limbic region of Descemet's membrane, are clinically pathognomonic. **Serum ceruloplasmin** (a copper binding protein) and serum copper are low, while **tissue copper** is elevated. Neuropathologic lesions are concentrated in the basal ganglia where one finds subtotal **rarefaction with neuronal loss to complete necrosis** with astrogliosis and eventual atrophy. Excessive copper has been identified in the basal ganglia, probably within glial cells.

The Wilson's disease gene at 13q14.3 is similar to several known **metal transport proteins with ATPase functions**. Presumably, the Wilson's gene is involved in copper transport across cell membranes. Several types of mutations, including deletions, single amino acid substitutions, and frameshifts have now been found in Wilson's patients. The gene product shares similarities with that underlying **Menke's disease**, an X-linked disorder of copper metabolism that affects young children and is fatal within a few years. Menke's patients, who show decreased serum and tissue copper levels, do not absorb copper properly and suffer from defects in copper-requiring enzymes. These enzyme deficiencies lead to neuronal degeneration and mental retardation, abnormal hair, hypopigmentation, and vascular disease due to abnormal collagen formation.

Hepatic encephalopathy exhibits neuropathologic features virtually identical to those of Wilson's disease, except for the putaminal necrosis, and is usually seen in association with **Laennec's cirrhosis** in the **ethanol** abuser, but is also seen with post-hepatic cirrhosis, toxic hepatitis, and urea cycle enzyme deficiencies. It is believed that the

major endogenous toxin in this condition is **ammonia**. Tremors and profound alterations in consciousness are poorly reflected by the paucity of neuropathologic lesions. The most responsive cell in the CNS during liver failure is the **protoplasmic astrocyte** of gray matter, particularly of globus pallidus, cerebral cortex and dentate nucleus. These astrocytes undergo nuclear hypertrophy, vesiculation and lobulation and are referred to as **Alzheimer type II astrocytes** [MBD-13]. This change should not be confused with the Alzheimer changes of neuritic plaques and neurofibrillary degeneration. Dr. Alzheimer has several things named for him.

Uremic encephalopathy. Patients with profound uremia as a result of end stage renal disease may also develop an encephalopathy with depression of consciousness. The most consistent neuropathologic change is that of protoplasmic astrocytosis. The pathogenesis is poorly understood.

Reye's Syndrome. Reye's syndrome is an acute encephalopathy, usually of childhood, characterized by both severe and **diffuse cerebral edema** and **fatty change of liver**. The exact pathogenesis is unclear, but it is usually seen in the setting of **viral infection** and treatment with **aspirin**. Since aspirin has been contraindicated in children suffering from viral illnesses, the incidence has fallen off dramatically. Neuropathologic changes are nonspecific in that the brain shows evidence of cerebral edema and subsequent herniation. Ultrastructural examination of both liver and brain has revealed **abnormal swollen and pleomorphic mitochondria**. It is believed that this mitochondrial dysfunction results in the accumulation of free fatty acids, which are toxic to the CNS.

Ethanol abuse. Individuals who abuse ethanol show a constellation of neurologic signs and symptoms to the metabolic consequences of ethanol abuse. However, physicians, particularly in the emergency room, should always consider the possibility of **traumatic CNS** or PNS lesions in alcoholic patients who manifest neurological signs and symptoms. It is difficult to decide whether the metabolic lesions commonly seen in alcoholics are the result of the toxic effects of ethanol, poor nutrition, or a combination of factors. Patients who die of **acute ethanol intoxication** reveal nonspecific changes of cerebral congestion, edema and punctate hemorrhages. Likewise, there is no characteristic pathologic change associated with **delirium tremens** or withdrawal seizures (rum fits). The chronic alcoholic, on the other hand, shows a characteristic combination of **atrophy of the anterior-superior cerebellar vermis** [MBD-14,15], **peripheral neuropathy** and, to a lesser degree, cerebral atrophy. The neuron appears to be the most vulnerable cell. Vermal atrophy is due to loss of Purkinje cells and internal granular neurons with atrophy of molecular layer. The peripheral neuropathy seen in these patients is due to **axonal** degeneration. Alcoholic cerebral atrophy, however, is a more variable lesion, initially affecting the dorsolateral aspects of the frontal lobes. There is considerable evidence to suggest that there is an alcoholic dementia that is distinct from the Korsakoff psychosis. It also should be emphasized that, although acute Wernicke's disease and Wernicke-Korsakoff syndrome are encountered frequently in alcoholic patients, these diseases are related to thiamine deficiency and not to alcohol *per*

se. Alcoholics with cirrhosis also commonly develop hepatic encephalopathy with Alzheimer type II gliosis.

SUPPLEMENTARY READING:

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DEVELOPMENTAL DISORDERS

Dr. Phyllis Faust

DEVELOPMENTAL DISORDERS

I. DISORDERS OF EARLY DEVELOPMENT

These developmental disorders are thought to result from the failure of normal differentiation of neuroectodermal and mesodermal elements during the first month of gestation (see Table 1). This is the time when the neural fold develops, the underlying mesodermal structures develop (these will form the protective structures enclosing the nervous system), and the neural tube forms. Normally, the anterior closure of the neural tube has taken place by the 26th day, the posterior closure by about the 28th day.

- A. Anencephaly** - [DD-1] This disorder results from a failure of the anterior neural fold to form a neural tube, representing some injury between 18 and 26 days of gestation. The incidence of this disorder ranges from about 0.5 to 3 per 1000 births, varying from country to country and year to year. It is thus a relatively common disorder. In anencephaly, the cord, brain stem, and cerebellum are often intact, but above these lie only small amounts of disorganized neuronal-glial and vascular tissues ('area cerebrovasculosa'). This absence of brain tissue is associated with a deficiency or underdevelopment of the squamous bones of the cranial vault (acrania). Eyes are present (optic vesicles form at day 18) and usually normal; these infants typically have protruding "toad's head" exophthalmic eyes associated with shallow orbits. Optic nerves are poorly organized and terminate blindly in the orbit. In more severe cases, the neural tube defect may also involve the midbrain, pons and cerebellum, and these structures may thus also be absent or partially present. Anencephalics are either still born or die within a few days after birth, with cardiac and respiratory function dependent on presence of hindbrain structures. Antemortem diagnosis is from elevated α -fetoprotein in the amniotic fluid.
- B. Spina bifida, Cranium bifidum** - [DD-2] These refer to failure of fusion of the vertebral column or posterior skull, respectively. This results in a cleft or defect in bone through which dura, meninges, and brain or cord may herniate. These occur in a spectrum of severity. In a **meningocele**, dura and meninges protrude through a posterior defect in spinal bone. This is usually covered by skin. In a **myelomeningocele**, dura, meninges, spinal roots with and without the cord protrude. This is most common in lumbar and lumbo-sacral regions. It can be associated with Arnold-Chiari malformation (see below). An **encephalocele** is a protrusion of dura, meninges, and brain tissue through a defect in the skull. In **spina bifida occulta**, there are malformed spinal arches, but no herniation of dura, meninges, or cord takes place. It is covered by skin. This is the most benign form of these states.

Table 1. Neural Tube Defects

Disease	Clinical Features	Pathologic Features	Pathogenesis
Anencephaly	<p>> Incompatible with independent existence.</p> <p>> Detected in early gestation by ultrasound, raised α-fetoprotein levels in maternal serum.</p> <p>> Usually sporadic, occasionally familial.</p>	<p>> Most of intracranial contents replaced by ragged, caviatated, vascular mass (area cerebrovasculosa). Variable extension to spinal cord.</p> <p>> Skull absent or hypoplastic. Shallow orbits, eyes protrude.</p> <p>> Area cerebrovasculosa contains mass of small blood vessels mixed with disorgani-zed neuroepithelial tissue.</p>	<p>> Failure of anterior neural tube closure; injury at 18-26 days of gestation.</p> <p>> Folic acid deficiency increases incidence.</p> <p>> Teratogen effect suspected. Genetic factors may a play role.</p> <p>> Largely unknown etiology.</p>
<p>Spina bifida:</p> <ul style="list-style-type: none"> ● Meningocele ● Myelomeningocele ● Myelocele ● Spina bifida occulta 	<p>> May occur at any level but lumbosacral is most common.</p> <p>> Lesions above T12 often associated with other malformations , more common in females.</p> <p>> Lesions below T12 more often solitary, less severe neurologic sequelae.</p>	<p>> Meningocele = herniation of arachnoid and dura covered by atrophic epidermis.</p> <p>> Myelomeningocele = herniation of spinal cord, nerve roots and meninges covered by a delicate membrane or skin.</p> <p>> Myelocele = flat, open lesion; mass of vascular/neuroepithelial tissue, no skin covering.</p> <p>> Spina bifida occulta = mild form, closed lesion; cord may be tethered; overlying tuft of hairy skin or cord lipoma.</p>	<p>> Defect in formation of posterior vertebral arches +/- defect in spinal cord.</p> <p>> Largely unknown pathogenesis. Many different genetic defects in rodents, indicating multifactorial process.</p>
Encephalocele	<p>> 75% of cases in occipital region. Rarely parietal or frontoethmoid location.</p> <p>> Less common than anencephaly and spina bifida.</p>	<p>> Herniated tissue covered by skin. Variable degree of malformation in herniated tissue and underlying brain. Often connects to underlying brain by thin gliotic stalk.</p>	<p>> Herniation of dura, meninges and brain tissue through a skull defect.</p>
Arnold-Chiari Malformation (type II)	<p>> Infants present with signs of increased intra-cranial pressure, cranial nerve palsies, signs of brainstem or cervical cord compression, or signs of cerebellar involvement.</p>	<p>> Hydrocephalus</p> <p>> Small, malformed posterior fossa.</p> <p>> Downward displacement of brainstem and cerebellum with herniation of cerebellar tonsils.</p> <p>> Lumbosacral myelomeningocele.</p>	<p>> Neurologic defects thought secondary to defect in formation of posterior fossa. Small size results in hydrocephalus and brainstem abnormalities.</p> <p>> Association with spina bifida not understood.</p>

- C. Other **cord** anomalies include **split cord malformations (SCM) (DD-3)**. A Type I SCM (also called **diastematomyelia**) consists of two hemicords, each contained within its own dural tube and separated by a dura-sheathed rigid osseocartilaginous median septum. A Type II SCM (also called **diplomylelia**) consists of two hemicords housed in a single dural tube separated by a nonrigid, fibrous median septum.

Syringomyelia is a cystic cavity in the center of the cord, often in the cervical region. This leads to damage of crossing sensory fibers (pain and temperature), but spares posterior column function. As the cavity enlarges, it may encroach on anterior horns and pyramidal tracts, leading to motor dysfunction. Although many syrinxes are thought to be congenital, they do not usually become symptomatic until early adulthood. Some are associated with spinal cord tumors. The term hydromyelia refers to a dilated central canal. Some authorities do not distinguish between syringomyelia and hydromyelia, but consider them to be variations along a spectrum of one disorder.

D. Arnold-Chiari malformation - [DD-4] – The most common type of this malformation has four cardinal features including: 1) hydrocephalus, 2) a small, malformed posterior fossa, 3) downward displacement of brain stem and cerebellum with herniation of the cerebellar tonsils through the foramen magnum, and 4) a sacral myelomeningocele. The pons and medulla are kinked from downward pressure. The brainstem is displaced so much that the lower cranial nerves actually course upward. Various theories have been proposed to explain this malformation, none of which completely explain this disorder. Nonetheless, a combined mechanistic theory postulates that the CSF leak (due to sacral myelomeningocele) early in gestation lowers CSF pressure and which then leads to underdevelopment of the posterior fossa. Subsequent growth of the hindbrain and cerebellum in this small posterior fossa leads to hydrocephalus and displacement of brainstem and cerebellum.

II. DISORDERS OF CELL MIGRATION AND PROLIFERATION

These are disorders in which immature neurons, which line the ventricular cavities in the embryonic brain, fail to migrate properly to their cortical destination. This leads to a host of anomalies, characterized by disorganization of gyral patterns and of cortical cellular architecture, and by the presence of heterotopias (ectopic accumulations of neurons in the white matter). Migration disorders are increasingly recognized as a major cause of seizures and mental retardation in children due to the more frequent use of magnetic resonance imaging studies.

- A. The most common types of neuronal migration disorders are **lissencephaly, polymicrogyria, and focal heterotopia**. **Lissencephaly** is a condition that actually represents a spectrum of gyral abnormalities, ranging from absence of sulcal formation (**agyria**, or smooth surfaced brain) to gyri that are large and

few in number (called **pachygyria or macrogyria**) [DD-5]. The brain may show combinations of agyria and pachygyria in patients with classical lissencephaly. In **polymicrogyria**, there is an excess of small, shallow sulci, giving a wrinkled appearance to the brain. All of these show abnormal lamination patterns in the cortex and often heterotopias. Affected children are usually retarded, often quadriplegic and experience seizures. **Focal heterotopia** is a milder condition in which a mass of ectopic neurons is present in the white matter. In this condition, the overlying cortex is normal in appearance.

- B. Agenesis of the corpus callosum** can occur by itself, when it is asymptomatic, or in conjunction with other anomalies, such as migration disorders.
- C. Focal heterotopia** is most commonly a sporadic disorder, lacking specific genetic inheritance pattern. **Polymicrogyria** is often associated with *in utero* destructive lesions, for example due to hypoxia (e.g. next to a porencephaly, see section IVC below) or infection (most commonly cytomegalovirus). However, recent studies suggest that many cases of polymicrogyria have a genetic basis.

Lissencephaly shows several genetic inheritance patterns, including hemizygous due to a chromosomal defect, autosomal recessive and X-linked. Deletions on chromosome 17p13.3 in many patients with lissencephaly (“**classical lissencephaly**”) have led to identification of the **LIS1** gene. While LIS1 is a rather promiscuous protein with several potential cellular functions, recent studies suggest that LIS1 plays important roles in microtubule organization and nuclear movement within migrating cells, and thereby affect the neuronal migration process. In addition, LIS1 mutations may also affect the proliferation of neuronal progenitor cells, leading to decreased brain size in severe lissencephaly patients. A gene responsible for X-linked lissencephaly (so called **double-cortex lissencephaly**) has been identified (called “doublecortin”, DCX) and shown to be a microtubule binding protein. In females with this disorder, there is a symmetric, bilateral band of heterotopic gray matter in the subcortical white matter that underlies an apparently normal cerebral cortex. Due to random X-inactivation in females, these heterotopic neurons are postulated to have the abnormal DCX allele, whereas the neurons in the appropriately positioned cerebral cortex have the normal DCX allele. A more severe lissencephaly phenotype is seen in males with DCX mutations. Lastly, in the X-linked dominant disorder called **bilateral periventricular heterotopia**, multiple nodules of neurons accumulate adjacent to the ventricular system. The filamen-1 gene is defective, which is an actin binding protein. These genetic data indicate that the regulation of the neuronal cytoskeleton, including actin and microtubule filaments, is a key component of neuronal migration in cerebral cortex.

III. SKULL DEVELOPMENT ANOMALIES

- A. **Craniosynostosis** is the premature closure of cranial bone sutures. This leads to deformities in the shape of the skull. At birth, suture lines are separated by a few mm. By 3 months, the posterior fontanelle closes; by 6 months, suture lines begin to close; by 20 months, the anterior fontanelle closes, and by about 8 years, basal skull bones have ossified. Thus, in young children, increases in intracranial pressure can result in separation of the suture lines, with consequent excessive increase in head size.

IV. CEREBRAL PERINATAL LESIONS

The most common ones are related to perinatal asphyxia. See Table 2.

- A. **Periventricular leukomalacia** refers to the bilateral necrosis of the deep white matter adjacent to the ventricles in the cerebral hemispheres. It is probably secondary to inadequate perfusion of deep white matter during periods of hypotension. The premature brain is particularly susceptible to small fluctuations in blood pressure, which are commonly seen in these infants, as these immature cerebral blood vessels may have poor “autoregulation” (whereby blood pressure is maintained by vascular constriction even if there is a drop in perfusion pressure). This lesion is seen most commonly in premature infants but may also occur in term neonates.
- B. **Germinal plate hemorrhage** of the lateral ventricles is seen in premature infants born before 32-22 weeks of age. [DD-6] The bleeding occurs from thin-walled capillaries. The germinal plate is a periventricular structure that contains cortical and strial progenitor cells that will eventually migrate away to populate these brain regions. By 32-33 weeks, most of these cells have left this region, thus the volume of the germinal matrix is greatly reduced and the risk of hemorrhage in this region is greatly reduced. Blood often ruptures into ventricles, then follows CSF pathways through the ventricles into the basal subarachnoid space. In some cases, hemorrhage extends into the brain parenchyma. Intraventricular hemorrhage can lead to hydrocephalus, since blood and consequent fibrosis in the subarachnoid space leads to problems in resorption of CSF. The incidence of germinal plate hemorrhage in premature infants has decreased dramatically in recent years due to technical improvements in neonatology.

The clinical manifestations of perinatal lesions are protean. Many fall under the category of **cerebral palsy**. This is a general term, which does not refer to a specific injury or disease. It describes a non-progressive motor disorder acquired circumnationally. Affected individuals are commonly spastic (upper motor neuron signs), with symptoms reflecting the distribution of the lesions. Periventricular leukomalacia leads to spastic diplegia (i.e.: mostly in the legs). Basal ganglia lesions lead to extrapyramidal motor disorders such as choreoathetosis or dystonia.

B. Infarcts result from hypotension, venous stasis, or thrombosis. These are often cortical, sometimes in a “watershed” distribution (between two arterial territories). If a large infarction occurs early in gestation (around 5-6 months) a **proencephalic** state occurs [DD-7]. This is a hole in the brain whereby there is now a communication between the ventricle and subarachnoid space. At these early stages of development, the brain does not react to tissue destruction with extensive scarring. However, as neuronal migration to the cortex is going on during this time, there are often gyral abnormalities and/or heterotopias adjacent to the proencephalic lesion. Cortical infarcts that occur toward the end of gestation or during the early postnatal period produce a malformation pattern termed **multicystic encephalopathy** [DD-8]. In these infants, the brain reacts to tissue injury with extensive astrocytic scarring and contains multiple cavities in the cerebral hemispheres. Many of these patients have had disturbed parturition with prolonged labor, cyanosis at birth, resuscitation, seizures or neurologic symptoms within a few days of birth. Basal ganglionic abnormalities also accompany perinatal asphyxia. Neuronal loss and scarring in the basal ganglia is referred to as **status marmoratus**.

VI. NEURO CUTANEOUS SYNDROMES (PHAKOMATOSES)

This group of disorders is characterized by proliferations, which are either hyperplastic or neoplastic, are either benign or malignant, and occur in association with a variety of malformations. They are termed neurocutaneous syndromes as the constellation of lesions often affects the nervous system and skin. "Phakomatosis" (Greek *phakos*: lens shaped) refers to the occurrence, in many, of nodular retinal lesions.

A. Neurofibromatosis Type I (NF1), also known as **von Recklinghausen's disease**, is a hereditary, autosomal dominant disorder with an incidence of ~1 in 3,500 live births. The characteristic phenotype includes multiple cafe-au-lait spots (macules of light brown pigmentation on the skin), peripheral nerve neurofibromas, meningiomas, gliomas (especially optic nerve gliomas), ependymomas and other brain tumors, and pheochromocytomas (which may present with hypertension). The pathognomic lesion is the “plexiform neurofibroma” in which multiple adjacent nerves are infiltrated by tumor, and more commonly occur in deep nerve plexuses (e.g. brachial plexus, sacral plexus). These lesions may encase major nerves, blood vessels or other vital structures, leading to great difficulty to completely resect. The disorder is of variable penetrance, and thus different individuals can manifest different phenotypes and varying degrees of malformation. Mental development is

Table 2. Cerebral Perinatal Hypoxic-Ischemic Lesions

Disease	Clinical Features	Pathologic Features	Pathogenesis
Porencephaly	<ul style="list-style-type: none"> > History of some maternal disaster, e.g. attempted abortion, poisoning, hypoxia/shock, fetal infection or twinning. > Surviving infants may have congenital hemiplegia, mental retardation, seizures, spasticity. 	<ul style="list-style-type: none"> > Smooth walled defect surrounded by an abnormal gyral pattern. > Defect communicates with subarachnoid space and possibly the ventricle. > Absence of glial reaction in surrounding brain. 	<ul style="list-style-type: none"> > Damage to developing brain in second trimester (~18-27 weeks) involving circulation of major cerebral artery. > Most commonly occurs over Sylvian fissure or central sulci.
Germinal Matrix Hemorrhage	<ul style="list-style-type: none"> > Occurs mostly in low birth weight premature infants under 34 weeks gestation. > Infants with respiratory distress, congenital heart disease, coagulopathy. > Extent of hemorrhage determines prognosis. 	<ul style="list-style-type: none"> > Hemorrhage(s) in matrix zone, most commonly over head of caudate and thalamus > Small bleeds confined to matrix zone. Larger bleeds rupture into ventricle or adjacent brain parenchyma. > Hydrocephalus may occur acutely or after fibrous organization of blood. 	<ul style="list-style-type: none"> > Hemorrhage from fragile microcirculation of germinal matrix region. > Hypoxic stress leads to failure of autoregulation and overperfusion in matrix zone.
Periventricular Leukomalacia	<ul style="list-style-type: none"> > Affects ~ 5% of all hospital births, 35% of low birth weight premature newborns. > Surviving infants develop spastic motor dysfunction. 	<ul style="list-style-type: none"> > Infarcts in white matter adjacent to ventricles. > Lesions with macrophages surrounded by astrocytic gliosis. 	<ul style="list-style-type: none"> > Impaired perfusion to vascular watershed zone of developing white matter. > Poor autoregulatory capacity of immature cerebral blood vessels.
Multicystic Encephalopathy	<ul style="list-style-type: none"> > History of reduced fetal movement, twin dying in utero, or perinatal asphyxia. > Present at birth with seizures, hypertonia, irritability, microcephaly. > Death within weeks or months. 	<ul style="list-style-type: none"> > Multiple cysts in large areas of cerebral white matter and deep gray matter. > Extensive glial scarring surrounding cysts filled with macrophages. 	<ul style="list-style-type: none"> > Extensive ischemic damage to developing brain in third trimester, during birth or early postnatal period.

variable, but ~80% of children with NF1 have significant cognitive problems with perception, attention and executive functioning. Clinical diagnosis of NF1 requires two of seven “Cardinal Clinical Features” that include:

- A. 6 or more café-au-lait macules over 5 mm in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals
- B. 2 or more neurofibromas of any type or 1 plexiform neurofibroma
- C. Freckling in the axillary or inguinal regions
- D. Optic glioma
- E. 2 or more Lisch nodules (iris hamartomas)
- F. A distinctive osseous lesion such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudarthrosis
- G. A first degree relative (parent, sibling, or offspring) with NF1 by the above criteria.

The affected gene is on chromosome 17q11.2, encodes a protein ("neurofibromin") related to GTPases that interact with cellular GTP-binding proteins like ras, and possibly exerts a tumor suppressor effect by regulating the levels of activated ras.

- B. Neurofibromatosis Type 2 (NF2)** is also inherited via an autosomal dominant mode. It is less common than NF1, with an incidence of ~1/40,000. The pathognomic lesion is bilateral schwannomas of the VIIIth nerve (occurs in 90% of patients), leading to symptoms such as hearing loss, tinnitus, disequilibrium and headache. NF2 patients may also develop schwannomas and neurofibromas of other cranial and spinal nerves and meningiomas (50% of patients). There is also an increased incidence of developing ependymomas or astrocytomas, particularly in the spinal cord. More than 90% of patients also develop eye lesions, the most common being a juvenile cataract. These patients do not develop the cutaneous café-au-lait spots that are characteristic of NF1 and neurofibromas tend to locate in deeper rather than superficial cutaneous nerves. The gene, located on chromosome 22q12, encodes a protein ("Merlin") that resembles a family of proteins involved in binding the plasma membrane of a cell to underlying cytoplasmic cytoskeletal proteins. How mutations exert oncogenic effects is not entirely understood, but the Merlin protein is viewed as a tumor suppressor. Its deficiency leads to unmediated progression through the cell cycle due to the lack of contact-mediated tumor suppression.
- C. Tuberous Sclerosis (TSC)** is an autosomal dominant disorder of variable penetrance, with a frequency of about 1:30,000. Two thirds of TSC cases develop from sporadic genetic mutations. Characteristic lesions include **adenoma sebaceum** (angiofibromas) on the face, intracranial tumors including **subependymal gliomas** [DD-9], usually benign, and **cortical tubers** [DD-10], which are collections of large, bizarre astrocytes and neurons

in the cerebral cortex and white matter. TSC patients may also develop a particular type of brain tumor called “subependymal giant cell astrocytoma”, which grows in the cerebrum beneath the ventricle, often in the region of the foramen of Monro, and thus may lead to hydrocephalus. In TSC there are also hamartomas in several other organs, including rhabdomyomas of the heart and renal adenomas and cysts. Many affected individuals are mentally retarded, and most suffer seizures. TSC is caused by mutations in either of two genes, TSC1 (chromosome 9q34) and TSC2 (chromosome 16p13.3), which encode for the proteins hamartin and tuberin, respectively. These proteins act as tumor suppressors and normally function as a complex in the mTOR signaling pathway to regulate cell growth and division.

- D. Sturge-Weber Syndrome** is a rare disease that includes facial and intracranial angiomas. It is often associated with mental retardation, seizures and glaucoma. The characteristic facial lesion is a "port-wine stain" or nevus on the upper part of the face in a trigeminal distribution. There may be angiomas in the choroid of the eye. In the cerebral cortex, ipsilateral to the facial nevus, there is **leptomeningeal angiomatosis**, sometimes extending over a large area of the cerebral hemisphere. The underlying atrophic brain may **calcify** (seen on skull X-rays or CT scans). The cortical lesion produces contralateral facial seizures, hemiparesis or hemiplegia that begins in infancy and may worsen with age. About 50% of patients will have glaucoma. This disorder does not have a hereditary tendency but occurs sporadically.

SUPPLEMENTAL READING:

1. "Malformations of the Nervous System," by B.N. Harding, pp. 521-638; in Greenfield's Neuropathology, 6th ed., D.I. Graham and P.L. Lantos, Eds.; Arnold, London, 1997.
2. "Perinatal Brain Damage," by Hanna C. Kinney, pp. 537-587; in Greenfield's Neuropathology, 6th ed., D.I. Graham and P.L. Lantos, eds.; Arnold, London, 1997.
3. "Congenital Malformations of the Nervous System" by M.G. Norman and S. K. Ludwin, pp 207-280; in Textbook of Neuropathology, 2nd ed.; R. L. Davis and D. M. Robertson, Eds.; Williams and Wilkins, Baltimore, 1991.
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NEOPLASTIC DISEASES

Peter Canoll, M.D., Ph.D.

NEOPLASTIC DISEASES

General Considerations

CNS tumors are relatively rare. The annual incidence is 10-20 in 100,000 for intracranial tumors and 1-2 per 100,000 for intraspinal tumors. However, most CNS tumors are associated with a poor prognosis and approximately 2.5% of all cancer deaths in the United States are due to brain tumors. CNS tumors account for about 20% of all childhood cancers. Most childhood brain tumors are located in the posterior fossa (particularly the cerebellum), whereas in adults most brain tumors occur in the cerebral hemispheres. In adults approximately 75% of neoplasms arise from neuroglial or meningeal cells and approximately 25% are derived from metastases. In children, over 95% of the neoplasms would arise from indigenous cells, since metastatic disease is so uncommon in this age group. Metastatic deposits are about as frequent as the most malignant neuroglial neoplasm (glioblastoma multiforme) in adults, each constituting approximately 25% of intracranial neoplasms. This means that approximately half of the CNS neoplasms in adults are capable of killing these patients within a year of diagnosis. Other lesions such as meningiomas and nerve sheath tumors may be totally removed and patients may have completely normal life spans or may show evidence of local recurrence. In contrast to intracranial lesions, intraaxial spinal cord neoplasms are rarely metastatic or high-grade. The vast majority are primary. Ependymoma is the commonest of the intraaxial neoplasms. However, in the spine intraaxial neoplasms are less common than extraaxial ones, such as meningioma and nerve sheath tumor.

The histopathologic terms "low grade" and "high grade" are defined similarly as in general pathology, but they do not convey the same clinical message for CNS neoplasms that they do for most systemic neoplasms. A histologically benign, or low-grade, lesion in the CNS may be lethal to the patient because of its size or location. For example, a small histologically benign meningioma at the foramen magnum may represent a life-threatening condition. Consequently, the location and size of the lesion are often more important than its histologic features. The clinical symptoms caused by a brain tumor also depend on the location of the tumor. For example, tumors involving the cerebral cortex are likely to cause seizures and/or focal cognitive dysfunctions whereas tumors in the cerebellum typically cause ataxia. Finally, the way primary brain tumors grow and spread is different from other types of tumors. Even the most malignant brain tumors rarely metastasize to other organs. Rather, they spread by infiltration of the surrounding brain tissue, or less frequently, they spread in the leptomeningeal space or disseminate by via the cerebrospinal fluid.

Most common types of brain tumors

Neoplastic transformation may involve virtually any cell of the central and peripheral nervous system (neurons, astrocytes, oligodendrocytes, ependymal cells, meningotheial cells, etc.). There are over 120 different types of tumors listed in the WHO classification of nervous system tumors. We will focus on the most common types tumors. These include:

- A)-Astrocytomas (pilocytic astrocytomas, Diffuse astrocytomas, GBM)
- B)- Oligodendrogliomas
- C)- Ependymomas

- D)-Neuronal and mixed neuronal-glial tumors (Neurocytoma,, ganglioglioma)
- E)-Embryonal tumors (medulloblastoma, PNET)
- F)-Meningiomas
- G)-Nerve sheath tumors (schwannoma and neurofibroma)
- H)-Metastatic tumors

Details concerning specific tumor types:

A. Astrocytoma

There are several different histologic types of astrocytomas described. We will limit our discussion to the 2 most common types: diffuse fibrillary astrocytomas (the most common type of brain tumors in adults) and pilocytic astrocytomas (one of the most common type in children). In general, the histologic types do have some prognostic value, e.g. pilocytic astrocytomas tend to behave less aggressively than diffuse fibrillary astrocytomas. At the present time, WHO classification divides diffuse fibrillary astrocytomas into three grades: astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III) and glioblastoma multiforme (WHO grade IV). The histological features on which this grading system is based can be remembered using the acronym **AMEN**: **A** = nuclear atypia; **M** = mitosis; **E** = endothelial proliferation; **N** = necrosis.

Pilocytic Astrocytomas (WHO grade I) are generally circumscribed, slow growing, often cystic astrocytomas (**figure ND 3**). They are the most common glioma in children and young adults. They can occur anywhere in the CNS but preferred sites include cerebellum (pilocytic astrocytomas account for 85% of all cerebellar gliomas in children), optic nerve, diencephalon and brainstem. The clinical presentation and prognosis depends on the location of the tumors. Cerebellar pilocytic astrocytomas usually present with clumsiness, headache, nausea and vomiting. These tumors can often be completely resected and have a very good prognosis. Pilocytic astrocytomas of the optic nerve often produce visual loss. These tumors are associated with neurofibromatosis type-1 (Von Recklinghausen disease) and may involve both optic nerves. Pilocytic astrocytomas involving the diencephalon and brainstem present with hydrocephalus and brainstem dysfunction. Due to their location, total resection of these tumors is often not possible, and they are associated with a worse prognosis. Pilocytic astrocytomas are composed of bipolar cells with long “hairlike” processes (“pilo” means hairlike in greek). Eosinophilic inclusions called **Rosenthal fibers** are often present (**figure ND 4**). While there may be a considerable degree of nuclear atypia in these tumors, this does not correlate with an increased biologic growth rate. Thus, it is important to recognize this entity and not misclassify the lesion as a higher-grade astrocytic neoplasm. The molecular/genetic alterations associated with pilocytic astrocytomas are different from those seen in diffuse astrocytomas and they do not progress to GBM (see below), although they occasionally progress to higher grade tumors called malignant pilocytic astrocytoma when an increased mitotic rate is seen.

Diffuse astrocytomas (WHO grade II) represent 10-15% of all astrocytic brain tumors. They have a peak incidence in the 3rd and 4th decade. They may be located

anywhere in the CNS but are most commonly located in the cerebral hemispheres. Seizures are a common presenting manifestation of the tumor, although in retrospect, subtle abnormalities such as speech difficulties, changes in vision or motor dysfunction (depending on the location of the tumor) may have been present earlier. Neuroimaging studies can be variable, but typically show an ill-defined low-density non-enhancing lesion. Astrocytomas are diffusely infiltrating tumors that enlarge and distort but may not destroy anatomical structures (**figure ND 1**). Histology shows the tumors to be composed of neoplastic astrocytes with varying degrees of nuclear atypia on the background of a loosely structured, often microcystic tumor matrix (**Figure ND 2**). Cellularity is moderately increased. Mitotic figures are rare or absent. At the infiltrative edge of the tumor glioma cells are intermingled to varying degrees with reactive brain elements (entrapped neurons, reactive astrocytes, etc.) making it impossible to determine the true margin of the tumor. In fact, individual glioma cells often migrate several centimeters from the tumor to populate histologically normal appearing brain. There is no endothelial proliferation or necrosis. Thus, these tumors lack the features indicative of malignancy, yet they carry a rather dismal prognosis (mean survival time of 6-8 years). The treatment of choice is surgery. However, because glioma cells diffusely infiltrate the brain and migrate long distances from the tumor, some glioma cells invariably escape surgical resection and the tumors eventually recur. The second surgical specimens often show histological features of progression towards malignancy (increased nuclear atypia, mitoses, endothelial proliferation and necrosis). Depending on the extent of malignant progression the recurrent tumor may be up-graded to **anaplastic astrocytoma (WHO grade III) (figure 5)** or **GBM (WHO grade IV)**. There is increasing evidence that the progression from low-grade to high-grade astrocytoma is associated with a cumulative acquisition of multiple genetic alterations.

Glioblastoma Multiforme (WHO grade IV) is the most common primary brain tumor in adults (it accounts for approximately 25% of all intracranial neoplasms and 60% of all astrocytic tumors). GBMs are also the most malignant astrocytic tumor, with an average survival of less than one year after surgery. GBM occurs at any age, but is most commonly seen in adults between 45 and 70 years. The clinical history is usually short (less than 3 months in more than 50% of the cases) unless the GBM developed from a lower grade diffuse astrocytoma (so called secondary GBM). The patients often present with seizures and non-specific neurological symptoms including headache, personality changes, or rapid development of increased intracranial pressure. Neuroimaging shows an irregularly shaped lesion with a peripheral ring-like zone of contrast enhancement surrounding a dark central area of necrosis. Grossly, GBMs appear as variegated lesions with areas of necrosis and hemorrhage and often cross the corpus callosum giving rise to a butterfly shaped lesion (**figure ND 6**). As the name “multiforme” implies, the histopathology of GBMs can be highly variable, even within the same tumor. While some regions show a high degree of nuclear pleomorphism with numerous multinucleated giant cells, other areas may be highly cellular but rather monotonous. The astrocytic nature of the neoplastic cells may be easily identifiable in some regions, but difficult to recognize in others due to the high degree of anaplasia. Thus, the diagnosis of GBM is usually based on the characteristic histological features rather than the identification of certain cell types. These include nuclear atypia, mitoses, marked endothelial proliferation and necrosis. The necrotic areas are often

surrounded by a peripheral accumulation of pseudopalisading tumor cells so called **pseudopalisading necrosis (figure ND 7)**.

B. Oligodendroglioma

Oligodendroglioma (WHO grade II) is somewhat less common than astrocytic neoplasms. It is most common in the fourth and fifth decades. Oligodendroglioma is frequently found in the cortex and white matter of the cerebral hemispheres. Because of their (sometimes) slow growth, these tumors can present with a long prior history of seizures. Like astrocytomas, oligodendrogliomas are diffusely infiltrating gliomas and therefore, for the same reasons, eventually recur after surgical resection. They are composed of sheets of cells with round regular nuclei and clear cytoplasm (giving them a fried egg appearance) and a delicate network of branching capillaries (chicken wire vasculature) (**figure ND 8**). Oligodendrogliomas may progress to Anaplastic oligodendrogliomas (WHO grade III), which show increased nuclear atypia, mitoses, endothelial proliferation and necrosis. As a group, oligodendrogliomas have a median post-operative survival time ranging from 5-10 years. However, recent studies have shown that tumors associated with certain genetic alterations (loss of heterozygosity of chromosomes 1p and 19q) are more responsive to chemotherapy and have a better prognosis.

C. Ependymoma

Ependymomas (WHO grade II) are slow growing tumors originating from the ependymal cells that line the ventricular system, arising most commonly in the posterior fossa and spinal cord. These tumors are relatively rare, accounting for 3-9% of all neuroepithelial tumors. They are most common in children and young adults where they account for about 30% of all intracranial tumors in children under 3 years of age. As with other gliomas, the clinical presentation depends on the location of the tumor. Signs of hydrocephalus and increased intracranial pressure (headache, nausea, vomiting) predominate in infratentorial tumors. Involvement of the cerebellum may cause ataxia. Motor and sensory deficits represent the major manifestations of spinal tumors. Ependymomas are typically well-demarcated, moderately cellular gliomas composed of cells with monomorphic nuclei. Distinctive histological features include perivascular pseudorosettes and ependymal rosettes. **Perivascular pseudorosettes** represent tumor cells arranged radially around blood vessels and occur in the great majority of ependymomas (**figure ND 9**). **Ependymal rosettes** are composed of tumor cells arranged around a central lumen. Ependymal rosettes are diagnostic for ependymoma but are seen in only a minority of cases. As with other gliomas, the histological features associated with malignancy include increased nuclear atypia, mitotic activity, endothelial proliferation and necrosis. Tumors showing these features are given the diagnosis anaplastic ependymoma (WHO grade III).

D. Neuronal and Mixed Neuronal-Glial Tumors

There are several different types of brain tumors that contain neoplastic cells showing neuronal differentiation. These tumors are far less common than gliomas and they tend to occur in children and young adults. **Central neurocytomas** (WHO grade II) are composed of uniform round cells that express neuronal markers such as synaptophysin and have a low proliferation rate. These tumors are typically located in the lateral ventricles near the foramen of Monro. The treatment of choice is complete surgical resection. The clinical

course of central neurocytomas is usually benign. Local recurrence may occur, but dissemination through the CSF is rare. **Gangliocytomas** (WHO grade I) are well differentiated, slowly growing tumors composed of large multipolar neurons that often have dysplastic features. The cells typically have large nuclei with prominent nucleoli and stain positive for neuronal markers such as synaptophysin. These tumors sometimes contain a neoplastic glial component (**ganglioglioma**). The histologic grade of gangliogliomas usually depends on the grade of the glial component, which may range from low grade (WHO grade I or II) to anaplastic (WHO grade III) to GBM (WHO grade IV). Gangliocytomas are typically well-circumscribed tumors. Gangliogliomas have a tendency to extend into the adjacent leptomeningeal space.

E. Embryonal Tumors

Embryonal tumors are poorly differentiated malignant brain tumors (WHO grade IV). They occur predominantly in the pediatric population. There are several different types of embryonal tumors including medulloblastoma, supratentorial primitive neuroectodermal tumors (PNET) and ependymoblastoma. We will limit our discussion to medulloblastoma, which is the most common of the embryonal brain tumors (they account for approximately 30% of all pediatric brain tumors). By definition, medulloblastomas arise in the cerebellum. They are composed of densely packed cells with hyperchromatic nuclei and scant cytoplasm and there is high mitotic activity (**figure ND 10**). The tumor cells often show evidence of some neuronal and/or glial differentiation. For example, tumors may stain focally for neuronal markers (such as synaptophysin) and astrocytic markers (such as GFAP). Other areas may show little or no evidence of differentiation. The tumors often disseminate through the CSF to form distant metastases in the spinal cord (drop metastases). Medulloblastomas are rapidly proliferating, very aggressive tumors and the prognosis of untreated patients is dismal. However, they are highly radiosensitive and the 5-year survival rate after total resection and radiation therapy is as high as 75%.

F. Meningioma.

Meningiomas (WHO grade I) are benign tumors that are attached to the dura mater and composed of neoplastic meningotheial (arachnoidal) cells. They most commonly occur in adults with a female bias (approximately 3:2 female to male ratio). The majority of meningiomas occur over the cerebral convexities. Other common sites include the base of the brain (olfactory grooves, sphenoid ridges, parasellar regions), optic nerve, posterior fossa and spinal cord (most commonly thoracic). They are slow growing masses that elicit neurological symptoms by compression of adjacent structures. Neuroimaging typically shows a dural-based homogeneously enhancing mass. They grow as a well circumscribed (often firm-rubbery) mass (**figure ND 11**). There are several different histologic subtypes (syncytial, fibroblastic, transitional, meningotheial, etc.), which have no apparent predictive value. One rare exception to this rule is papillary meningioma, which is associated with a more aggressive course. Histological features commonly seen in meningiomas include lobular growth pattern with cellular whorls and concentric calcifications called psammoma bodies (**figure ND 12**). Meningiomas (of any histological subtype) that show increased mitotic activity, increased cellularity, a sheet-like growth pattern or areas of necrosis are considered atypical meningiomas (WHO grade II) or malignant meningiomas (WHO grade III) depending on the severity of these changes. These tumors are associated with a much worse

prognosis (the median survival for a patient with a malignant meningioma is less than 2 years after surgery). Even low-grade meningiomas may invade dura and bone but they rarely invade brain. The presence of brain invasion connotes a greater likelihood of recurrence and a worse prognosis.

G. Nerve Sheath Tumors.

These lesions may be found within the central nervous system or, as expected, in the peripheral nervous system. Intracranial examples usually are found in the VIII cranial nerve (**figure ND 13**); spinal examples usually involve dorsal roots. Benign lesions usually are divided into two types: **schwannoma or neurofibroma**. Both are histologically benign. The neurofibroma is usually seen in the setting of **neurofibromatosis**, so-called Von Recklinghausen's disease, an autosomal dominant disease usually divided into two relatively distinct variants: peripheral (Type I, NF1 gene on chromosome 17) and central (Type II, NF2 gene on chromosome 22). Consequently, these patients are expected to have multiple lesions, which may be either intracranial, peripheral or both. They also have an increased risk of developing neuroectodermal malignancies. Neurofibromas, particularly large lesions involving major nerve plexi, are more commonly encountered in NF type I and have a greater chance of undergoing malignant change than the solitary neurofibroma. The schwannoma is more typically seen in NF type II and in these patients almost invariably with the acoustic nerve (acoustic neuroma). Schwannoma is histologically characterized by a monomorphic population Schwann cells which are arranged either in dense fascicles (Antoni A) with palisading of nuclei (**Verocay bodies**) (**figure ND 14**) or in a looser more myxomatous background (Antoni B). These tumors grow in an eccentric fashion on the periphery of nerves and thus can be excised with significant preservation of nerve function. The neurofibroma, on the other hand, appears to be composed of at least two cells, the Schwann cell and the perineurial cell. In contrast to the schwannoma, neurofibromas diffusely infiltrate the nerve and thus their resection leads to loss of function supplied by that nerve.

H. Lymphoma.

Primary CNS lymphomas are most commonly seen in immunosuppressed patients (almost all are HIV+). These neoplasms are histologically identical to systemic lymphoma. The vast majority are diffuse large B-cell type (98%) and over 95% contain Epstein-Barr virus (EBV) nucleic acids. In these tumors, EBV oncoproteins, together with changes in cellular gene expression, is thought to play a role in driving the high rate of cell division. Neuroimaging shows one or more enhancing lesions. Lymphomas can be highly infiltrative and histologically show a characteristic angiocentric growth pattern.

I. Metastatic Carcinoma

Intracranial metastasis is seen in 25% and intraspinal metastases is seen in 5% of cancer patients. The most common origins of brain metastases include lung (50%), breast (15%) and malignant melanoma (10%). Metastatic lesions tend to be multiple and well demarcated (**figure ND 15**), in contrast to the single infiltrative quality of primary neoplasms of the CNS. The tumors often have histological features that are similar to the primary tumor. Metastases are usually located in the cerebral hemispheres, most commonly at the gray-white junction. Breast and prostate carcinomas also commonly metastasize to dura mater, and pulmonary, breast and gastric carcinomas not infrequently seed the leptomeninges (meningeal

carcinomatosis). Thus, these types of metastatic conditions can often be diagnosed from CSF cytology obtained after lumbar puncture.

J. Craniopharyngioma

Craniopharyngiomas are uncommon non-neuroepithelial neoplasms that occur predominantly in the suprasellar region during the first two decades of life (10% of intracranial tumors in children). This neoplasm also occurs in adults, but at much lower frequency. Craniopharyngiomas often present with headache (due to ventricular compression and resultant hydrocephalus) and visual changes (due to optic nerve/chiasm/tract compression). Craniopharyngiomas are usually cystic, irregular, nodular masses of tissue with viscid contents described as "machine oil." The cyst wall is lined by a squamous epithelium that has a prominent peripheral palisaded layer of columnar cells (adamantinomatous pattern). The epithelium keratinizes without normal maturation, giving rise to nests of keratin in the tumor ("wet-keratin"). The tumors commonly contain calcific debris. In adults, the tumor has a papillary growth pattern and the peripheral palisading layer is not present. Radical excision is rarely curative and may lead to hypothalamic dysfunction and psychological abnormalities as well as hypopituitarism. Recurrence is common.

Molecular-genetic alterations in brain tumors

It is now widely appreciated that DNA alterations underlie most if not all forms of human neoplasia. Recent studies have made substantial progress in identifying the biologically important genetic changes in gliomas and other brain tumors. One general category of DNA alteration that seems to be particularly frequent in glioblastomas is gene amplification. The gene **EGFR** encoding the membrane receptor for epidermal growth factor is amplified (present in many copies) in up to 50% of glioblastomas. This suggests the possibility of an autocrine pathway of growth stimulation in the tumor cells. The second category of chromosomal alterations that has received intense scrutiny is chromosomal loss. Losses of genetic material are thought to release the tumor cells from normal growth inhibition by a class of genes referred to as "tumor suppressors". Recurrent chromosomal losses in gliomas include loss of chromosomes 9p, 10q, 17p, 19q and 22q. The **p53** gene on chromosome 17p and the p16 gene on chromosome 9p are mutated or deleted in a subset of glioblastomas. Both of these genes normally serve to keep cell division in check via indirect or direct inhibition of cyclin-dependent protein kinases. p53 has additional functions in regulating the cell's response to stresses like DNA damage and hypoxia, again with a net effect such that its loss from the cell promotes tumorigenesis. The **PTEN** tumor suppressor gene, identified by Dr. Parsons here at Columbia and residing on chromosome 10q, encodes a lipid-phosphatase, which when deleted is thought to render tumor cells resistant to programmed cell death (apoptosis). Many additional tumor suppressor genes relevant to glioma pathogenesis remain to be isolated, and in some instances their identification may aid in diagnosis. For example, chromosome loss studies indicate that the tumor suppressor gene on chromosome 19q is highly specific for oligodendrogliomas, rather than astrocytomas. The finding of recurrent loss of the small chromosome 22 (carrying the NF2 gene) in gliomas is also interesting in view of the even more frequent loss of this same chromosome in other distinct types of brain tumors, including meningiomas and schwannomas, as well as ependymomas. The NF2 gene encodes a protein that localizes to the inner surface of the cell membrane, and it may transmit signals restraining cell proliferation.

Radiologic appearance of tumors and grading

The use of magnetic resonance imaging, with its multiplanar capabilities and multiple modalities (T1, T2, +/- contrast, flair, diffusion weighted imaging), has greatly advanced diagnostic capabilities for evaluating tumors of the CNS. While a complete understanding of these principles is beyond the scope of this course, a basic understanding of the meaning of contrast enhancement in brain tumors is appropriate.

The presence of contrast enhancement reflects a high vascularity in the lesion and associated breakdown of the blood brain barrier. As primary CNS tumors become more malignant (i.e. higher grade) the vascularity of the lesions tend to increase due to tumor induced vascular proliferation and this leads to contrast enhancement. A low grade diffusely infiltrating astrocytoma or oligodendroglioma (WHO grade II) will not be contrast enhancing. Some contrast enhancement will be seen in anaplastic tumors (WHO grade III) and this becomes more extensive as gliomas progress to glioblastoma multiforme (WHO grade IV). Primitive neuroectodermal tumors are also strongly contrast enhancing, as are metastatic carcinoma and lymphoma.

However, the presence of contrast enhancement does not always mean that a CNS tumor is a high-grade lesion. Meningiomas, which are generally low-grade lesions, are strongly contrast enhancing. As these tumors are derived from arachnoid cells, they do not have a blood-brain barrier and thus show enhancement due to a high vascularity. Pilocytic astrocytomas (WHO grade I) also show contrast enhancement, which is thought to be due to degenerative changes in blood vessels (slow growing tumor) rather than their proliferation as seen in high-grade diffuse gliomas. Thus, in trying to grade CNS neoplasms on the basis of radiologic examination, contrast enhancement does increase in diffusely infiltrating gliomas as they become more malignant, but one cannot equate enhancement with high-grade lesions.

SEIZURES AND EPILEPSY

Hyunmi Choi, M.D.

I. Distinguish between seizure and epilepsy

Epilepsy

Chronic disorder, characterized by recurrent unprovoked seizures

Several different seizure types may coexist in an individual with epilepsy

May either be due to genetic factors (idiopathic) or symptomatic (associated with pathologic process in the brain)

Seizure

Clinical event due to transient physiologic dysfunction of brain characterized by abnormal hypersynchronous discharge of a group of cortical neurons

Particular clinical feature depends on function of underlying cortical area

Occur in acute neurologic (e.g. meningitis) or medical condition (e.g. hyponatremia)

II. Seizure types

Classification of Epileptic seizures

I. Partial seizures	II. Generalized seizures
a. simple partial seizures	a. Absence seizures
b. Complex partial seizures	b. Myoclonic seizures
c. Partial seizure evolving to generalized tonic-clonic seizure	c. Tonic-clonic seizures
	d. Tonic seizures
	e. Clonic seizures
	f. Atonic seizure seizures

- A. Partial (focal or localization) epilepsy
 - Begins in certain part of brain
 - Clinical manifestation depends on function of underlying cortex
 - May generalize into tonic-clonic seizure
 - Motor cortex – repetitive rhythmic clonic movement in contralateral limb
 - Somatosensory – tingling sensation in contralateral limb
 - Autonomic – flushing, piloerection
 - Psychic (temporal lobe): déjà-vu, fear,
- 1. Simple partial
 - consciousness intact (“aura”)
 - Jacksonian march – seizure over motor strip, manifesting clinically as twitching in contralateral limb distal part (i.e. fingers moving up the arm to shoulder)
- 2. Complex partial
 - May start with aura – déjà vu, metallic taste in mouth, fear
 - Impaired consciousness
 - May begin with motionless stare with maintenance of posture followed by automatisms (semi-purposeful motion, like patting, rubbing, lip-smacking, chewing)
 - confusion, language impairment if seizure arose from dominant hemisphere
- B. Generalized epilepsy
 - Epileptic discharge in brain generalized from onset, affecting brain simultaneously
- 1. Absence seizure
 - Genetic predisposition
 - Onset at 5-7 years of age
 - brief episodes of stare
 - no post-ictal confusion
 - resume previous activity
 - associated with 3-Hz spike wave discharge on EEG
- 2. Generalized tonic clonic seizure
 - Sudden loss of consciousness
 - No warning
 - Loud brief cry due to laryngeal/diaphragm contraction
 - Tonic phase – stiffening of limbs
 - Clonic phase – rhythmic contraction of all muscle groups
 - Postictal phase – lethargy, confusion, headache, sleep
- 3. Myoclonic seizure
 - Involuntary sudden lightning-like contraction of a group of muscles
- 4. Tonic seizure
 - Brief sudden extension of all limbs
 - Seen in Lennox-Gastaut syndrome (multiple seizure types and mental retardation)

III. Common causes of seizures as related to age group

- A. Idiopathic – genetic predisposition
- B. Focal abnormality
 - Stroke
 - Hemorrhage
 - Head trauma
 - Subdural (esp in alcoholics and elderly)
 - Vascular malformation (e.g. arterio-venous malformation)
 - Neoplasia
- C. Metabolic**
 - Hyper- or hypoglycemia
 - Hyponatremia
 - Hypocalcemia
 - Hypomagnesmia
 - Hypoxia
 - Non-ketotic hyperosmolar state
 - Uremia
- D. Infection**
 - Meningitis
 - Encephalitis

IV. Routine evaluation of a patient for new-onset seizures

- A. Screen for acute medical or neurologic condition
- B. Clinical history
- C. Physical exam
- D. Blood test to detect -
 - Infection
 - Abnormal electrolytes – glucose, calcium, magnesium
 - Liver and kidney function
- E. Lumbar puncture in suspected cases of meningitis or encephalitis
- F. Urine and blood toxicology test in suspected cases of illicit drug use
- E. CT or MRI**

V. Anticonvulsant treatment

A single seizure occurring in the setting of an acute brain injury which is reversible does not constitute epilepsy and does not require long-term antiepileptic drug therapy

- A. Use single medication when possible (monotherapy)
- B. Increase the dose to seizure control or toxicity
- C. If no significant response, switch to another appropriate drug, and again increase until seizure control or toxicity
- D. Use therapeutic serum drug level as a guideline and not as absolute

E. Consider two drug only when monotherapy fails
(Pippenger and Lesser 1994)

VI. Commonly used anticonvulsants and their indications and side effects

A. Common drugs for seizure types

Absence seizure

Ethosuximide, valproic acid

Simple partial, complex partial, or partial seizure progressing to generalized tonic clonic seizure

Carbamazepine, Phenytoin, lamotrigine, valproic acid

Generalized tonic-clonic seizure (generalized epilepsy)

lamotrigine, valproic acid, levetriacetam

Myoclonic epilepsy

valproic acid, levetiracetam

Common antiepileptic drugs

Drug	Usual adult dose (per 24 hr)	Half-life hr	Therapeutic level (g/ml)	Side effect
Carbamazepin (Tegretol)	800 -1600	11-22	8-12	Drowsiness, blurred vision, diplopia, dysequilibrium, leukopenia, hepatic failure
Phenytoin (Dilantin)	300 -400	22	10-20	Ataxia, dysarthria, gingival hyperplasia, hirsutism, acneiform eruption, hepatic failure
Phenobarbital	90-180	100	15-35	Sedation, depression, loss of concentration
Valproic acid (Depakote)	1000-3000	15-20	50-120	Weight gain, hair loss, tremor, thrombocytopenia, liver failure, pancreatitis
Lamotrigine (Lamictal)	200-500	24	4-20	Rash, dizziness, headache

DISEASES OF MYELIN

Phyllis L. Faust, M.D., Ph.D.

DISEASES OF MYELIN

I. Demyelinating Diseases

- A. Multiple Sclerosis
 - 1. Chronic
 - a) Classical (Charcot)
 - 2. Acute variants
 - a) Disseminated (Marburg)
 - b) Concentric sclerosis (Balo)
 - c) Neuromyelitis optica (Devic)
- B. Acute disseminated encephalomyelitis
 - 1. Classical
 - a) Postinfectious encephalomyelitis
 - b) Postvaccinal encephalomyelitis
 - 2. Hyperacute
 - a) Acute hemorrhagic leukoencephalitis
- C. Progressive multifocal leukoencephalopathy
- D. Subacute sclerosing panencephalitis

II. Dysmyelinating and Hypomyelinating Diseases

- A. Metachromatic leukodystrophy
- B. Globoid cell leukodystrophy (Krabbe's disease)
- C. Adrenoleukodystrophy, Adrenomyeloneuropathy
- D. Alexander's disease

III. Myelinolytic Diseases

- A. Central pontine myelinolysis
- B. Vitamin B12 deficiency
- C. HIV-associated vacuolar myelopathy
- D. Aspartoacylase deficiency
(Spongy degeneration of infancy;
Canavan; Van Bogaert-Bertrand)

DISEASES OF MYELIN

The myelin sheath is a **specialization of the plasma membrane** of **oligodendrocytes** in the central nervous system and **Schwann cells** in the peripheral nervous system. It is a compact multilamellar membrane spiral that in electron micrographs appears as alternating dark and light lines. The dark or "major dense" lines represent the apposition of the cytoplasmic aspects of the oligodendrocyte or Schwann cell membrane; the light "interperiod" line represents the apposition of the extracellular membrane faces. Ensheathment of axons by myelin permits the rapid "saltatory conduction" of action potentials. Diseases affecting the myelin sheath interfere with normal conduction and cause signs and symptoms referable to the specific parts of the nervous system involved.

Myelin is susceptible to a number of disease processes, and there are several ways of classifying diseases involving myelin. **Primary diseases of myelin** are those in which the myelin sheaths (or their oligodendrocytes or Schwann cells) are involved but axons are relatively preserved. "**Secondary demyelination**" is frequently a consequence of primary or concomitant axonal loss due to neuronal degeneration, hypoxia-ischemia, trauma, edema or infection. Primary diseases of myelin may be classified by etiology or by pathology. **Etiologies** include autoimmune, viral, genetic and toxic-metabolic. A pathology-based classification divides these diseases into four broad categories: **demyelination, dysmyelination, hypomyelination and myelinolysis.**

Demyelinating diseases are generally **inflammatory**, sporadic, and characterized by the immune-mediated destruction of **biochemically normal** myelin and its supporting cells; axons are generally spared. The target is usually either central (e.g. multiple sclerosis) or peripheral myelin (e.g. idiopathic polyneuritis), reflecting the significant antigenic differences between these two myelins. **Dysmyelinating** diseases (leukodystrophies) are generally non-inflammatory, familial, and characterized by the **confluent** destruction of (presumably) **chemically abnormal myelin** and its supporting cells; axonal loss is more prevalent than in demyelinating or myelinolytic diseases. Involvement of both central (especially cerebral) and peripheral myelin may occur, reflecting the biochemical similarities of these myelins. In **hypomyelinating** diseases, there is a similar confluent abnormality in white matter, but there is a general paucity of myelin deposition during development. Thus, there is a reduced quantity of myelin lipids and proteins rather than the chemically abnormal myelin seen in the dysmyelinating diseases. Although the myelin is chemically normal in these diseases, they are often categorized as leukodystrophies due to the diffuse nature of the process. **Myelinolytic** diseases are **non-inflammatory** and characterized by **intramyelinic edema** of chemically normal myelin with relative sparing of the supporting cells and axons, at least in the early stages. Intramyelinic edema is recognized as a splitting of the myelin sheath at the interperiod line.

A summary of representative diseases from each category is offered below. More detailed descriptions of these and other diseases of myelin can be found in the supplementary reading.

DEMYELINATING DISEASES

Table 1. DEMYELINATING DISEASES

Disease	Clinical Features	Pathologic Features	Pathogenesis
Multiple Sclerosis	<ul style="list-style-type: none"> > Peak age of onset 20-40 years; > Episodic signs and symptoms referable to different parts of the neuraxis (disseminated in time and space) 	<ul style="list-style-type: none"> > Demyelinative plaque; > Loss of myelin, relative preservation of axons; > Acute plaques with macrophages and lymphocytes; Chronic plaques with gliosis 	<ul style="list-style-type: none"> > Environmental agent (? viral infection); > Immunologic factors (?autoimmune reaction precipitated by viral infection); > Genetic factors
Acute Disseminated Encephalomyelitis (ADEM)	<ul style="list-style-type: none"> > Acute onset after viral infection or vaccination; > diffuse involvement of brain and spinal cord; monophasic; most patients with good recovery 	Perivenous demyelination and inflammation	Immune destruction of myelin due to T-cell mediated hypersensitivity reaction
Acute Hemorrhagic Leukoencephalopathy (AHL)	Acute onset of neurologic signs, rapid progression to coma and death	Necrosis of blood vessels in white matter; ring- and ball-shaped perivascular hemorrhages	Hyperacute form of ADEM
Progressive Multifocal Leukoencephalopathy (PML)	<ul style="list-style-type: none"> > Focal neurologic deficits (e.g. dysarthria, limb weakness, visual changes, ataxia, seizures); > Relentless progression over a few months, death 	Demyelination with nuclear viral inclusions in oligodendrocytes, large atypical astrocytes macrophages	Reactivation of latent JC virus as a result of impaired T-cell immunity;

Multiple sclerosis

Multiple sclerosis (MS) is a common CNS disease. It is the prototypic and most frequently encountered demyelinating disease in humans. MS is characterized by multiple **plaques of inflammatory demyelination** that are **disseminated in time and space**. The prevalence varies with **genetic background** and **latitude** and usually affects young people (20-40 years of age), particularly women. The clinical presentation varies. Most commonly MS presents as episodic signs and symptoms (**attacks** or **exacerbations**) referable to different parts of the neuraxis, particularly the optic nerves, spinal cord and brainstem. Such attacks are followed by complete or partial **remission** and subsequent **relapses** ("chronic relapsing" multiple sclerosis). Attacks appear to be precipitated by infection, trauma, pregnancy or excessive heat; however controlled studies often fail to confirm these observations. The earliest presentation may be that of a young woman who complains of paresthesias or visual difficulties and yet, when tested, does not show any objective abnormalities (signs). When the third or fourth such episode

occurs or some objective sign can be detected, the diagnosis of MS is then seriously considered. Rarely, MS has an acute presentation and in these instances must be differentiated from acute disseminated encephalomyelitis (see below) or a brain tumor.

There is no completely reliable laboratory test available at the present time to diagnose these patients at their initial presentation, however several types of tests are helpful in supporting this diagnosis. **Magnetic resonance imaging (MRI)** is capable of demonstrating multiple discrete lesions in the CNS, even at early stages of the disease. **Evoked potentials** (visual, auditory, and somatosensory) can also help demonstrate clinically silent lesions. Analysis of **cerebrospinal fluid** frequently shows evidence of inflammation (mild mononuclear pleocytosis, elevated IgG levels or oligoclonal IgG bands on electrophoresis) or myelin breakdown (elevated myelin basic protein levels).

The pathologic hallmark of multiple sclerosis, the **demyelinative plaque**, is a sharply demarcated lesion devoid of myelin staining [DM-1]. Plaques are often multifocal and asymmetric [DM-2]. Sites of predilection include the pial surface of the optic nerves and chiasm, spinal cord and basis pontis and the periventricular white matter of the cerebrum, cerebellum and brainstem - that is, regions in proximity to **cerebrospinal fluid** and to **deep cerebral veins**. However, all areas of white matter, and those of gray matter containing myelinated axons, may exhibit demyelination in chronic MS. **Shadow plaques**, which display a subtotal loss of myelin staining due primarily to **partial remyelination**, are also commonly observed in the chronic form [DM-1].

The gross and microscopic appearances of demyelinated plaques vary with their age. **Acute** lesions are grossly pink to chalky-white and may be soft and edematous; microscopically, variable numbers of **lymphocytes** (helper and suppressor/cytotoxic T cells), **plasma cells** and macrophages, particularly around small venules, are associated with loss of myelin but preservation of axons [DM-3,4]. Whether oligodendrocytes are lost at this early stage is still a matter of debate, but most evidence indicates that the loss of oligodendrocytes follows damage to myelin. The perivenular myelinated axons appear to be affected first (perivenous demyelination) and are in immediate physical contact with **macrophages**, which are presumed to cause **separation** and **thinning of myelin lamellae**. Reactive astrocytosis is also prominent at this stage, but lipid-laden macrophages appear later. With time the lesions become firm (sclerotic) and gray. This **chronic** lesion consists primarily of demyelinated axons and a profusion of astrocytic processes [DM-5]. The peripheral nervous system is spared.

The etiology of MS is still poorly understood, but **genetic, environmental, and immunologic** factors appear to play some role in its pathogenesis. The risk of the disease is highest in monozygotic twins and increased in first degree relatives compared to nonrelated individuals. MS in Caucasians is associated with **HLA** phenotypes. This association is believed to confer an immune responsiveness to whatever the etiologic antigen may be. Two environmental factors appear important. People living in **northerly latitudes** (colder climates) have a higher prevalence (northern U.S.: 30-60/100,000) than warmer climates (southern U.S.: 5/100,000). Some argue that this is related to similar genetic backgrounds of people living in the northern latitudes of Europe and North

America. For example, Japan at latitude 40° north (like northern U.S.) has a prevalence of only 4/100,000. A second environmental factor appears to be an infectious agent that is contracted before the age of **15 years**. Measles **virus** remains the most persistent contender, but a retrovirus may be the culprit. There is a wealth of evidence that immune forces are operative in MS: **elevated IgG in CSF** and plaques, oligoclonal IgG bands in CSF, decreased peripheral suppressor/helper T cells during relapses, plasma cells and Ia-positive macrophages in acute lesions, direct physical role for macrophage in demyelination and capping of surface IgG on these macrophages. The participation of cytokines, such as **interleukins** and **tumor necrosis factors**, in the pathogenesis of MS has been recognized recently. Clinical studies show that beta-interferon may be of value in the early stages of MS. To summarize, MS is believed to represent an autoreactivity to myelin antigens in genetically predisposed individuals. This autoreactivity is thought to be precipitated by exposure to an infectious agent early in life.

Acute Disseminated Encephalomyelitis

In contrast to multiple sclerosis, this disease is uncommon, affects children more than adults and is usually seen following a viral infection or vaccination. The onset is acute and typically there is diffuse involvement of the brain, spinal cord and meninges. This disease is usually **monophasic**, that is, patients generally have just one episode of CNS signs and symptoms. A minority of patients have a polyphasic course that may be difficult to distinguish from MS.

Postinfectious encephalomyelitis most commonly follows measles (rubeola) infection. Less commonly, it follows smallpox, chickenpox and rubella. Typically symptoms occur 3-5 days following the appearance of the viral exanthem. The majority of patients with postinfectious encephalomyelitis completely recover, if appropriately treated with steroids, while approximately 10% die and approximately 10% demonstrate persistent deficits.

Postvaccinal disease usually occurs 10 days following a viral vaccination. Historically, the most important causes of postvaccinal encephalomyelitis are rabies vaccines produced in brain tissue (no longer done in this country) and smallpox vaccine (no longer administered). The mortality rate was high and residual deficits in survivors were common. More recently, influenza vaccination has been implicated in this disease. The prognosis in these patients is similar to those with postinfectious encephalomyelitis.

All areas of the neuraxis may be affected. **Perivenous demyelination**, reminiscent of that seen in early multiple sclerosis lesions, is the histologic hallmark [DM-6]. However, inflammatory cells are **largely lymphocytes** and discrete perivenous lesions are the rule rather than the exception. Some confluence of individual lesions does occur, which may be appreciated well on MRI scans. This pathogenesis of acute disseminated encephalomyelitis appears to represent an **immune** destruction of myelin, which is **not** dependent upon direct invasion of the brain by virus. Recent evidence indicates that some viral proteins share homologies with myelin basic protein, the encephalitogenic protein used to produce experimental allergic encephalomyelitis (EAE) in rodents. **Experimental allergic encephalomyelitis, an autoimmune, inflammatory demyelinating disease,**

appears to be an excellent model for this human disease. Chronic forms of EAE have also been developed, which appear to model some features of chronic multiple sclerosis.

Acute hemorrhagic leukoencephalitis

Acute hemorrhagic leukoencephalitis (Weston Hurst disease) is thought to be an hyperacute form of acute disseminated encephalomyelitis. This usually occurs in childhood and there may be an antecedent viral infection (influenza, chicken pox, measles) or a vaccination. The onset is dramatic and often asymmetric due to the predominance of lesions in one cerebral hemisphere. Pathologically, these lesions are characterized by **necrosis of blood vessels** with a marked fibrinous exudate, ring-shaped hemorrhages and neutrophilic inflammatory cells. Perivenous demyelination with significant axonal loss also is noted. The mortality rate in this disease is high.

Progressive multifocal leukoencephalopathy (PML)

PML is an infectious disease usually seen in **immunocompromised** adults. The agent belongs to the papovavirus group B, which has been named JC (the patient's initials from whom the virus was first isolated) and should not be confused with CJ (Creutzfeldt-Jakob) disease). Focal **cerebral** signs or symptoms are seen. The CSF is normal. Grossly, the lesions are variable in size, multiple, granular and usually restricted to the deep white matter. Microscopically, **primary demyelination** with marked, often bizarre, astrocytosis is observed. **Oligodendrocytes** are diminished within the lesions; their nuclei are enlarged and exhibit amphophilic viral **inclusions**. Viral antigens and particles have been demonstrated in these inclusions and rarely in the bizarre astrocytes. The pathogenesis of PML centers on the infection of oligodendrocytes by papova virus with their subsequent lysis and demyelination. Although the reactivation of a latent virus appears to play a fundamental role, it must be emphasized that both the chronicity of its clinical course ("**slow infection**") and the lack of immune and inflammatory host responses set this disease apart from classical latent infections, such as varicella-zoster. This infection has currently gained prominence in HIV infected patients. This disease entity is illustrated in the infectious disease section of this syllabus.

Subacute sclerosing panencephalitis (SSPE)

SSPE is another "slow infection" of the CNS, which is related to a traditional virus (**measles** most often, also rubella), and is manifested as **inflammatory demyelination** with infection of oligodendrocytes and neurons (occasionally astrocytes). This is predominantly a disease of children, characterized by the insidious onset of behavioral changes and mental deterioration followed by myoclonus, ataxia and sometimes seizures. After a period of stupor, the patient dies. About half the patients are known to have had measles prior to the age of 2 years. The precise pathogenesis of SSPE is still disputed, but may involve a mutant virus, an abnormal host response and a defect in the **viral M protein**.

DYSMYELINATING AND HYPOMYELINATING DISEASES

The diseases included under this rubric usually are referred to as **leukodystrophies**, since they affect white matter rather than gray matter. These are mainly inherited disorders, most commonly autosomal recessive, that affect infants and children, but rare adolescent

and adult forms are also recognized. In children, these diseases pursue a progressive downhill course with death approximately 6 months to several years following the onset of CNS symptoms. Most demonstrate diffuse, confluent absence of cerebral and cerebellar white matter with significant axonal loss, but with relative sparing of arcuate (superficial, subcortical) fibers [DM-7]. Accumulation of characteristic myelin breakdown products is seen by light or electron microscopy. The peripheral nervous system may also be involved and other organs may show abnormalities. Each type of leukodystrophy has a characteristic microscopic appearance, which, in contrast to the gross lesions, allows one to separate these diseases pathologically. The **dysmyelinating** diseases are characterized by the presence of chemically abnormal myelin whereas in **hypomyelinating** diseases there is a paucity of myelin deposition during development.

**Table 2. DYSMYELINATING and HYPOMYELINATING DISEASES
(LEUKODYSTROPHIES)**

Disease	Clinical Features	Pathologic Features	Pathogenesis
Metachromatic Leukodystrophy	Late-infantile form most common; onset 1-2 years with progressive motor disability, intellectual decline, rapid demise	Dysmyelination with metachromatic deposits of sulfatide in the brain, spinal cord, peripheral nervous system and kidney .	> Arylsulfatase A deficiency (lysosomal enzyme) > Autosomal recessive
Krabbe's disease	Most often presents in infancy (3-5 months) with hyperirritability, psychomotor regression, peripheral neuropathy, visual disturbances, seizures; death by age 2	Dysmyelination in CNS with multinucleated macrophages/globoid cells; Peripheral neuropathy	> Galactocerebroside beta-galactosidase deficiency (lysosomal enzyme) > Autosomal recessive
Adreno-leukodystrophy	Childhood form (age 4-8) with loss of skills, behavioral problems, hearing and visual changes, impaired coordination, adrenal insufficiency. Adult form with spastic paraparesis, adrenal and testicular insufficiency.	Inflammatory demyelination; Needle-like trilamellar inclusions by EM Adult form results from degeneration of axons, long tract signs.	> Defective ATP-binding cassette transporter of peroxisomes (ALDP); > Reduced capacity for beta-oxidation of very long chain fatty acids > X-linked inheritance
Alexander's Disease	Infants with increased head size, psychomotor retardation, spasticity	Hypomyelination with Rosenthal fibers in glial processes	> Mutations in glial fibrillary acidic protein, an intermediate filament of astrocytes; > Usually sporadic

Metachromatic Leukodystrophy (MLD)

MLD is a lysosomal storage disease due to a deficiency of **arylsulfatase A**. This enzyme catalyzes the degradation of a glycosphingolipid abundant in myelin. Deficiency of this enzyme results in the accumulation of **sulfatide** that can be demonstrated with **metachromatic stains** such as toluidine blue or an acid modification of the cresyl violet technique. ("Metachromatic" materials change the color of the dye in these stains, e.g. will stain brown rather than blue with a cresyl violet stain). Metachromatic deposits can be found in brain, peripheral nerve, renal tubular cells and a few other extraneural tissues [DM-8]. Ultrastructurally, abnormal membrane-bound inclusions are seen. These inclusions have several appearances and descriptive names such as "prismatic" inclusions and "herringbone" or "tuffstone" bodies. Diagnosis of metachromatic leukodystrophy is made by measurement of arylsulfatase-A activity in peripheral blood leukocytes, cultured fibroblasts, amniotic fluid cells or chorionic villi. Urinary sulfatide excretion also supports the diagnosis. A variety of mutations in the arylsulfatase-A gene (chromosome 22q) have been identified. Therefore, mutation analysis can also be performed, but this is most useful in families in which the specific mutation has been characterized.

Krabbe's Disease (Globoid Cell Leukodystrophy)

Krabbe's disease (also a lysosomal storage disease) is due to a deficiency of **galactocerebroside beta-galactosidase (chromosome 14)**. This enzyme hydrolyzes **psychosine**, (galactosylsphingosine) in addition to galactocerebroside. Accumulation of **psychosine** has been shown to be toxic to oligodendrocytes and myelin in experimental animals. At the light microscopic level, **Krabbe's disease** demonstrates an accumulation of **PAS positive**, uninucleated and **multinucleated** epithelioid cells ("**globoid cells**") [DM-9]. Globoid cells are monocyte derived and undergo this characteristic transformation in this disorder. Ultrastructurally, abnormal inclusions demonstrating curvilinear tubular profiles and crystalloid cross-sectional contours are characteristic. Diagnosis is made by assay of galactocerebroside beta-galactosidase in blood or cultured fibroblasts.

Adrenoleukodystrophy

Adrenoleukodystrophy (ALD) is an X-linked disease that affects the adrenal cortex and testis, in addition to the nervous system. The typical patient is a 4-8 year old boy who shows neurologic impairment, such as attention deficit, hearing and visual disturbances and impaired coordination, and adrenal insufficiency. The disease usually progresses to a vegetative state within 2 years. Female heterozygotes occasionally develop neurological problems, but these are less severe than in males. An adult, chronic form of ALD, **adrenomyeloneuropathy**, often presenting as spastic paraparesis and adrenal or testicular insufficiency, is found within kindreds of ALD. Long tracts of spinal cord are primarily involved.

The demyelination of ALD shows **marked lymphocytic infiltrates** and lipid-laden macrophages [DM-10], and for this reason, many originally considered ALD to be a childhood form of multiple sclerosis (Schilder's disease). Characteristic lamellar and crystalloid inclusions are observed in adrenocortical, Leydig, Schwann, CNS macrophage and, probably, oligodendrocyte cytoplasm.

The characteristic biochemical abnormality in ALD is a marked increase in **very long chain fatty acids**, predominantly esterified to cholesterol. This led to the idea that ALD is a peroxisomal disorder. A mutation in a gene encoding a peroxisomal membrane protein has been identified in all patients studied so far. This gene does not appear to encode a very long chain fatty acid-CoA synthase, as had been expected. Rather, this gene encodes a protein that is a member of the adenosine triphosphate binding cassette ("ABC") transporter protein family. These proteins are involved in the ATP-dependent transport of amino acids, ions and proteins in many organisms. The CFTR protein of cystic fibrosis is a member of this family. It is hypothesized that this protein is involved in the transport of substrates or enzymes critical for very long chain fatty acid oxidation into the peroxisome.

Alexander's disease

This is a very **rare disease with largely sporadic inheritance**. Rare cases with autosomal recessive inheritance have been identified. The infantile form is characterized by psychomotor retardation and megalencephaly. Infantile Alexander's disease is characterized as a predominantly hypomyelinating leukodystrophy because there is a marked deficiency in myelin formation. However, the primary abnormality is probably in astrocytes. The characteristic pathologic abnormality in this disease is numerous **Rosenthal fibers** that are present in astrocyte processes that line the pial surface, blood vessels and ependyma. Rosenthal fibers contain large quantities of alpha B-crystallin, which is a small heat shock protein. The role that these inclusions play in the pathogenesis of this disease is unknown. Peripheral nerve myelin is normal.

Recent genetic studies have demonstrated that the majority of patients with Alexander's disease have a mutation in the gene encoding for glial fibrillary acidic protein (GFAP). GFAP is an intermediate filament protein of astrocytes and is an important component of the cytoskeleton. Studies in transgenic mice have shown that overexpression of a normal GFAP gene results in formation of Rosenthal fibers in brain astrocytes. In Alexander's disease patients it is postulated that the GFAP mutation alters the functioning of this protein, leading to the cellular stress response and formation of Rosenthal fibers. This disease illustrates the importance of astrocytic function for the formation/maintenance of CNS myelin.

MYELINOLYTIC DISEASE

Myelinolytic diseases are characterized by intramyelinic edema. The splitting of myelin disrupts the interperiod line, suggesting that the fluid accumulation, while within the myelin sheath, is extracellular. A number of diseases of diverse etiologies can be included in this category. Only a few will be discussed.

Central pontine myelinolysis, a recently discovered disease (1959), exhibits **primary demyelination** classically in the mid-dorsal pontine crossing fibers, but involvement of several brain regions outside the pons have been described [DM-11]. Generally, areas in which there is close admixture of gray matter with its rich capillary network and white matter with its susceptible myelin sheaths are characteristically at risk. Intramyelinic edema has been observed. Axonal loss is also significant and reactive axonal spheroids are common. Patients who demonstrate central pontine myelinolysis at autopsy may have been asymptomatic or have shown severe problems such as coma and quadriplegia, depending on the extent of the lesion. Many patients with this disorder are initially hyponatremic and then undergo rapid correction of serum sodium. It is believed that a too rapid correction of the hyponatremia results in extravascular hypernatremia in the affected areas and intramyelinic edema. The recent recognition of this lesion seems to coincide with the advent of **intravenous lines**, which has allowed clinicians to infuse large quantities of fluids and electrolytes rapidly.

Subacute combined degeneration of the spinal cord is due to **vitamin B12** deficiency. Vacuolization of the posterior and lateral columns of the spinal cord is seen by light microscopy, and electron microscopy shows intramyelinic edema. AIDS patients with no detectable nutritional deficiency can also show a progressive myelopathy with identical pathological features. In these patients, the condition is known as **HIV-associated vacuolar myelopathy**. This condition is believed to result from the HIV infection, however the virus generally cannot be isolated from affected tissue.

Table 3. MYELINOLYTIC DISEASES

Disease	Clinical Features	Pathologic Features	Pathogenesis
Central Pontine Myelinolysis	> Rapid onset of confusion, limb weakness, gaze palsies, hypotension, coma > Often fatal within weeks	> Loss of myelin in basis pontis; > Intramyelinic edema; > Some axonal loss	Rapid correction of hyponatremia
Subacute Combined Degeneration of the spinal cord	Paresthesias in lower limbs, loss of fine touch, vibration and position sense; progresses to spastic paraparesis, ataxia lower limb anesthesia	> Vacuolization of posterior and lateral columns in the spinal cord > Intramyelinic edema	> Vitamin B-12 deficiency (pernicious anemia) > Defective methylation of myelin basic protein
HIV-associated Vacuolar myelopathy	> Spastic paraparesis, ataxia, incontinence > Affects up to 25% of patients with AIDS	> Vacuolization of posterior and lateral columns in the spinal cord > Intramyelinic edema	Unclear; Direct viral infection of macrophages versus indirect effect of HIV infection
Canavan's Disease	> Presents in infants (2-6 months) with megalencephaly, psychomotor retardation, hypotonia, blindness; > Rapid progression to spastic quadriplegia, decerebration, seizures	> Vacuolar change in white matter of cerebrum and cerebellum > Intramyelinic edema > Alzheimer type II astrocytes in cortex	Aspartoacylase deficiency (lysosomal enzyme) > Accumulation of N-acetyl-aspartic acid > Autosomal recessive, Ashkenazi Jewish ancestry

Aspartoacylase deficiency has been well described using several names including **spongy degeneration of infancy, Canavan disease, van Bogaert-Bertrand spongy degeneration**. Deficiency results in accumulation of N-acetyl-aspartic acid. N-acetyl-aspartic acid is normally a very abundant amino acid in the mammalian nervous system however its function is completely unknown. Aspartoacylase deficiency is an **autosomal recessive** disease, primarily affecting those of **Ashkenazi** Jewish ancestry. It usually presents at 2-6 months of age with psychomotor retardation and hypotonic flaccidity and progresses to spastic quadriplegia, decerebration and seizures. Neuropathologic lesions are generally confined to the central nervous system. **Megalencephaly** and increased brain weight is typical. The histopathologic hallmark is a vacuolar alteration, initially of subcortical white matter and deep gray matter, which progresses to involve all cerebral and cerebellar white matter [DM-12]. The vacuoles in white matter primarily correspond to the **intramyelinic** accumulation of **fluid**. In addition to this, the astrocytes in deep cortex and white matter also become vacuolated. By light microscopy they resemble **Alzheimer type II astrocytes**, even though hepatic disease is not present. At the

ultrastructural level, both protoplasmic and fibrous astrocytes demonstrate elongated mitochondria with abnormal cristae and matrices. The ultrastructural observations suggest that the **astrocyte** may play a significant role in the pathogenesis of this disease. Diagnosis is made by detecting elevated levels of **N-acetyl-aspartic acid** in urine.

SUPPLEMENTARY READING:

1. "Demyelinating Diseases" by J.W. Prineas and W.I. McDonald, pp. 813-896, in *Greenfield's Neuropathology*, Volume 1, 6th ed., by D.I. Graham and P.L. Lantos, eds., Arnold, London, 1997.
2. "Demyelinating Diseases" by C. S. Raine, pp. 627-714 in *Textbook of Neuropathology*, 3rd ed., by R. L. Davis and D. M. Robertson, Eds., Williams and Wilkins, Baltimore, 1991.

NEUROMUSCULAR DISEASES

Arthur P. Hays, M.D.

NEUROMUSCULAR DISEASES

INTRODUCTION

- The Motor Unit
- Regeneration
- Classification of Neuromuscular Disease

PERIPHERAL NEUROPATHIES

- Myelinopathies
 - Guillain-Barre Syndrome
 - Chronic Inflammatory Demyelinating Polyneuropathy
 - Charcot-Marie-Tooth Disease
- Axonopathies
 - Wallerian Degeneration
 - Distal Axonopathies (Dying Back Neuropathies)

AMYOTROPHIC LATERAL SCLEROSIS (NEURONOPATHY)

DISEASES OF SKELETAL MUSCLE

- Neurogenic Disorders of Muscle (Secondary to Neuropathy or Diseases of the Motor Neuron)
- Myopathies
 - Duchenne Muscular Dystrophy
 - Inflammatory myopathies
 - Mitochondrial Diseases
 - Other Myopathies

INTRODUCTION

Neuromuscular diseases are caused by dysfunction of motor nerve cells, peripheral nerve and skeletal muscle. Weakness is the chief symptom, but peripheral neuropathies can also produce sensory and autonomic symptoms with or without motor dysfunction. The clinical findings can help classify patients with neuromuscular disorders (Table I), but they overlap. Therefore, diagnosis often requires serum creatine kinase activity, electrodiagnostic studies and biopsy of muscle or nerve (or both).

TABLE I: CLINICAL FEATURES AND LABORATORY TESTS IN NEUROMUSCULAR DISORDERS

	NEUROPATHY	MYOPATHY
Weakness	distal	proximal
Sensory loss	+	0
Diminished tendon reflexes	early	late
Serum creatine kinase	+/-	+++
CSF protein	may be elevated	normal
Electromyography	neurogenic	myopathic

The Motor Unit

Motor units consist of two major functional types, one composed of **fast-twitch** muscle fibers and the other **slow-twitch** fibers. The two different fiber types can be distinguished and visualized in tissue sections by histochemical stains. The histochemical stain for myosin ATPase is the standard method for evaluating fiber types in human neuromuscular disease [NM-12]. **Type I** fibers are pale in the ATPase reaction, **rich in mitochondria** and dependent on oxidative phosphorylation as a chief source of energy. The fibers **contract slowly** and resist fatigue with repetitive

contractions. Their major functions include maintenance of posture and prolonged, low-intensity motor activity as in jogging. **Type II** fibers are dark in the ATPase reaction and poor in mitochondria, and they use chiefly **anaerobic glycolysis** for generating energy. These fibers are recruited for use during vigorous motor activity such as sprinting or lifting heavy weights with maximal exertion. They **contract quickly** and fatigue more rapidly than type I fibers. In contrast to some mammalian species, each human muscle is composed of both fiber types, intermingled in a **mosaic** pattern in transverse sections stained for ATPase [NM-12]. The muscle fibers of a single motor unit are not grouped together but normally are distributed widely over a large area of muscle. All of the fibers of the unit have the same histochemical type, an expression of the capacity of motor neurons to determine muscle fiber type.

Regeneration

The **peripheral nervous system (PNS)** and **skeletal muscle** has substantial capacity to regenerate axons, Schwann cells and muscle fibers in response to injury. Two different forms of regeneration occur in the axons: 1) The well-known regenerative response of axons proximal to the site of axotomy. 2) Sprouting of terminal axons of intact motor units, a process that can be induced locally by denervation of neighboring muscle fibers. These axonal sprouts can grow and supply adjacent denervated muscle fibers, a phenomenon known as collateral reinnervation. Schwann cells and muscle satellite cells act as the cellular basis of regeneration of myelin sheaths and muscle fibers.

Classification of Neuromuscular Diseases

Major gaps exist in our knowledge of the etiology and pathogenesis of neuromuscular diseases such as inclusion body myositis, Guillain-Barré syndrome, and amyotrophic lateral sclerosis (ALS). As a result, classification of these disorders is based largely on which populations of cells are affected morphologically and clinically. Neuromuscular disorders have been separated into five general categories: myelinopathies, neuronopathies, axonopathies, disorders of neuromuscular transmission, and myopathies. The disorders discussed in this lecture have been selected to illustrate basic pathologic principles of disease in four of these major categories. Disorders of neuromuscular transmission, myasthenic syndromes, will not be discussed.

PERIPHERAL NEUROPATHIES

Neuropathies are disorders that primarily affect the PNS, which includes all neural processes, nerve cells, and their supporting elements that lie outside the entry and exit zones of the spinal and cranial nerve roots. The Schwann cells and their ganglionic counterparts, the satellite cells, further distinguish it from the central nervous system (CNS). Hence, the first and second cranial nerves are excluded, as they are extensions of the brain and are composed of cells of the CNS. Using this narrow definition, the

peripheral neuropathies do not include diseases of the motor neurons (for example ALS) because the cell body is a component of central neural origin. The distinction between motor neuron diseases and peripheral neuropathies is artificial, however, and overlap exists in the functional and structural features of both classes. For this reason, some investigators prefer to classify ALS and other motor neuron diseases as a form of neuropathy.

Symptoms and signs of peripheral neuropathy often begin **distally** in the extremities and later involve proximal regions of limbs if the disease progresses. The cause of the distal distribution is not understood in detail, but there is presumably more than one mechanism. If multifocal lesions of nerves are random, then the longer nerve fibers, which serve the distal region of limbs, have a greater probability of being affected than shorter fibers. Examples include the **axonopathy** of vasculitic neuropathy and the **myelinopathy** of Guillain-Barre syndrome. In **distal axonopathies** (dying back neuropathy), interference with axoplasmic flow may account for the greater dysfunction of the longest nerve fibers. This pattern of degeneration typifies many toxic, metabolic and genetic disorders of the PNS.

Myelinopathies

Guillain-Barré Syndrome (GBS)

GBS is an acute or subacute monophasic illness. The peripheral nerves of most patients are characterized by multiple foci of **segmental demyelination** (a myelinopathy) [NM-1] and **mononuclear inflammatory cell** infiltration of the peripheral nervous system. This disorder is believed to be an autoimmune disorder of myelin, often triggered by an acute respiratory or gastrointestinal infection (see below); the most common form of GBS is known as acute inflammatory demyelinating polyneuropathy (AIDP). More recently, neurologists identified an axonal variant of GBS in Mainland China; the disorder is uncommon in this country. The variant presents as an acute motor axonal neuropathy (AMAN) or an acute motor and sensory axonal neuropathy (AMSAN).

Epidemiological and clinical features: GBS is the most common acute or subacute neuropathy (0.6-1.9 cases/100,000 population worldwide). It occurs in people of all ages but is most common after the fourth decade. Two-thirds of patients suffer an acute infectious illness, often with influenza-like symptoms or diarrhea, one to six weeks prior to the onset of symptoms. Viruses (CMV, EBV, etc.) and *Campylobacter jejuni*, a bacterium that causes diarrhea, cause most of these infections. Other illnesses, surgery, and pregnancy can also precede the neuropathy. Most cases are sporadic, but several epidemics of GBS have been reported. In 1976, a large number of people in United States received swine influenza virus vaccine and developed a slightly increased risk of Guillain-Barré syndrome. This was widely publicized and created concern about subsequent

vaccination, but other flu vaccines have not been associated with this risk. No association with specific HLA haplotypes has been reported in most studies.

Sensory symptoms, often with pain, usually herald the onset of GBS. These symptoms are followed within hours by weakness in the lower extremities. The symptom spreads over hours and days to involve symmetrically the arms, trunk, face, and, occasionally, the extraocular and pharyngeal muscles. Weakness becomes the most important manifestation and requires ventilatory assistance in about one third of patients. Clinical signs of weakness are associated with depressed or absent deep tendon reflexes. Autonomic manifestations are common but are usually not prominent.

Clinical recovery usually begins two to four weeks after onset of symptoms and continues over the ensuing weeks or months. Plasmapheresis or intravenous gamma immunoglobulin quickens recovery. About 10% of patients die of their disease and another 15% have severe residual disability. A small percent develops a chronic or relapsing form of the illness (see below).

Laboratory: Cerebrospinal fluid shows elevation of protein in most patients at maximal weakness but may be normal during the first few days of illness. No pleocytosis is found in most patients except for patients who also have HIV infection. Electrophysiological studies of the PNS usually demonstrate **conduction block** of the nerve action potentials in the early stage and later display **slowed motor conduction velocity**.

Pathology: The chief histopathological features of nerve in AIDP consist of foci of perivenular infiltration with lymphocytes and monocytes associated with segmental demyelination of nerve fibers. Remyelination occurs later as the patient recovers [NM-1, 2]. Deposits of C3d (a fragment of the C3 component of complement) and membrane attack complex (C5b-9) have been observed on the outer (abaxonal) surface Schwann cell membrane of myelin sheaths during the early stage of the disease. This finding and high titers of circulating autoantibodies to myelin glycolipids supports the idea that AIDP is antibody-mediated.

Axons are spared relative to demyelination, but nerves often show Wallerian degeneration of mild degree. The cause of this axonal degeneration is not known, but possible mechanisms include a secondary or bystander effect of the inflammatory response or a direct antibody attack of axons as well as myelin sheaths (see below). The loss of axons is thought to be responsible for the residual weakness in 15% of patients who do not recover strength.

The earliest pathological event is the migration of lymphocytes across the walls of venules into the endoneurium, where they become "activated" and attract blood-borne monocytes. The monocytes, rather than lymphocytes, attack the myelin sheaths based on electron microscopic examination. The myelin sheath is stripped away and the myelin fragments are phagocytosed by the monocytes, acquiring the

morphological features of macrophages. After about one week, the Schwann cells begin to form new myelin sheaths along the denuded segments of axons based on studies of experimental animals. The new myelin internodes are generally shorter and thinner than those they replace [NM-2]. The conduction of action potentials in these nerve fibers is slower than normal but does not produce detectable weakness. Rather, weakness correlates with conduction block and axonal degeneration in this disorder.

The **axonal form of GBS** has been defined by pathological studies of the PNS. Peripheral nerves in these patients show axonal degeneration with little or no pathological signs of segmental demyelination. Deposits of C3d, C5b-9 and IgG have been observed on the axolemma, most pronounced at the nodes of Ranvier, in the initial phase of the disease. The monocytes first appear at the nodes and periaxonal space between the axon and the myelin sheath and are later associated with degeneration with subsequent removal of cellular debris. The axonal variant has a higher mortality and residual disability than AIDP.

Pathogenesis: The pathogenesis of the demyelinating form of GBS is not understood in detail, but an autoimmune response to myelin and axons is thought to be important because:

1. Experimental allergic neuritis (EAN) is induced by inoculation of animals with a homogenate of peripheral nerve myelin, purified myelin glycoproteins (P0, P2 or PMP22) or certain glycolipids (galactocerebroside, GD1b) together with Freund's adjuvant. The disorder resembles AIDP.
2. High titer circulating autoantibodies to myelin are found in patients during the active stage of disease. The autoantigens have not been identified in most patients with AIDP but a minority recognizes specific glycoproteins (P0, P2 or PMP22) or gangliosides (GM1, GD1b, galactocerebroside) of peripheral myelin.

GM1 ganglioside is also expressed in the axolemma. High titers of anti-GM1 and GD1a antibodies have been found in more than half of patients with the axonal variant of GBS.

3. The chemical structure of a carbohydrate group in lipopolysaccharide of *Campylobacter jejuni* closely resembles the oligosaccharide chains shared by GM1 and GD1a ganglioside, other glycolipids and glycoproteins. These findings suggest molecular mimicry acting through an immune response to the bacterium. The antibodies to the bacterium could then crossreact and attack carbohydrate epitopes of peripheral nerve myelin and axolemma.

4. Patients with GBS given plasmapheresis or intravenous gamma globulin recover more rapidly than untreated patients when therapy is started early in the course of the illness.

Chronic Inflammatory Demyelinating Polyneuropathy (Chronic Guillain-Barre Syndrome)

Chronic inflammatory demyelinating polyneuropathy (CIDP) resembles GBS, but differs in several respects:

1. The clinical course of CIDP is multiphasic (relapsing, or stepwise) or slowly progressive.
2. A recognized antecedent viral illness is uncommon in CIDP.
3. An association of CIDP with HLA haplotypes (A1, B8, DRw3, and Dw3) has been recognized.
4. Hypertrophic changes ("onion bulbs") may be present in peripheral nerves in CIDP.
5. The disorder responds to plasmapheresis and intravenous gamma globulin, but treatment with glucocorticoids is often recommended for long-term treatment because it is less expensive.

In CIDP, the peripheral nerve shows monocyte-mediated segmental demyelination and segmental remyelination resembling GBS. In addition, the nerve exhibits a characteristic structure known as an **onion bulb** [NM-3]. This structure consists of a remyelinated segment of a nerve fiber surrounded by one or more concentric layers of redundant Schwann cell processes, when viewed in transverse section [NM-3-5]. Onion bulbs are produced by repeated cycles of segmental demyelination and remyelination occurring over a period of months or years. Inflammatory cells are often sparse or absent in this disorder. The resemblance of CIDP to GBS suggests an antibody-mediated disorder, but analysis of serum has not demonstrated high titer autoantibodies to myelin in most patients.

Charcot-Marie-Tooth Disease (Hereditary Motor and Sensory Neuropathy, HMSN I and HMSN II)

Charcot-Marie-Tooth disease (CMT) is the most common hereditary neuropathy, a clinically and genetically heterogeneous disorder. The characteristic clinical features include an often childhood onset of weakness in distal leg muscles, very slow progression, atrophy of leg muscles (stork leg or inverted champagne bottle appearance) and foot deformity (pes cavus and hammer toes). The most frequent

type of CMT (type 1 or CMT I) consists of palpably enlarged nerves (**hypertrophic neuropathy**), slowed nerve conduction velocity and pathological features of a chronic myelinopathy including prominent onion bulbs. This disorder is usually inherited in an autosomal dominant pattern. Mutations of several different genes have been identified and linked to the syndrome to date. The most commonly affected gene encodes a major protein of peripheral myelin, known as PMP22. Most of the patients have a duplication of a 1.4 Mb sequence located on chromosome 17 resulting in three copies of the *PMP22* gene.

Axonopathies

Wallerian degeneration

If a nerve trunk is severed, conduction of an action potential distal to the site of transection fails in three to four days and both axons and myelin sheaths degenerate. During the first hour after transection, terminal loops of myelin retract causing the nodal gap to widen (paranodal demyelination). By two or three days, myelin sheaths and corresponding axons begin to separate into trains of myelin ovoids (myelin debris) [NM-6, 7]. **Macrophages** appear in large numbers derived largely from blood-borne monocytes. By the fourth day, Schwann cells begin to proliferate and line up within the tube formed by the basal lamina remnant of the degenerating nerve fiber. These longitudinal arrays of Schwann cells are known as the **bands of Büngner**. Myelin debris is slowly removed and, if regeneration is prevented, bands of Büngner are eventually replaced by connective tissue.

Within hours, axonal sprouts appear at the cut end of the proximal stump. If these regenerating axons reach the bands of Büngner, they then grow at an average rate of 1-2 mm per day within the old basal lamina sheath. Axonal contact with the proliferated Schwann cells inhibits further mitotic activity and induces the cells to form a series of new myelin internodes, which are shorter and thinner than normal internodes. More than one axonal sprout grows down a single band of Büngner, eventually producing a **regenerative cluster of thinly myelinated fibers** within the original basal lamina.

In comparison with remyelination, axonal regeneration is slow and often incomplete. The extent of functional recovery depends on the age of the individual and the degree to which the transected ends are approximated. The functional outcome is better at a distal site of transection.

During the first few days after transection of a motor axon, the body of the nerve cell begins to undergo **axonal reaction** or central chromatolysis. The cell swells, the contour becomes rounded, the nucleus migrates to the periphery, and Nissl substance becomes dispersed centrally leaving a peripheral rim of Nissl granules. The changes reach a maximum at two to three weeks after transection and persist

until regeneration is complete. If regeneration of axons is prevented, the cell body of the motor neuron will eventually disappear after months or years.

Distal axonopathies

Exogenous toxins, metabolic dysfunction and certain hereditary disorders often cause distal axonopathies. The onset of sensory dysfunction and weakness begins distally and progresses slowly. If toxic exposure or metabolic disorder can be recognized early and eliminated, progression can be reversed with gradual, often complete, recovery. Diabetic neuropathy is the most common form of neuropathy. It usually begins in the distal part of the lower extremities indicating that the disorder first affects the longest nerve fibers.

The pathologic changes consist of degeneration of the distal portion of an axon. The degeneration appears in teased myelinated fibers as a linear train of myelin ovoids, indistinguishable from Wallerian degeneration. The proximal surviving part of the axon often develops segmental demyelination and remyelination. The effect on the myelin sheath is presumably secondary to the abnormality of the axon. Exposure to acrylamide and hexacarbon solvents (n-hexane, methyl n-butyl ketone) produces a distal axonopathy associated with **accumulation of 10 nm neurofilaments** in axons of large myelinated nerve fibers. Similar pathological findings occur in the CNS.

How toxins cause neuropathy is not known, but abnormalities of axonal transport may cause preferential degeneration of the distal part of long or large diameter axons. Degeneration advances proximally (dying back phenomenon) until exposure to the toxic substance is eliminated and the axon is allowed to regenerate. If toxins affect the central nervous system as well, neurological deficits may persist after toxic exposure is eliminated, because of the limited capacity of the CNS to regenerate.

AMYOTROPHIC LATERAL SCLEROSIS (LOU GEHRIG'S DISEASE)

Clinical: This fatal disease usually begins in the fifth decade or later with fasciculations, progressive muscle weakness and wasting. Muscular cramping is common and often the initial symptom of illness. Weakness and wasting begins in one hand in a third of patients, but it can start in the shoulders or pelvic girdle, bulbar muscles, or elsewhere; eye muscles are nearly always spared. Spasticity may cause stiff gait. Hyperreflexia and sometimes Babinski reflexes may be observed on neurologic examination. As the disease progresses, other muscles become affected and the weakness becomes symmetrical.

Eventually, the patient develops quadriplegia, bulbar paralysis, and respiratory muscle failure. Death usually occurs two years to five years after onset of symptoms.

Pathology: There is widespread **loss of motor neurons** and fibrillary astrocytosis in ventral horns of the spinal cord [NM-8]. Depletion of nerve cells also takes place in the motor nuclei of cranial nerves V, VII, IX, X, XI, and XII, most commonly affecting the nucleus of the hypoglossal nerve. Motor nuclei of III, IV and VI are spared. The precentral gyrus has a reduction in the number of Betz cells as well. Degeneration of axons and myelin sheaths is found in the pyramidal tracts of the spinal cord [NM-9] and in ventral spinal nerve roots. The **degeneration of pyramidal tracts** is most pronounced at thoracic levels, but becomes progressively less severe at rostral levels and is often impossible to detect in pons and higher levels using routine myelin stains. This has suggested that amyotrophic lateral sclerosis (ALS) is a distal axonopathy of the CNS.

A small percent of the remaining motor neurons exhibits intracytoplasmic granular and filamentous inclusions, known as **skein-like inclusions**. These inclusions are composed of TDP-43, a TAR DNA-binding protein that regulates gene expression and splicing. The skein-like inclusions are usually ubiquitinated [NM-10]. TDP-43 is also expressed in inclusions and neurites in the most common form of frontotemporal dementia (see DEGENERATIVE DISEASE AND DEMENTIA in this syllabus). Focal **accumulation of 10 nm neurofilaments** is observed also in motor axons in spinal cord; these large swellings are known as axonal spheroids [NM-11]. The swellings resemble the accumulation of neurofilaments in the neuropathies caused by acrylamide and hexacarbons. Central chromatolysis of motor neurons is inconspicuous in patients with ALS.

Pathogenesis: The cause of motor neuron disease in most patients is not known. Postulated causes include toxins, viruses, and an autoimmune disorder. About 10% of patients with ALS are familial and some of them have been linked to point mutations of the gene for Cu/Zn superoxide dismutase. This form of ALS exhibits an autosomal dominant pattern of inheritance. Studies of the disorder suggest that the mutant enzyme has an unknown toxic (gain of function) effect on motor nerve cells. This gain of function hypothesis is consistent with the autosomal dominant pattern of inheritance. In addition, rare familial forms of ALS are caused by mutations of the TDP-43 gene (*TARDBP*).

DISEASES OF SKELETAL MUSCLE

Neurogenic Disorders of Muscle

Weakness and wasting of muscles are characteristic signs of motor neuron diseases and motor neuropathies, but the clinical features may be indistinguishable from the weakness that occurs in primary disease of muscle (myopathy). However, the pathologic findings in a muscle biopsy of a lower motor neuron disorder are so distinctive that they can be used for diagnosis. The cardinal features of neurogenic disorders (peripheral

neuropathies, radiculopathies, and motor neuron diseases) include groups of atrophic muscle fibers (**group atrophy**) [NM-14], groups of fibers of the same histochemical type (**fiber type grouping**) [NM-15], and **target fibers** [NM-16]. These pathologic alterations develop slowly over a period of weeks or longer. In most of these diseases, all motor neurons and motor axons are not affected simultaneously, but some of the nerve cells degenerate while others are spared. By comparison, interruption of all motor nerve fibers to a muscle, a common maneuver in experimental studies, causes atrophy of all fibers. In this case, the mosaic pattern of type I and type II fibers in ATPase stains are retained for weeks in the denervated state when regeneration of nerve is prevented.

Fiber type grouping and group atrophy of muscle fibers are believed to occur as a consequence of collateral reinnervation [NM-17]. By gradual remodeling of the motor unit, a single neuron can innervate many contiguous muscle fibers. Because the nerve supply determines the histochemical type of a muscle fiber, remodeling of motor units eventually yields fiber type grouping. If an axon of such an enlarged motor unit then undergoes degeneration, then the corresponding muscle fibers will undergo atrophy as a group.

Myopathies

The myopathies are disorders that exhibit muscle dysfunction without evidence of denervation. The cause of the disease may reside in the muscle fibers themselves, as in most inherited myopathies, or it may be extrinsic to muscle, as in the myopathies caused by various endocrine diseases. The muscle biopsy may show a selective atrophy of type 2 muscle fibers as the only abnormality in Cushing's syndrome, hyperparathyroidism and other disorders with muscle weakness. A large group of myopathies are characterized by necrotic fibers and regenerating fibers, and these abnormalities are attended by fibrosis of the endomysium when the disorder is chronic. Duchenne muscular dystrophy and inflammatory myopathies illustrate these alterations in the next two sections.

Duchenne Muscular Dystrophy

Clinical Features: Duchenne muscular dystrophy (DMD) is an **X-linked**, recessive disorder and the most common inherited myopathy of children. The affected gene in Duchenne dystrophy encodes a 427 kD protein known as **dystrophin**. The disease begins with progressive weakness of proximal limb muscles early in childhood. Affected children rise from the floor to an upright position by using his hands and arms to "walk" up his own body (Gower's sign) due to lack of hip and thigh muscle strength. Mild enlargement of calf muscle is usually observed. Patients become confined to a wheel chair by age 12, and they usually die by the middle of the third decade as respiratory muscles become progressively involved. Serum activity of **creatine kinase** is markedly elevated, even during infancy before the onset of clinical symptoms. A milder variant of the disease, known as Becker muscular dystrophy, is an allelic form of DMD.

Pathology: Muscle biopsy shows **necrotic muscle fibers**, groups of regenerating fibers, and hypercontracted (hyaline) fibers [NM-18]. As the disease progresses, there is excessive variation in muscle fiber size and increased fibrous connective tissue and adipose tissue. These nonmuscle tissues can eventually replace all of the muscle fibers at the end stage of disease.

Pathogenesis: Dystrophin has amino acid sequence similarities with alpha-actinin and spectrin suggesting that it is one of the cytoskeletal proteins. The protein is located chiefly at the surface membrane of muscle fibers. It is thought to link actin with the surface membrane and the extracellular matrix by binding and acting through a group of integral membrane glycoproteins. One of them, dystroglycan, binds to the major protein of the basal lamina protein (α 2-laminin or merosin). Dystrophin is absent or barely detectable in muscle fibers of DMD patients [NM-19], presumably interrupting the linkage of the cytoskeletal proteins to extracellular proteins. This idea is supported by mutations of genes that encode certain dystrophin-associated membrane glycoproteins, which produce a phenotype that can resemble Duchenne dystrophy or Becker dystrophy.

Serum levels of creatine kinase and other enzymes of muscle seem unusually high in Duchenne dystrophy in comparison to a rather low proportion of muscle fibers that have necrosis. This observation in the 1970's suggested that the function of the surface membrane is abnormally leaky. The membrane abnormality is thought to cause muscle cell dysfunction and death of muscle fibers, probably triggered by influx of extracellular calcium into the sarcoplasm.

Inflammatory myopathies

There are three major forms of inflammatory myopathy, namely, **polymyositis**, **inclusion body myositis** and **dermatomyositis** (Table II). Clinical findings and the muscle biopsy distinguish these three disorders. Polymyositis and dermatomyositis respond to glucocorticoids, but inclusion body myositis does not as a rule. Inclusion body myositis is the most common disorder in tertiary hospitals because it is refractory to treatment and is often referred to specialists.

TABLE II. INFLAMMATORY MYOPATHIES

DISEASE	AGE	GENDER	CLINICAL	BIOPSY	TREATMENT
Polymyositis	Adults	F > M	Proximal muscle weakness.	Random single fiber necrosis & regeneration; cytotoxic T cells in endomysium.	Glucocorticoids.
Inclusion body myositis	Adults	M >> F	Proximal muscle weakness with early onset distal weakness.	Similar to polymyositis but with fibrosis, rimmed vacuoles and congophilic inclusions.	No response to glucocorticoids or other immunomodulatory agents.
Dermatomyositis	Adults & children	F > M	Proximal muscle weakness; rash in face, chest & limbs; malignancy in 10% of adults.	Perifascicular atrophy; ; CD4+ T cells and B cells in perimysium; immune complexes in vessels; endothelial tubuloreticular aggregates.	Glucocorticoids, intravenous gamma globulin.

Polymyositis.

Clinical Features: Polymyositis is an acquired myopathy of adults. Women are affected more often than men. Weakness affects proximal limb muscles and sometimes accompanied by dysphagia. Symptoms progress slowly for several weeks or months. Serum creatine kinase (CK) activity is usually moderately elevated. A characteristic electromyogram helps to confirm the diagnosis. Most patients are treated with glucocorticoids and about 70% improve or recover. Patients with polymyositis do not have an increased risk of malignancy in most recent studies.

Pathology: Characteristic findings in the muscle biopsy include scattered necrotic fibers, regenerating fibers, and mononuclear inflammatory cells, chiefly lymphocytes [NM-20]. The inflammatory cells are located around muscle fibers and small blood vessels of the endomysium. There is little or no fibrosis as would be expected in a subacute disorder. Inflammatory cells are absent in about one third of biopsies and the muscle is normal in a few percent of them. These atypical biopsies might be a consequence of focal expression of pathologic changes in polymyositis. They might also occur because the syndrome is heterogeneous in etiology and includes cases that are not autoimmune.

Pathogenesis: The etiology and cause of muscle fiber necrosis in this disorder are not understood but is thought to be an autoimmune disorder.

Lymphocyte marker studies have indicated that most of the mononuclear cells in the tissue are cytotoxic T cells and express CD8. A few of the inflammatory cells invade muscle fibers before they become frankly necrotic. In addition, surface membrane of muscle fibers show widespread expression of major histocompatibility complex class I antigens (MHC class I antigens are normally undetectable in muscle fibers). These observations suggest that autoaggressive T cells cause the disorder.

Inclusion body myositis.

Clinical features: Patients develop slowly progressive weakness of proximal and distal muscles, especially the finger flexors. It is the most common myopathy in people over the age of 50, and most of them are men. Serum CK activity is normal or mildly elevated. The electromyogram resembles that of polymyositis. The disorder usually does not respond to glucocorticoids or other immunomodulating agents.

Pathology: The muscle biopsy findings resemble those of polymyositis, but they show the pathology of a chronic disorder including prominent fibrosis of the endomysium. The muscle fibers display vacuoles that contain basophilic granules at the periphery (rimmed vacuoles). These vacuoles are not specific but are absent in polymyositis or dermatomyositis. Eosinophilic inclusions are present in some vacuoles and are weakly congophilic and require fluorescence to amplify the staining signal using filters for rhodamine and Texas red. Electron microscopic examination reveals that the amyloid inclusions are composed of abnormal filaments with a paired helical filament substructure. The inclusions are diagnostic of this disorder.

Pathogenesis: The pathogenesis of this disorder is not understood. Cytotoxic T cells predominate in the endomysium and occasionally invade myofibers with otherwise normal structure. Muscle fibers also express MHC class I antigens. Although these features suggest a T cell-mediated disorder, it is not clear why patients do not respond to immunosuppression. The inclusions are composed of the β -amyloid peptide, tau and other proteins found in Alzheimer's disease. There was no association between these two disorders in one epidemiological study.

Dermatomyositis.

Clinical features: Dermatomyositis resembles polymyositis clinically, but patients also develop a characteristic rash over the nose, cheeks, chest and extensor surfaces of the limbs. Muscle aches and tenderness may occur. Females are affected more commonly than males; the disorder occurs in both children and adults. About 10% of patients over the age of 40 develop a

malignancy. The neuromuscular disorder responds to glucocorticoids, other immunosuppressive agents and intravenous gamma globulin.

Pathology: The muscle biopsy exhibits atrophy of muscle fibers along the periphery of muscle fascicles (perifascicular atrophy). Some biopsy samples show necrotic and regenerating fibers, also predominating at the edge of muscle bundles. Lymphocytes and a few plasma cells infiltrate chiefly the perimysium. Markers indicate that most of the lymphocytes are B cells and CD4-positive helper T cells. The main target of the disorder is the blood vessel. These show immune complexes of immunoglobulins and membrane attack complex in vascular walls. Electron microscopy demonstrates ultrastructural evidence of endothelial cell injury and tubuloreticular aggregates. These endothelial inclusions are composed of smooth endoplasmic reticulum and are found in certain other disorders (systemic lupus erythematosus and HIV infection).

Pathogenesis: The pathology of dermatomyositis suggests an antibody-mediated disorder that injures blood vessels and results in ischemic injury of muscle fibers. No target antigen has been identified for this disorder or any of the other inflammatory disorders. The hypothesis that the disorder is caused by autoantibodies is supported by the response of patients to intravenous gamma globulin.

Mitochondrial Diseases

Inherited defects of mitochondrial metabolism are an uncommon but conceptually important group of disorders. Historically, diseases of muscle were recognized first and designated as **mitochondrial myopathies**, but others affect the CNS as well as muscle and are known as the **mitochondrial encephalomyopathies**. The nervous system, skeletal muscle, heart, kidney and other organs can be affected in different combinations as part of a multisystem disease.

Nuclear DNA (nDNA) encodes most mitochondrial proteins, but **mitochondrial DNA (mtDNA)** specifies thirteen of the 80 or so polypeptide subunits of the electron transport chain. The inherited diseases of mitochondria (mitochondrial cytopathies) can be classified genetically into two broad groups, defects of nDNA and defects of mtDNA. Point mutations, deletions and duplications of mtDNA have been identified and linked to several syndromes of the mitochondrial encephalomyopathies.

The diseases of mtDNA defects have a **maternal pattern of inheritance** in contrast to the Mendelian pattern produced by nDNA mutations. All of the mtDNA of the zygote are derived from the oocyte. Each cell has many mitochondria, and each organelle contains several copies of the mitochondrial genome. If some copies of the mtDNA of a zygote have a mutation, they are passed randomly to subsequent

generations of cells. At birth or later, it is probable that rare cells would contain only mutant genomes (**mutant homoplasmy**) and others would have only normal genomes (**wild-type homoplasmy**). Most cells would receive a mixed population of mutant and normal mtDNA (**heteroplasmy**). If the mutation is deleterious, it can result in dysfunction depending on the balance between mutated and wild type genomes. Clinical expression correlates with the percent of mutant genes in the affected tissue. This finding indicates that the proportion of mutated mtDNA must exceed a threshold to cause clinical dysfunction.

The pathological signature of an mtDNA mutation is accumulation of mitochondria in muscle fibers. The excessive organelles are expressed as aggregates of reddish granular material in the sarcoplasm demonstrable by the modified Gomori trichrome stain [NM-21], compared with normal muscle in [NM-13]. The abnormality has been termed a **ragged red fiber** because of the irregular contour of the reddish deposits at the fiber periphery. Deletions and point mutations of mtDNA in these diseases often impair the activity of complex IV (**cytochrome c oxidase** or COX), a multiunit protein that is encoded in part by mtDNA. Histochemical stains for ragged red fibers are often deficient for COX activity. By contrast, the ragged red fibers stain intensely for **succinate dehydrogenase** (complex II or SDH) [NM-21], a complex that is exclusively encoded by nDNA. The increased activity of SDH reflects the proliferation of mitochondria, which is one of the many proteins that are synthesized in the cytoplasm and imported into the mitochondrion. The impairment of oxidative/phosphorylation causes dysfunction of myofibers. Death of nerve cells and astrocytosis occurs in the CNS.

Other Myopathies

Muscle biopsy has a particularly important role in diagnosis of infants with hypotonia. Several rare myopathies have morphologically distinctive features; examples include the rod bodies in nemaline myopathy and the central sarcoplasmic lesions of central core disease [NM-22]. The pathologic findings separate these rare, relatively benign, autosomal dominant disorders from Werdnig-Hoffman disease, a fatal autosomal recessive disorder of motor neurons in infancy [NM-14].

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**The Patient with Visual Loss:
Localization of Neuropathologic Disease and
Select Diseases of Neuropathologic Interest**

Steven A. Kane, M.D., Ph.D.

**The Patient with Visual Loss:
Localization of Neuropathologic Disease and
Select Diseases of Neuropathologic Interest**

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The Edward S. Harkness Eye Institute

key: nasal = medial, temporal = lateral

Ocular anatomy and understanding the localization of neurologic disease

Beside the eyes and extra-ocular structures the visual system occupies a seemingly disproportionate representation in the central nervous system. Visual loss can be understood by combining neuropathologic disease principles with knowledge of ocular embryology and anatomy.

Slide 1 The study of a shared embryology forms the basis for the subspecialty neuro-ophthalmology. The optic stalk, an outpouching of the neural tube, begins to resemble the extra-cranial afferent visual system after the first month of gestation. The bulbous ending of this stalk invaginates, creating an apex-to-apex arrangement of epithelial cells derived from inner and outer layers. Eventually all of the layers of the eye, including the 10 layers of the retina, will form from these cells. The outer layer cells become the outer layers of the globe and retina. The inner layer cells become the inner layers of retina including the ganglion cell layer where the cell bodies of the optic nerve reside. The axons of these ganglion cells travel between their cell bodies and the posterior hyaloid of the vitreous body to exit the eye through the lumen of the optic stalk and form the optic nerve.

Slide 2 Nowhere in the human body does function depend so critically on anatomy. The unique aspect of sensory transduction made possible by the eye, the end organ of the afferent visual system, is optics. Neuro-transduction occurs in the retina and neuro-transmission occurs in the optic nerve.

Slide 3 The anatomy of the ocular fundus, also known as the posterior pole, should be well known to all physicians. Features of the ocular fundus important for the majority of systemic diseases can be appreciated by appropriate use of a direct ophthalmoscope. The cross section of the optic nerve, the optic disc, is located 15 degrees nasal to the line of sight. There are normal ranges of its color, contour, and vascular arrangement. The retinal vessels leave the optic disc and permit localization of the transparent retina. The macula is the part of retina permitting normal central vision and reading. Histologically the macula is the portion of retina where the ganglion cell layer is more than one cell body thick. Clinically the macula is found between the branching temporal vascular arcades. The surface contour of the foveal depression in the center of the macula creates characteristic light reflections. The red-orange luminance of the ocular fundus comes from the underlying retinal pigment epithelium and the more posterior choroid, a thick blood filled layer of loosely organized vessels.

Slide 5 An enhanced appreciation of the optic nerve can be gained by studying axon bundles in the nerve fiber layer of the retina during direct ophthalmoscopy. Axons of the temporal ganglion cells branch around the fovea before entering the superior and inferior rims of the optic disc. They do not cross the horizontal raphe. The group of axons transmitting information from foveal cones linearly into the temporal rim of the optic disc is called the papillomacular bundle.

Slide 6 Each optic nerve carries all of the visual sensory information from the ipsilateral eye. The fovea divides the visual world into right and left. Axons of ganglion cells nasal to the macula cross the midline at the optic chiasm. Each downstream optic tract contains nearly equal mixtures of nasal and temporal retinal ganglion cell axons and carries information about the contralateral hemianopic portion of the visual field. Downstream from this right and left sided spatial segregation of visual information the optic nerve axons synapse in the lateral geniculate where information is further segregated. This physiologic segregation includes separation of visual information according to motion and contrast sensitivity. The thalamic axons form the optic radiations where information from the visual world is further spatially segregated before entering the visual cortices.

Slide 7 The pattern of visual loss may localize the lesion to the eye, optic nerve, optic chiasm, optic tract, thalamus, optic radiation, or visual cortices. The disease course and accompanying symptoms may clarify its nature. For example, vascular compromise usually produces sudden visual loss. Inflammatory disease usually produces subacute visual loss. Compressive processes usually produce slow, gradual visual loss.

Slide 8 The pattern of visual loss can be described by visual field testing ranging from simpler confrontation techniques such as finger wiggling or finger counting to computer directed quantitative threshold determination at multiple sites that can be followed with established statistical methods. The results of perimetry are described in polar coordinates. The origin represents the point of ideally constant visual fixation. A scotoma is an area of the visual world where detection of a stimulus is more difficult or impossible. The symmetry and pattern of scotomas reflect the disturbance along the afferent visual pathway and thereby localize the lesion.

CATARACTS

Slide 9 Significant undiagnosed refractive errors and media opacities such as **cataract** cause diffuse depression of the visual field, similar to looking through a dirty window. The effects of retinal and optic nerve lesions can be predicted from known anatomy. The severity of potential causes of impaired vision ranges from sub-clinical signs to no light perception.

Slide 10 Any physician caring for children needs to be able to interpret the **red pupillary reflex** elicited by a direct ophthalmoscope or, as in this photograph, by a camera flash. Also known as the **Bruckner reflex**, this optical effect gives valuable information about the eye's optics and the health of the posterior pole. Identify the sister with bilateral cataract.

Slide 11 An ominous cause for loss of the Bruckner reflex in a child less than 4 years old is **retinoblastoma**, a neoplasia of photoreceptors that is the most common intraocular malignancy in children. **The most common presenting signs of retinoblastoma are acquired leukocoria, e.g. white pupil, and sensory strabismus.** A family history of this disease is highly valuable for screening purposes. The responsible gene and mutations are well studied. Metastatic spread occurs along the optic nerve. Early detection can lead to curative treatment.

Slide 12 The pathologic signature of this tumor is the **Flexner-Wintersteiner rosette**, small tubules comprised of neoplastic photoreceptors. Tumors can be subretinal or preretinal with vitreous seeding.

RETINAL CAUSES OF IMPAIRED VISION

Slide 13 **Retinal causes of visual loss** include **vascular, inflammatory, infectious, and structural diseases.** In rhegmatogenous retinal detachment a hole in the retina allows fluid to enter and accumulate in the subretinal space. Visual loss can be sudden or gradual and is often painless. Signs of retinal disease include hemorrhage, infarction, exudation of large proteins from the vascular compartment, and elevation of the transparent retina. All physicians should have familiarity with common retinal causes of visual loss. Age-related macular degeneration occurs in two forms. The “dry” form causes slow, gradual visual loss and is accompanied by atrophy of the retinal pigment epithelium. The “wet” or exudative form causes visual distortion followed by rapid, marked visual loss and is accompanied by proliferation of abnormally friable neovascular tissue in the subretinal space, exudation, bleeding, scarring, and photoreceptor wipeout. Neither form is associated with swelling of the optic disc. Diabetic retinopathy and hypertensive retinopathy result in damage to the retinal vascular compartment and will be described below.

Slide 14 The **symptoms of optic nerve disease** are **blurred vision**, either involving central vision or peripheral vision, **dimming of vision with secondary decreased pupillary response to light, decreased color perception**, and characteristic patterns of **visual field loss**: centrocoecal and arcuate scotomas, the former usually quite symptomatic and the latter often asymptomatic.

Slide 15 **Centrocoecal scotoma** is a horizontally oval blind spot that includes the visual representations of the fovea (the point of fixation), the optic disc (the physiologic blind spot), and retina beneath the papillomacular bundle (the connecting area of visual field). This scotoma is caused by loss of function of axons in the papillomacular bundle.

Slide 16 During direct ophthalmoscopy with a white light, the centrocoecal scotoma is accompanied by pallor of the optic disc most conspicuous along its temporal rim. This pallor represents atrophy of axons with corresponding visible loss of capillary support. There is prominence of the retinal vessels, particularly along the path of the papillomacular bundle and within the macula, giving the retina a crinkly appearance.

Slide 17 During direct ophthalmoscopy with a green (red-free) light, visualization of the nerve fiber layer is enhanced and the fundus appearance becomes clarified. As

determined after the first month of gestation, axons in the nerve fiber layer of the retina travel anteriorly over the ganglion cell layer, joining to exit the eye as the optic nerve. Loss (atrophy) of bundles of axons creates ruts in the retinal surface parallel to the orientation of these axons. Significant atrophy of nerve fiber layer and ganglion cells causes the internal limiting layer of retina to drape over the remaining retinal vessels onto the underlying inner plexiform layer of retina, giving the retina a crinkly appearance along the papillomacular bundle and within the macula.

Optic atrophy is a clinical sign of disease affecting the nerve fiber layer and optic disc accompanied by functional loss. It is not a diagnosis but is a common sign shared by a myriad of diseases.

Slide 18 Axons in the papillomacular bundle are very sensitive to metabolic insults, both endogenous and exogenous from and demyelinating disease. Bilateral symmetric, chiefly temporal optic atrophy suggests one of these disorders. Dominant optic atrophy can occur in successive generations or spontaneously. Leber's hereditary optic atrophy is associated with a mitochondrial enzyme mutation and causes sudden visual loss in otherwise healthy young people.

Slide 19 Unilateral optic atrophy suggests diseases of **ischemic, compressive, and inflammatory origins**. Interruption in the vascular supply of the optic nerve creates cranial nerve paresis with sudden painless onset of symptoms. Compressive optic neuropathy is accompanied by slow, often insidious and painless visual loss. Inflammatory conditions are often accompanied by pain exacerbated by eye movement. The optic nerve is surrounded by the origins of the four rectus muscles at the orbital apex. Trigeminal receptors in the inflamed perineural tissues can be stimulated by muscle activity and globe palpation.

Slide 20 Anterior ischemic optic neuropathy is accompanied by **sudden, painless visual loss** due to **infarction of the optic disc**. Pallid disc swelling evolves into atrophy 4-6 weeks later, a time course typically consistent with ganglion cell soma death following axon damage (Wallerian degeneration). Idiopathic anterior ischemic optic neuropathy is associated with an anatomically crowded optic disc.

Slide 21 Giant cell arteritis is an important cause of one of the few ophthalmic emergencies, **sudden painless visual loss**, because it is treatable, not necessarily to regain the vision in the affected eye but to preserve vision in the other eye. It is a **subacute, granulomatous disease** affecting the arteries in several organ systems. Visual loss usually occurs from central retinal artery or ophthalmic artery obstruction. Knowledge of the early non-ophthalmic symptoms as well as the emergent nature of sudden painless visual loss is important for any physician who cares for the elderly. As in all diseases, early detection can decrease morbidity and mortality.

Giant cell arteritis is also called **temporal arteritis** because the temporal artery is often exquisitely tender when involved and is the most common artery biopsied to confirm the presence of this systemic disease. Neuropathologic signs are panarteritis, intimal

hyperplasia, and fragmentation of the internal elastic lamina associated with multinucleated giant cells.

Slide 22 Compressive optic neuropathy such as due to meningioma is usually accompanied by insidiously slow, painless visual loss with progressive enlargement of scotomas. The appearance of the optic disc lags behind tumor enlargement.

Slides 23-24 Inflammatory optic neuropathy is usually associated with **optic nerve demyelination** and **pain exacerbated by eye movements**. Subacute visual loss can range from subtle symptomatic loss of central vision (acuity) or asymptomatic loss of peripheral vision to no light perception. Disease in children is often bilateral with visible swelling of the optic discs. Disease in young adults is often unilateral and associated with inflammation of the retrobulbar myelin sheaths as best seen during T1-weighted orbital MRI with fat suppression following injection of gadolinium. These people initially have normal appearing optic discs, hence the statement, “Optic neuritis is a disease when the patient sees nothing and the internist sees nothing.” The presence of white matter plaques during brain MRI correlated with eventual diagnosis of multiple sclerosis during the Optic Neuritis Treatment Trial.

Slide 25 Optic atrophy is a **common end sign of many diseases** purely ocular as well as systemic. As we have seen, sometimes the pattern of atrophy and visual loss can suggest a diagnosis or localize the lesion. However a diagnosis is best considered by all of the “company” a sign does or doesn’t keep.

Slide 26 Glaucoma describes many different diseases characterized by **elevated intraocular pressure** and **optic atrophy** associated with **saucerization of the optic disc**. Acute pain, red eye, and visual change associated with corneal edema producing halos around lights characterizes acute angle closure glaucoma, an ophthalmic emergency. The most common type of glaucoma, chronic open angle glaucoma, is a leading cause of blindness. Elevated intraocular pressure creates an “intraocular compressive optic neuropathy” with initial loss of axons usually predominantly entering the optic disc at its superior and inferior poles resulting in vertical elongation and saucerization of the optic disc cup. The usual pattern of early visual loss is therefore arcuate scotoma reflecting damage to these axon bundles that branch around the fovea.

Slide 27 Retinal degeneration, like optic atrophy, is a **sign with many causes**. Retinal vascular narrowing is the earliest sign of this disturbance of outer retinal layer or retinal pigment epithelium function. Also known as pigmentary retinopathy, retinal degeneration is accompanied by release of pigment from damaged retinal pigment epithelial cells that can migrate into the retina, appearing as focal pigment aggregates or larger “bone spicules.” Pigmentation within the intact retinal pigment epithelium can be irregular. Causes include genetic, neurodegenerative, and toxic disorders.

Slide 28 Obstruction of the central retinal artery, usually due to embolic or inflammatory disease, causes sudden complete loss of vision and infarction of the inner retina. The outer retina receives its oxygen supply from the underlying choroid by passive

diffusion and survives. The retinal pallor surrounds residual hyperemia beneath the fovea where only cones and glial Muller cells, components of outer retina, survive. Central retinal artery obstruction is one cause of the “cherry red spot” sign. Recanalization of the obstructed vessel often occurs, leaving a fundus with ghost vessels, vascular narrowing, and optic atrophy.

PAPILLEDEMA

Slide 29 Papilledema refers to optic disc swelling specifically due to increased intracranial pressure. Causes of elevated intracranial pressure include structural, neoplastic, inflammatory, hemorrhagic, thrombotic, and infectious disorders. The earliest sign of papilledema is increased hyperemia of the optic disc and obliteration of the optic disc cup.

Slide 30 Papilledema develops when increased intracranial pressure causes distension of the subarachnoid space leading to centripetal rotation of the meninges and scleral canal, effectively choking the optic disc. There is **stasis of axoplasmic flow and swelling** of neuropil.

Slide 31 Swelling of the optic disc with hemorrhages, exudates, and vascular distension can be marked as in this obese 12-year-old boy with idiopathic intracranial hypertension. Acuties were initially 20/200 because of submacular fluid. Despite treatment final acuities in the presence of optic atrophy were 20/30 OD with near total wipeout of peripheral vision and counting fingers OS.

Slide 32 In addition to elevated intracranial pressure, swelling of the optic discs occurs in the presence of **inflammatory, ischemic, thrombotic, infiltrative, and hypertensive diseases**. There are also normal variants of optic disc structure that create the appearance called pseudo-papilledema.

Slide 33 The remaining types of visual field loss as illustrated in figures B-H can now be understood with knowledge of visual system anatomy from optic chiasm to visual cortices. Visual field test results in figures B and C reflect chiasmal disease. Each example has temporal arcuate field loss due to involvement of nasal retinal axons that cross the midline in the chiasm. Figure B occurs when a single lesion involves all of the superior fibers of the right intracranial optic nerve and its inferior nasal fibers that begin to cross the midline just as they enter the chiasm. Figure C, bitemporal hemianopia, occurs when the nasal crossing fibers in the chiasm are asymmetrically involved.

CHIASMAL, OPTIC TRACT AND OTHER VISUAL PATHWAY LESIONS

Slide 34 Lesions of the chiasm are usually compressive. Inflammatory disease such as sarcoidosis can also cause isolated chiasmal syndromes.

Slide 35 Optic tract syndromes and lesions downstream along the visual pathway cause homonymous hemianopia, visual field loss through each eye restricted to the same side of the visual world. Congruity refers to the degree of symmetry of homonymous field loss between eyes. For example, complete congenital absence of an optic tract causes

completely congruous homonymous hemianopia. Its detection is often incidental in adults. Acquired homonymous hemianopic field loss due to optic tract disease is usually grossly incongruous. For example, a left optic tract syndrome typically can cause nearly complete right-sided homonymous visual field loss through the right eye with incomplete right-sided homonymous field loss through the left eye. This pattern of field loss is termed incongruous and results because axons forming the optic tract are still relatively spatially segregated according to right and left eyes, hence a small lesion can affect axons from one eye more than axons from the other eye. Because of this spatial segregation of visual information, optic tract lesions can be associated with mild asymmetry in pupillary responses to light. Etiologies are usually structural or vascular, most commonly neoplasia in children and vascular compromise in adults.

Slide 36 We can now appreciate that the completely congruous homonymous hemianopic visual field loss in figure D has limited localizing value. This pattern can result from large optic tract lesions that encompass all axons from each eye as well as from smaller lesions in the optic radiations where there is homogeneous mixing of axons carrying information from each eye to the level of individual ocular dominance columns. Localization in the presence of such congruity is accomplished by combining the pattern of visual loss with other deficits such as somatosensory or motor loss. Figure E is an example of incongruous homonymous hemianopia.

Figures F-H are typical of lesions affecting the temporal, parietal, and occipital lobes. The lesion in Figure F involves the right optic radiation beneath the temporal lobe. The lesion in Figure G is due to watershed infarction following cardiac arrest at the right parietal-occipital junction with sparing of the macular representation. The lesion in Figure H is bilateral, asymmetric homonymous hemianopia with central macular preservation following bilateral infarction in the posterior cerebral artery circulations.

OPHTHALMOLOGIC SIGNS OF SYSTEMIC DISEASE

Slide 37 The study of the eye with a magnifying glass and direct ophthalmoscope creates opportunity to directly observe the more invisible pathology present within other organ systems. **Copper** released from liver associated with **Wilson's disease** does not only end up in **peripheral Descemet's membrane as Kayser-Fleischer rings**. It becomes deposited throughout the body with early symptoms usually associated with predilection for deposition in basal ganglia.

Slide 38 The description "**cherry red spot**" is not specific for acute retinal infarction immediately following central retinal artery obstruction. Storage material accumulates within retinal ganglion cell bodies in several metabolic **lysosomal disorders**. Because the ganglion cell layer is normally thickened in the macula, these distended cell bodies create a visible perifoveal opacification of the otherwise transparent retina. The prominence of the normal choroidal vasculature beneath the fovea is also described as a cherry red spot.

Slides 39-40 Diseases causing **pigmentary retinal degeneration** share the disturbance of pigment within retinal pigment epithelium cells as well as migration of pigment from devitalized cells into the retina.

Slide 41 Several neurodegenerative diseases are associated with optic atrophy. Many of these are typically called “white matter diseases” or leukodystrophies.

Slide 42 The clinical signs of **diabetes** are protean. Examination of the retinal vasculature reveals the extent of disease. **Microaneurysms**, tiny ectasias in capillary walls that develop after pericyte death, are the earliest clinical sign. **Exudation of serum proteins** and **hemorrhage** occur with moderately advanced disease. In advanced disease damaged portions of the capillary bed become nonperfused. Ischemic retina produces angiogenic factors that promote growth of fragile neovascular tissue that bleeds, scars, and disturbs ocular anatomy and function. Similar compromise of the optic disc called **diabetic papillitis** results in swelling of the optic disc. **Neovascular glaucoma** develops when peripheral iris becomes scarred to peripheral cornea thereby blocking access of aqueous humor to the trabecular meshwork. Fluctuating serum glucose levels cause similar fluctuations in aqueous humor with correspond swelling and shrinkage of the crystalline lens leading to **cataract** formation.

Slide 43 The signs of **hypertensive disease** are also protean. The earliest sign in the retinal vasculature is **arteriolar narrowing** because of auto-regulation and arteriolar spasm. **Hemorrhage, exudation** of large serum proteins, **choroidal infarction**, and **swelling with eventual infarction of the optic disc** can occur when the normal mechanisms of auto-regulation are overwhelmed.

Slide 44 The **phacomatoses**, disorders characterized by **hamartomas**, abnormally organized masses of tissue normally found in that area of the body, often have ophthalmic involvement. **Neuro-fibromatosis type I** can involve skin, bone, brain, and viscera. **Lisch nodules, tiny hamartomas within the iris stroma** best detected with a slit lamp, are visually insignificant but diagnostically important. When present, visual loss is usually associated with the presence of optic nerve glioma, a typically indolent tumor.

Slide 45 **Tuberous sclerosis** is characterized by hamartomas in skin, kidney, eye, brain, and heart. Hamartomas in the brain are often called **tubers**. The most disabling feature of this disease is epileptic encephalopathy. **Retinal astrocytoma** is a highly specific sign of this disease in yet asymptomatic infants.

Slide 46 **Sturge-Weber syndrome** is defined by cutaneous vascular anomaly usually in the V1 dermatome (“port-wine stain”), **childhood glaucoma**, and leptomeningeal angioma associated with epileptic encephalopathy.

Slide 47 **von Hippel-Lindau syndrome** is defined by **angiomas and capillary hemangioblastomas in retina, brain, and viscera**. The inheritance, dominant with incomplete penetrance, can alert the physician to the possible effects of hemorrhage and exudation from these lesions. It is a cause of non-rhegmatogenous retinal detachment.

Slide 48 **Wyburn-Mason syndrome** is associated with a dramatic fundus appearance with potential involvement of orbit, nasopharynx, and midbrain. There is vascular

prominence in the fundus because of high flow shunting of blood due to the absence of an intervening capillary bed (**arteriovenous malformations**). The ophthalmologist's recognition that a potentially life threatening arteriovascular malformation in the midbrain may exist is critical.

Slide 49 In summary, visual loss can be understood when knowledge of neuropathophysiology is combined with knowledge of ocular embryology and anatomy. The pattern of visual loss may identify the lesion site. The disease course and accompanying symptoms may clarify its nature.

TRAUMATIC DISEASES

Andrew J. Dwork, M.D.

MECHANISMS OF BRAIN INJURY

ANATOMIC CONSIDERATIONS

INJURIES OF THE SCALP AND SKIN

Contusion
Laceration
Cut
Gunshot

INJURIES OF THE SKULL

Fracture
Gunshot Wound

MENINGEAL HEMORRHAGES

Subarachnoid
Epidural
Subdural
 Acute
 Chronic

TRAUMATIC LESIONS OF THE BRAIN

Contusion
Hemorrhage
Diffuse Axonal Injury
Concussion
Laceration
Gunshot Wound

COMPLICATIONS OF HEAD INJURY

Infection
Post Traumatic Epilepsy
Cerebral Swelling
Cerebral Hypoxia

SPINAL CORD TRAUMA

Anatomic Considerations
Direct Injuries
Indirect Injuries
Complications

I. MECHANISMS OF BRAIN INJURY

The mechanisms by which trauma to the head produces injury to the brain can be placed into five categories:

1. Mechanical damage produced directly by the traumatizing force
2. Space occupying accumulations of blood
3. Infection
4. Swelling of brain
5. Ischemia

II. ANATOMIC CONSIDERATIONS

The adult skull is rigid but not entirely inflexible. An impact may cause considerable momentary deformity. Fractures are probably preceded by extreme degrees of such deformity.

Certain parts of the skull are relatively fragile: the squamous portion of the temporal bone, the orbital roof (floor of anterior fossa), and the portions of the base of the skull that are perforated by foramina. All of these portions are particularly susceptible to fractures, and the first two are also susceptible to direct penetration by sharp instruments. The skull forms a protective shell for the brain. The brain can move within this shell, but its movement is damped by the cerebrospinal fluid (CSF) in the subarachnoid space.

Movement of the brain is restricted at the brain stem by its continuity with the spinal cord, and to a lesser extent along the falx cerebri by the attachment of bridging veins and arachnoid granulations to the superior sagittal sinus.

The epidural and subdural spaces are potential spaces. The epidural space contains the middle meningeal artery, which runs in a groove on the inner surface of the squamous portion of the temporal bone. The subdural space is traversed by the so-called "bridging veins," which drain into the dural venous sinuses. Most of these extend from the superomedial edge of the cerebral hemispheres to the superior sagittal sinus. The falx cerebri forms an incomplete barrier between the right and left sides of the subdural space. The subarachnoid space, containing the blood vessels feeding and draining the brain, is highly vascular.

The scalp hair often completely obscures injuries. It must be shaved if wounds to the scalp are to be examined properly.

III. INJURIES TO THE SCALP AND SKIN

Scalp or skin wounds are classified as follows:

A. Contusion

A blunt wound resulting in soft tissue hemorrhage. The hemorrhage may be visible externally (as a “black and blue mark”) or may be evident only after dissection. Over the course of days, the hemorrhage gradually assumes a greenish-yellow color and may also move to a more dependent position.

B. Laceration

A tearing of tissue by stretching during a blunt impact. The edges may be fairly sharp but are generally irregular. The tear is often surrounded by a collar of abrasion and may also be accompanied by contusion. The definitive evidence of laceration, distinguishing it from a wound produced by a sharp instrument, is the presence of strands of tissue extending across the tear from one edge to the other. This phenomenon, known as “bridging,” is often subtle. It is best appreciated at the ends of the wound or in its deepest portions.

C. Incised, Cut, and Stab Wounds

These are wounds caused by sharp edged objects such as knives, scissors, and broken glass. The wounds produced a slit shaped defect with sharp edges, at least one sharp end, no bridging, and little or no surrounding abrasion. Retraction of the skin often gives the defect an ovoid shape.

D. Gunshot Wounds

The descriptions here refer to gunshots but other high velocity projectiles occasionally produce similar injuries. Wounds of entrance in the skin or scalp generally consist of a circular perforation surrounded by a collar of abrasion. Certain features of the entrance wound may indicate the range, i.e., the approximate distance of the muzzle from the skin at the time of firing. A contact wound (muzzle in contact with skin) is indicated by the presence of soot and unburned gunpowder within the perforation. Contact wounds in the scalp often have a stellate shape due to marginal lacerations produced by hot gasses spreading between the scalp and skull. A close range wound is characterized by stippling of the skin around the bullet hole. This stippling is caused by superficial penetration and burning of the skin by grains of powder, which may not remain in place. At very close range, the gunshot wound may also be surrounded by soot.

An exit wound is generally slit-shaped or stellate and is not surrounded by an abrasion collar. It is generally larger than the corresponding entrance wound. The shape and larger size are caused by deviation, as the bullet loses energy, of its major axis from its path of flight, and often also by deformity of the bullet.

IV. INJURIES TO THE SKULL

The principal injuries to the skull are fractures and gunshot wounds although stab wounds and chopping wounds (wounds produced by sharp, heavy objects) are sometimes encountered.

A. Fractures are depressed or linear.

1. Depressed fractures

Depressed fractures are generally caused by hard objects of small surface area (hammer, doorknob). The inner table of the skull is displaced inwards in the fractured area. The underlying dura mater may be lacerated. Depressed fractures may cause local injury or irritation to the brain and generally require surgical treatment.

2. Linear fractures

Linear fractures are generally caused by collision of the head with a broad surface. They may involve the vault of the skull or its base. Fractures of the base produce a risk of infection from air sinuses. The granulation tissue that initially fills the fracture is an incomplete barrier against infection, so the risk persists until the fracture is healed. Fractures are termed simple if the overlying integument is intact and compound if it is lacerated.

Fracture of the floor of the anterior fossa can produce CSF rhinorrhea or orbital hematoma [TD-1]. Fracture of the floor of the middle fossa can produce Battle's sign, a boggy ecchymosis behind the ear.

B. Gunshot wounds, if perpendicular to the skull, produce approximately circular defects from which linear fractures may radiate. The perforations are beveled in the direction of the bullet; hence, entrance perforations are wider on the inner table, and exit perforations on the outer.

V. HEMORRHAGES IN MENINGEAL SPACES

Before proceeding, a distinction should be drawn between open and closed head injuries because the complications of these two types of injury differ greatly. Open head injuries are those in which direct penetration or compound fracture exposes the cranial contents to the outside environment. Closed head injuries are those in which this does not occur. The hemorrhages in this section are of primary concern in closed head injuries.

A. Subarachnoid Hemorrhage

Subarachnoid hemorrhage is the type most commonly seen in closed head injury. It is produced by tears in small subarachnoid vessels or by extension from cerebral contusions. These hemorrhages are generally located over the cerebral convexities. They may be well-localized or diffuse, but in either case are usually small. They almost never act as space-occupying lesions and are generally of little morbid consequence, except in the rare instances in which they interfere with the flow of CSF.

B. Epidural Hematoma [TD-2]

Epidural hematoma is most commonly caused by laceration of the middle meningeal artery. This is usually the result of fracture of the squamous portion of the temporal bone but may occur without fracture, especially in children. The bleeding is arterial and is ipsilateral to the impact. The adherence of the dura mater to the skull tends to retard the accumulation of epidural blood, so the hematoma usually enlarges gradually over the course of hours or days. Rapidly increasing epidural hematomas act as mass lesions to shift the brain and produce herniations. They are medical emergencies that require removal of the blood through a burr hole.

C. Subdural Hematoma

Subdural hematoma is more common than epidural. It is caused by relative motion of the brain with respect to the skull and dura, tearing the bridging veins (see above) in the subdural space. Since the veins torn are usually those extending to the superior sagittal sinus, the hemorrhage is usually located over the cerebral convexity [TD-3]. The falx cerebri prevents extension of the hemorrhage from one side to the other, but hemorrhages can occur independently on both sides. The bleeding is usually venous, is usually but not always unilateral, and may be either ipsilateral or contralateral to the impact. Subdural hematoma can occur in whiplash type injuries without direct trauma to the head. Older people are more susceptible than younger, because shrinkage of the brain results in stretching of the bridging veins, rendering them more easily torn.

Survival after an acute subdural hematoma depends on many factors. Of particular importance are the size of the hematoma and the severity of coexisting injuries. If the victim does survive the acute phase, the dura mater gives rise to two neomembranes that encapsulate and gradually reabsorb the hematoma [TD-4]. These are called the inner membrane and the outer membrane. The outer membrane is adherent to the dura mater and is located between the inner dural surface and the hematoma. The inner membrane lies between the hematoma and the arachnoid, to which it usually is not attached. Both neomembranes are composed of fibroblasts and proliferating blood vessels, and they are infiltrated by macrophages and chronic inflammatory cells [TD-5]. The extent of development of the neomembranes allows the age of the hematoma to be estimated. The neomembranes begin to form at the end of the clot. The outer membrane proliferates more rapidly than the inner and is therefore thicker and more vascular. After a period of two to four weeks, the outer membrane contains a large number of thin-walled vascular channels.

The encapsulated blood begins to liquefy after about one week and is slowly reabsorbed completely [TD-6]. The membranes themselves appear eventually as a brown discoloration

on of inner surface of the dura mater. Microscopically, the resorbed subdural hematoma appears as a layer of fibrous tissue containing vascular channels and variable amounts of hemosiderin.

If very old, it may be difficult to distinguish from the dura mater itself

The distinction between acute and chronic subdural hematoma is clinical. An acute subdural hematoma reaches its maximum size, or becomes clinically apparent, within two or three days of the traumatic event and often within hours. A chronic subdural hematoma accumulates more slowly and may not become apparent until weeks or months after it begins to form. Chronic subdural hematomas are more common in the elderly because their brains are smaller. The increased stretching of their bridging veins makes them more susceptible to subdural hematoma in general, and the increased capacity of the subdural space allows a larger hematoma to form before becoming clinically evident. Patients on anticoagulant therapy are particularly susceptible to both acute and chronic subdural hematomas. The traumatic event leading to a chronic subdural hematoma is often so trivial as to go unnoticed.

Chronic subdural hematomas are often bilateral They usually cause considerable flattening of the cerebral convexities, with a surprisingly small degree of herniation or other displacement [TD-7]. (Flattening of the cerebral convexity by an acute subdural hematoma is also commonly seen but is generally less extensive and accompanied by a much greater degree of secondary displacement.) The pathogenesis of chronic subdural hematomas is uncertain -- one theory is that they arise from hemorrhages between layers of the dura mater. Another possibility is that, at least in some cases, they are caused by repeated hemorrhages from the vascular neomembranes of an originally small subdural hematoma,

Because the blood does not accumulate instantaneously in epidural and acute subdural hematomas, and because accompanying cerebral edema commonly contributes to the pathogenesis of herniation, loss of consciousness from epidural or acute subdural hematoma is sometimes preceded by a lucid interval. This is a period of consciousness following the traumatic event. It generally lasts between several hours and two days, and may itself be preceded by a brief period of concussive unconsciousness Early removal of the hematoma via burr hole or craniotomy will often prevent herniation and may sometimes reverse it. Prompt diagnosis and intervention are therefore of clinical importance. Unfortunately, even early treatment may be unsuccessful because additional swelling of the brain sometimes follows removal of the hematoma.

VII. TRAUMATIC LESIONS OF THE BRAIN

A. Contusion

The most common traumatic lesion of the brain is the cerebral contusion. This has two components: contusion hemorrhage and contusion necrosis. These usually coexist, but one component can be present without the other. The lesions are wedge-shaped. The base of the wedge is usually on the crest of a gyrus and the apex in the gyral white matter.

Fresh contusions [TD-8] consist of multiple tiny, linear, perivascular hemorrhages, mostly within the cortex. The necrosis, which involves all cellular elements, takes several hours to become microscopically apparent. With time, the hemorrhages enlarge and exert pressure on the surrounding tissue, which forms a border zone of neuronal ischemia and vascular, phagocytic, and astrocytic reaction. Because of the complete necrosis within the contusion, the entire reaction is derived from the border zone. The phagocytes invade the contusion proper, removing the blood and necrotic tissue. After three to six months, the lesion appears as a brown, glia-lined cystic defect that often communicates with the subarachnoid space [TD-9]. Contusions alone rarely result in the formation of glial-mesenchymal scars (see below). Occasionally, after hours or days, a cerebral contusion may give rise to a massive intracerebral hemorrhage (post-traumatic apoplexy). Usually, however, the contusions themselves are of little morbid consequence.

Cerebral contusions are caused by blunt trauma to the moving or movable head. Experiments indicate that the distribution of contusions is influenced by several conditions. Coup contusions are located on the same side of the brain as the impact. These are most prominent when a moving object strikes the stationary but movable head. Contrecoup contusions are located on the side of the brain opposite the impact and are most prominent when the moving head hits a stationary object. In such a case, coup contusions are less prominent than contrecoup contusions and may be entirely absent. The preponderance of coup contusions in the first case and contrecoup in the second may be due to the differing distribution of the CSF before and during the two types of impact, and its cushioning effect on subsequent impacts between the skull and the brain.

When skull fractures are present, cerebral contusions are frequently seen beneath the fracture lines, regardless of the type of impact. Herniation-type contusions can occur in any of the areas in which herniation usually occurs and are due to momentary displacements caused directly by the trauma.

Regardless of the type or location of impact, the following regions are most commonly contused: the orbital and straight gyri, the frontal and temporal poles, the inferior and inferolateral surfaces of the temporal lobes, and the cortical surfaces facing the Sylvian fissure.

B. Hemorrhage

Closed head injury may result in other types of intracerebral hemorrhage besides contusion. Most common are slit-shaped hemorrhages in the white matter [TD-10]. Large, rapidly fatal hemorrhages are also sometimes seen. Widespread small hemorrhages in the brain are seen chiefly in patients who die soon after injury. These forms of hemorrhage are presumably caused by stretching or shearing forces and are usually associated with severe diffuse axonal injury.

C. Diffuse Axonal Injury

Diffuse axonal injury (DAI) refers to axonal damage that commonly accompanies head injury. Originally thought to represent shearing of axons and to occur almost exclusively in cases of severe head injury, it is now believed to result more commonly from any local axonal injury that interferes with fast transport, which eventually gives rise to axonal swellings. There is some evidence of diffuse axonal injury in most cases of head injury with loss of consciousness. β -Amyloid precursor protein is a neuronal protein that is normally transported by fast axonal transport. Axonal concentrations under normal conditions are too low to be appreciated by immunohistochemistry. Within 1 hour of head injury, immunoreactivity for β -amyloid precursor protein becomes visible in white matter. Three hours after injury, immunohistochemistry for β -amyloid precursor protein begins to show axonal swellings, which reach a maximum diameter around 48 hours after injury, the time at which axonal swellings become visible on H&E or silver stains. The areas commonly involved are the brain stem, fornix, parasagittal white matter, internal capsule, thalamus, and corpus callosum. It is suspected that this damage is sometimes reversible, but this is difficult to prove.

Severe diffuse axonal injury is accompanied by immediate loss of consciousness. Victims are unlikely to regain consciousness, and if they do, they will be severely impaired neurologically. The presence of grossly visible hemorrhages in the corpus callosum or the dorsolateral portion of the rostral brainstem indicates that this type of injury has occurred, although it often occurs in the absence of hemorrhages.

D. Concussion

Concussion is a brief loss of consciousness beginning at the time of injury and usually followed by complete recovery. It is probably related to a mild or largely reversible form of diffuse axonal injury. Scattered microglial nodules in the brain stem and cerebral hemispheres have been seen in individuals who died of unrelated causes days after sustaining a concussion. Immunohistochemistry for β -amyloid precursor protein demonstrated axonal swellings in the corpus callosum and fornix in each of five concussion victims who died from unrelated causes 2-99 days later.

E. Laceration

Cerebral lacerations are tears in the brain seen after severe head injury with extensive fractures. They are seen mainly in cases of instant fatality, and evidence of contusion and hemorrhage is commonly absent. Lacerations are also seen following surgery on a severely swollen brain. A mushroom-shaped herniation protrudes through the craniotomy defect and its edges become lacerated.

F. Gunshot Wounds

Gunshot wounds to the brain produce a bullet tract of fairly uniform diameter. The tract may become hemorrhagic if the victim survives for more than a few minutes. Even if the bullet does not penetrate a vital center in the brain, death is usually very rapid. The moving bullet transmits a great deal of energy to the brain and produces widespread damage, sometimes evidenced by contusions at some distance from the wound tract.

VII. COMPLICATIONS OF HEAD INJURY

A. Infection

Penetrating wounds can pose a significant risk of infection. The heat produced when a bullet is fired is not sufficient to sterilize it, nor is the scalp sterile. Brain abscess is the most common infectious complication of penetrating wounds, but meningitis and epidural empyema can also occur.

B. Post-Traumatic Epilepsy

Post-traumatic epilepsy is another complication of penetrating wounds (including neurosurgical wounds), probably because the mixed glial-mesenchymal scar that follows these wounds acts as a seizure focus.

C. Cerebral Swelling

Hematomas, contusions, and penetrating injuries all carry a significant risk of producing cerebral swelling due to congestion and edema. This can raise intracranial pressure and cause herniation. Focal swelling is commonly seen around contusions. Contusions may also lead to swelling of an entire cerebral hemisphere, but this is more commonly the result of an ipsilateral acute subdural hematoma. Swelling of the entire brain may occur in children, sometimes following apparently minor trauma.

D. Cerebral Hypoxia

Head trauma is frequently accompanied by episodes of hypotension or hypoxia, due either to the head injury itself or to concurrent injuries to the rest of the body. Alone or in combination with raised intracranial pressure, such episodes often result in hypoxic damage to the brain.

VIII. SHAKEN BABY SYNDROME

The triad of subdural hemorrhage, retinal hemorrhage, and neurological impairment ranging from irritability to coma or death is sometimes seen in infants, with or without evidence of impact to the head. It is most common in young infants, with the majority of cases occurring before 6 months. Since the 1970's, this syndrome has been attributed to violent shaking of the infant, whose large head and weak neck muscles allow a whiplash-like effect. These findings may be accompanied by rib fractures (from grabbing the thorax) and by metaphyseal fractures of the long bones, from flailing of the limbs. Evidence of prior episodes of shaking is common. At autopsy, the subdural hemorrhage is rarely of sufficient volume to cause a significant mass effect, yet the brain is commonly swollen. Axonal spheroids are often seen, especially if immunohistochemical staining for amyloid precursor protein is performed to demonstrate them.

The pathophysiology of this disorder is extraordinarily controversial and has given rise to some of the most passionate letters to editors imaginable about a neuropathological topic. One issue is whether the forces generated by shaking are sufficient to cause axonal shearing. Some authors have claimed that this is impossible, that most cases are accompanied by some evidence of impact, and that when this is lacking, there still must have been impact, albeit

against an object, such as a cushion, that prevented injury to the scalp or skull. Others have claimed that the only axonal injury directly caused by the shaking is at the junction of the medulla and cervical spinal cord, which leads to apnea, and that any further axonal injury is due to hypoxia and increased intracranial pressure; which they claim produce patterns of axonal injury that can be distinguished from those produced by trauma. They have also proposed that the subdural and retinal hemorrhages are the result of increased intracranial pressure, rather than the direct effect of trauma. Thus, they conclude that the entire syndrome can result from hypoxia without trauma. This opinion has been challenged vigorously in the literature and in court. Related controversies, also with important implications in the prosecution of alleged baby-shaking, involve the reversibility of axonal damage and the question of whether infants can experience a lucid interval between trauma and loss of consciousness.

These issues are difficult to resolve because of the absence of disinterested witnesses to the handling of the infants. However, from cases without scalp injury and with a confessed shaking, it seems clear that whatever the mechanism, shaking alone can give rise to subdural and retinal hemorrhages with loss of consciousness and axonal injury. On the other hand, if evidence of direct impact to the head is present, it is probably impossible to tell whether there was shaking or not.

IX. SPINAL CORD TRAUMA

A. Anatomic Considerations

The spinal canal becomes narrower when flexed or extended. This is particularly true in the presence of traumatic instability, when the vertebrae or the pieces of fractured vertebrae may be properly aligned when the spine is straight but displaced into the canal with motion. Therefore, it must always be remembered that in the presence of injury to the bony spine, movement of the spine can cause serious compression injury to the spinal cord, even if no such injury occurred initially. **SUCH INJURY CAN AND MUST BE AVOIDED BY IMMOBILIZATION OF THE SPINE AT THE SCENE OF THE INJURY.**

The spinal canal is narrowest in its cervical portion, the spine is weakest at this level, and violent motion of the head can place the cervical spine under tremendous stress. Traumatic spinal injuries are thus most commonly cervical, and cervical spine injuries must be ruled out in the presence of violent injuries to the head or face.

Cranial or facial trauma can result in tearing of the ligaments that hold the odontoid process in place. Atlantoaxial dislocation [TD-11] can occur without fracture and must be ruled out by appropriate X-rays.

The caudal end of the spinal cord is at the level of the second lumbar vertebra. If the spinal cord is injured, the level of cord injury will often differ from that of spinal injury.

The vertebral spines protect the spinal cord in the midline. Posterior stab wounds are therefore likely to affect one side more than the other.

B. Direct Injuries to the Spine

These are caused by stab wounds or by bullets or other high velocity projectiles. As mentioned above, stab wounds are likely to involve one side more than the other, causing a complete or partial Brown-Sequard syndrome (ipsilateral paralysis and loss of vibratory and positional sensation with contralateral loss of pain and temperature sensation). Stab wounds tend to cause localized damage to the spinal cord with little intraparenchymal hemorrhage. Ascending and descending degeneration occur in a pattern predictable from the anatomy of the severed tracts.

As in the brain, the damage from gunshot wounds extends beyond the region penetrated, for similar reasons. The injuries tend to extend for several segments in either direction and to be fairly hemorrhagic. Gunshot wounds to the vertebrae can injure the spinal cord without penetrating it, by virtue of transferred energy alone.

Bullets frequently become trapped in the spinal canal, and in the early stages of injury they can move. Eventually, whether epidurally or intraparenchymally located, they become encased in fibrous tissue. The adjacent spinal cord loses its normal structure and becomes a mixed glial-mesenchymal scar, poorly demarcated from the meninges to which it had become adherent.

C. Indirect Injuries to the Spinal Cord

These are blunt force or compressive injuries secondary to spinal trauma. While they occasionally result from temporary spinal deformities, they are more commonly the result of spinal fracture or subluxation. It should be borne in mind that spinal instability may result in temporary deformity that is not appreciated at the time of examination but that has already caused injury to the cord.

Injury to the cervical spine is generally the result of cranial or facial injuries, commonly the result of motor vehicle accidents or falls. Motorcycle and diving accidents are particularly likely to result in such injuries. Thoracic spine fractures are more commonly the result of industrial accidents, such as mining cave-ins or collapsed roofs, in which weight falls on the victim.

The immediate effects of spinal cord compression are necrosis, hemorrhage, edema, and inflammation. The cord becomes swollen, and this swelling can extend the compressive injury. The edema resolves after two or three weeks, and the necrotic foci become infiltrated by phagocytes. This appearance can last for several years. During this period the blood becomes resorbed, which can result in the formation of a syrinx (cystic space within the spinal cord). Glial and mesenchymal scar tissue forms. In less severely damaged areas, the astrocytic component predominates, while in the most severely damaged areas the scar is entirely fibroblastic, the glia having been lost with the other elements of the cord. Eventually, the injured portion of the cord is reduced to scar tissue, which is adherent to, and indistinct from, the surrounding meninges. Degenerative changes in the long tracts occur in the predictable pattern.

D. COMPLICATIONS OF SPINAL CORD INJURY

Spinal cord injuries initially result in motor and sensory loss below the level of the lesion and in loss of sphincter control. Victims become bedridden or wheelchair-bound, with all the attendant problems, and they frequently require urethral catheterization. Common long-term sequelae include infected decubitus ulcers and urinary tract infections, and such infections often result in death years after the injury. High cervical injuries can cause respiratory paralysis.

Penetrating injuries can result in meningitis or the formation of abscesses.

Occasionally, a syrinx that forms during the resolution of a cord injury may enlarge years after the injury. This condition is known as post-traumatic syringomyelia. If the injury has resulted in a motor and sensory level, additional symptoms will appear if there is rostral extension of the syrinx, while caudal extension will be clinically silent.

SUPPLEMENTARY READING:

1. "Head Injury" by J. H. Adams, pp. 106-152 in Greenfield's Neuropathology, 5th ed.. J. H. Adams et al., Eds.: Oxford University Press. New York, 1992.
2. "Morphology of Cerebral Contusions" by R. Lindenberg and E. Freytag, in Archives of Pathology 63:23-41. 1957.
3. "Surgical Pathology of Subdural Hematoma Based on a Study of One Hundred and Five Cases" by D. Munro and H.H. Merritt, in Archives of Neurology and Psychiatry 35:64-78, 1936
4. "Forensic Neuropathology" by J. E. Leetsma. Raven Press. New York, 1988.
4. Wilkinson AE, Bridges LR, Sivaloganathan S. Correlation of survival time with size of axonal swellings in diffuse axonal injury. Acta Neuropathology (1999)98:127-202.

IMAGE GUIDE

We have attempted to enrich your exposure to Clinical Neuropathology through the use of (how many?) gross, light microscopic and ultrastructural photographs of common ("core") lesions. These images, contributed and reviewed by the relevant lecturers, have been arranged in the thematic order of the Syllabus. Due to the diversity of source material and the initial films, it has been difficult to provide you with flawless color reproductions of all lesions - despite numerous attempts. For example, some fresh (unfixed) brain specimens tend to have a slightly yellow tint, while the fixed specimens are more faithfully reproduced. Likewise, some hematoxylin-eosin stained sections tend to be more red than pink, while the special stains tend to display their true colors. In spite of these limitations, we believe that these images will prove to be a powerful tool in your learning process, and we encourage you to study them along with the Syllabus and refer to them throughout your clinical years.

For your orientation, all gross specimens are coronal sections and have been fixed in Formalin (10% formaldehyde) unless otherwise specified, all microscopic slides have been stained with the standard hematoxylin-eosin unless otherwise specified, and all electron micrographs have been stained with uranyl acetate-lead citrate or hydroxide. Some common special stains, their abbreviations and uses are listed below. As a general rule, coronal and transverse sections of the brain, brain stem, and spinal cord are presented from the posterior or caudal aspect (P-A view, like the usual chest X-ray). References to "right" and "left," therefore, correspond to both the viewer's and the anatomical right and left.

We have expanded the text of this guide, since your predecessors strongly recommended that this would be a significant improvement. Nonetheless, some lesions in the slides have not received comment, so that you can focus more easily on the major lesion. Don't expect to understand all aspects of these images completely. Additionally, there are some excellent atlases of Neuropathology available in the Health Sciences Library.

1. Okazaki, H, Scheithauer, BW. Atlas of Neuropathology.
RC347. 0377 1988 Q.
2. Esiri, MM, Oppenheimer, DR. Diagnostic Neuropathology.
RC346 E85 1989 Q.
3. Hirano, A. Color Atlas of Pathology of the Nervous System
RC347. .C58 1988 Q.
4. Schochet, SS, Nelson, J. Atlas of Clinical Neuropathology
RC347 .S34 1989 Q.

5. Weller, RO. Color Atlas of Neuropathology.
RC347 W46 1984 Q.

SPECIAL STAINS

1. **aCV** - acid cresyl violet - metachromatic lipid (brown to red)
2. **Ag** - silver carbonate - microglia (black)
3. **ATPase** - adenosine triphosphatase - type II muscle fibers (brown)
4. **AuCl** - gold chloride - astrocytes (black)
5. **Bo** - Bodian - axons (black)
6. **CV** - cresyl violet - Nissl substance, rough ER in neurons (blue)
7. **GFAP** - glial fibrillary acidic protein - astrocytes and their processes
8. **Golgi** - Golgi - axons, dendrites, dendritic spines (black-brown)
9. **Heid** - Heidenhain - myelin (blue)
10. **If** - immunofluorescence (fluorescent reaction product)
11. **Ip** - immunoperoxidase (brown reaction product)
12. **LFB** - Luxol fast blue - myelin (blue)
13. **Mahon** - myelin (blue)
14. **Meth Ag** - methenamine silver - fungi (black)
15. **Muci** - mucicarmine - mucosubstance (red)
16. **SDH** - succinate dehydrogenase (dark blue type I)
17. **NF** - neurofilament - axons
18. **Osmic** - osmic acid - myelin (black)
19. **PAS** - periodic acid-Schiff - carbohydrates (magenta)
20. **PTAH** - phosphotungstic acid hematoxylin - astrocyte processes, myelin (blue)

21. **Ret** - reticulin - type IV collagen and other connective tissue fibers (black)
22. **Thio S** - Thioflavine S - amyloid (yellow-green)
23. **Tol** - toluidine blue - standard semi-thin-section stain (myelin blue)

CELLULAR NEUROPATHOLOGY

Neuronal Perikaryon

CN-1. NEURONAL EOSINOPHILIA. **Hippocampal formation, Sommer's sector.** Pyramidal cell elongated and cytoplasm eosinophilic (examples shown by arrows). Nucleus dark, shrunken, and homogeneous (pyknotic)

Any interference with the neuron's oxidative metabolism (hypoxia, hypoglycemia, ischemia) can produce this picture. Recent work suggests that the common pathway of cell death may be excessive synaptic release of excitatory amino acid transmitter (glutamate) and a lethal influx of calcium through the NMDA receptor.

CN-2. NEURONAL ATROPHY. **Lumbar spinal cord, anterior horn.** Atrophic neurons (arrows) with contracted cytoplasm and pyknotic nucleus, and its normal counterpart (bottom left)

Cell atrophy is the major neuronal alteration in a variety of neurodegenerative diseases (for example, amyotrophic lateral sclerosis) in which the nerve cell dies - "...not with a bang, but a whimper." Which subset of neurons is selectively targeted is a key distinguishing feature between the neurodegenerative diseases.

CN-3. CENTRAL CHROMATOLYSIS. **Lumbar spinal cord, anterior horn.** Perikaryal distension with rounding of the cell contour and displacement of Nissl substance (fine bluish granules) to the periphery. Nucleus displaced to the margin of the cell. Enlarged nucleolus

The nerve cell's axon has been damaged or transected. If the damage occurs close to the cell body, especially proximal to the first internode, the cell will likely die. If the interruption is more distal, the changes shown are temporary. The "chromatolysis" reflects displacement of basophilic ribosomes from rough endoplasmic reticulum to the cytoplasm in an attempt to synthesize the cytoskeletal elements necessary for the reconstitution of the axon.

Axon

CN-4. WALLERIAN-LIKE DEGENERATION. **Medulla, transverse section. LFB** stain for myelin. Right and left medullary pyramids devoid of myelin. No abnormalities elsewhere

A particular "system," in this case the corticospinal projection, is affected selectively. In the CNS, this is referred to as secondary tract degeneration. As in Wallerian degeneration in the PNS, the loss of myelin is secondary to disintegration of the axon and the site of injury is cephalad or proximal, either in the axon or the cell body. In the CNS either the neuronal cell body or its axon is lost from a variety of causes and the distal axon and its myelin sheath disintegrate.

CN-5. DEMYELINATION (PRIMARY). **Lower medulla. Heidenhain** stain for myelin. Bilateral but asymmetrical loss of myelin involving different structures on the right and left sides (arrows).

This asymmetrical loss of myelin usually signifies a primary loss of myelin (the direct target of the disease is the myelin sheath) with preservation of the axons. This particular image is characteristic and, statistically, virtually diagnostic of multiple sclerosis.

CN-6. SPHEROID. **Centrum semiovale.** Red or pink swollen axons in a variety of sizes. (Examples shown by arrows).

This axonal reaction is common in a setting of trauma [TD-10] but ischemic insults can also produce similar lesions, as well as a rare degenerative disease called infantile neuroaxonal dystrophy. The contents of these spheroids vary with the nature of the insult and the state of the lesion.

Astrocyte

CN-7. NORMAL PROTOPLASMIC AND FIBROUS TYPES. **Cerebral cortex.** Immunoperoxidase for GFAP (glial fibrillary acidic protein, an intermediate filament protein of astrocytes, seen in brown).

Note many fine processes and connections to blood vessel (center).

CN-8. CYTOPLASMIC INCLUSIONS. **Floor of third ventricle.** Numerous and variably sized red to pink hyaline Rosenthal fibers (examples shown by arrows) among fine astrocytic cell processes.

This astrocytic alteration is common in neoplastic astrocytes of low grade in children (pilocytic astrocytomas). It is also the histologic hallmark of Alexander's disease, a rare leukodystrophy.

Microglia

CN-9. PHAGOCYTOSIS. **Centrum semiovale. LFB-PAS.** Numerous PAS-positive (red) vacuolated macrophages with fragments of myelin (blue)

The source of these scavenger cells can be microglia endogenous to the CNS or invading monocytes from the blood stream. In this case of brain infarction, the latter source predominates.

Endothelial Cells

CN-10. CELL LOSS. **Centrum semiovale.** Fibrinoid (red material) necrosis of endothelial cell (center) with circumferential leakage of erythrocytes (called a 'ring-ball hemorrhage').

Endothelial cell necrosis is an unusual lesion in the central nervous system, but it is the hallmark of the rickettsial disease, Rocky Mountain Spotted Fever.

CEREBROVASCULAR DISEASES

CVD-1. ACUTE INFARCTION (ENCEPHALOMALACIA). **Coronal section of cerebral hemispheres at the level of the hypothalamus.** Infarction, no more than a few days old, in distribution of left middle cerebral artery (territories of anterior and posterior cerebral arteries normal). Secondary edema with compression of ipsilateral ventricle, subfalcial displacement of midline structures, and herniation-distortion and congestion of hypothalamus. Severe congestion and diapedesis in sulcal depths of infarcted cortex and left hypothalamus. Dilatation of contralateral ventricle. Leptomeningeal congestion, right hemisphere

The patient died a few days after the stroke, when post-infarction edema caused downward transtentorial herniation and brain stem compression.

CVD-2. INFARCTION (ENCEPHALOMALACIA), OLD AND FRESH. Coronal section of cerebrum at level of thalamus. Cavitory ("cystic") infarction (encephalomalacia) of left hemisphere (involving the insula, frontal operculum, inferior frontal gyrus, most of centrum semiovale, internal capsule, and thalamus), years old, with enlargement of the ipsilateral lateral ventricle (hydrocephalus ex vacuo). Acute infarction in right cerebral hemisphere with massive swelling of centrum semiovale and right-to-left shift across the midline, including subfalcial herniation of cingulate gyrus

CVD-3. SECONDARY (DURET) BRAIN STEM HEMORRHAGE. Transverse section of brain stem, upper pons. Multiple fresh hemorrhages, most prominent about the midline

These hemorrhages are a common terminal consequence of acute transtentorial herniation in the rostral third of the brain stem, especially the midbrain. The rapidity with which the herniation develops and the magnitude of the forces generated are major conducive factors.

CVD-4. LACUNAR INFARCTS. Coronal section of right and left basal ganglia at the level of the mammillary bodies. Several small infarcts of different age, some of them hemorrhagic: the largest in right putamen, slit-like, old, cystic, blood stained; in right stria terminalis (inferior to caudate nucleus), recent, hemorrhagic; in right insular cortex; in subcortical white matter of right frontal operculum. On the left side: in internal capsule, extending into putamen; in caudate nucleus, with hemorrhagic extension in wall of frontal horn; at interface of internal capsule and outer segment of globus pallidus; in temporal lobe (left lower corner of field), structure uncertain.

CVD-5. HYPERTENSIVE INTRACEREBRAL HEMORRHAGE. Coronal section of cerebrum at level of thalamus and basal ganglia. Massive hemorrhage in deep gray nuclei and white matter of left hemisphere. Dissection of hemorrhage into frontal horn and displacement of fornix and septum pellucidum. Diffusion of hemorrhage into third ventricle. Acute obstructive hydrocephalus of right lateral ventricle (note temporal horn). Compression of right thalamus, subthalamic nucleus, and corpus striatum. Subfalcial herniation of left cingulate gyrus. Flattening of left hippocampus, severe, and of ventral outline of left temporal lobe. Severe downward herniation of left thalamus into incisural space of tentorium (funnel effect) with compression of contralateral substantia nigra. Sharp indentation of left parahippocampal cortex by edge of tentorium (note asymmetry of distance to midline)

Transmitted to the posterior fossa, the forces implicit in these supratentorial displacements are incompatible with brain stem function.

CVD-6. **SACCULAR (BERRY, CONGENITAL) ANEURYSM. Block dissection of anterior cerebral arteries and anterior communicating artery.**

Aneurysmal outpouching (center) with a thin dome, located at the junction of the anterior communicating artery and an anterior cerebral trunk. This unruptured aneurysm was an incidental finding at autopsy.

Saccular aneurysms occur at or near arterial junction points in the circle of Willis or along proximal segments of branches from the circle.

CVD-7. **SUBARACHNOID HEMORRHAGE. Ventral view of brain.** Blood in the subarachnoid space, concentrated along the base, at and near the midline, and posteriorly.

The source of the bleed (rupture of an aneurysm of the circle of Willis), together with gravity, account for the distribution of blood in the subarachnoid space.

CVD-8. **INTRAPARENCHYMAL DISSECTION OF ANEURYSMAL HEMORRHAGE. Coronal section of cerebrum, prefrontal.** Inverted-tear-shaped hematoma in right centrum semiovale, extending in from the olfactory sulcus. Interhemispheric subarachnoid blood distending sulcus above gyrus rectus. Tight sulci, right, ventrolateral (compare left side)

Aneurysmal hemorrhages are usually confined to the subarachnoid compartment, unless they originate in the Sylvian fissure or, as in this case, in the anterior cerebral artery, and the site of rupture of the aneurysm faces the brain.

CVD-9. **SACCULAR ANEURYSM. Aneurysm at low magnification, stained for elastic fibers (black).** Inner elastic membrane (wavy black line), smooth muscle layer (media), and slightly thickened intima of parent artery, best appreciated on top right, just before the origin of the aneurysm (left). Thin, purely collagenous wall of aneurysm, devoid of elastic and smooth muscle fibers

CVD-10. **ARTERIOVENOUS MALFORMATION. Coronal section of right temporal lobe.** Abnormally numerous, large, and malformed vascular channels replacing much of the opercular cortex and white matter of the superior temporal gyrus. Relatively small component of the malformation in the subarachnoid space of the Sylvian fissure

Arteriovenous malformations, the most troublesome of the different types of vascular malformations, usually encompass subarachnoid space and parenchyma, but the relative proportion in each compartment is variable. They may lie within the territory of one major artery only or they may be fed by more than one major artery.

INFECTIOUS DISEASES

ID-1. ACUTE SUPPURATIVE LEPTOMENINGITIS. Dorsal view of brain. Both cerebral hemispheres covered by pus in the subarachnoid space. Engorgement of leptomeningeal blood vessels

This pathologic picture is most often associated with infection by Neisseria, Streptococcus, Staphylococcus, Hemophilus influenzae or Escherichia coli.

ID-2. ACUTE SUPPURATIVE LEPTOMENINGITIS. Cerebral subarachnoid space and parenchyma. Predominance of polymorphonuclear leukocytes (better appreciated at higher magnification). Brain parenchyma and walls of blood vessels not infiltrated (no cerebritis/encephalitis and no vasculitis)

The cerebrospinal fluid in this condition characteristically shows an elevated protein and lowered glucose content.

ID-3. ASPERGILLOSIS. Caudate nucleus. Methenamine silver. Narrow, septated, branching hyphae in occluded blood vessel (right) and necrotic parenchyma (center)

Aspergillus invasion of blood vessel walls with resultant mural inflammation (vasculitis) is often accompanied by vascular thrombosis and infarction or vascular rupture and hemorrhage.

ID-4. MUCORMYCOSIS (Rhizopus). Internal carotid artery. Broad, non-septated hyphae within vascular lumen and wall (right)

ID-5. CRYPTOCOCCAL MENINGOENCEPHALITIS. Coronal section of brain through thalamus. Numerous small cysts in cerebral cortex (particularly para-Sylvian) and a few in thalamus. Focally thickened leptomeninges in left Sylvian fissure

The special character of the exudate in this disease is related to the accumulation of thick viscous material derived from the capsule of the causative organism, Cryptococcus neoformans.

ID-6. CRYPTOCOCCAL MENINGOENCEPHALITIS. Cerebral cortex. Mucicarmin stain. Distended space surrounding a thin-walled penetrating vessel in cortex . Numerous yeast cells (mucicarmin positive) in the Virchow-Robin space, continuous with subarachnoid space

ID-7. TABES DORSALIS. Spinal cord. Heidenhain. Severe loss of myelinated fibers in posterior funiculi and posterior roots. Anterior and lateral funiculi and ventral roots well myelinated

ID-8. HERPES SIMPLEX MENINGOENCEPHALITIS. Cerebral cortex. Cowdry Type A inclusion in nucleus || Marginated nuclear chromatin

The presence of Cowdry Type A intranuclear inclusions is the most helpful light microscopic feature of CNS viral infection from a diagnostic standpoint.

ID-9. RABIES ENCEPHALITIS. Canine cerebellar cortex. Bright red cytoplasmic inclusion (Negri Body) in Purkinje cell

Cytoplasmic inclusion bodies are a rather non-specific pathologic finding and they may be seen in diseases having diverse etiologies.

ID-10. CYTOMEGALOVIRUS. Ependymal cells. Cytomegalic change in ependymal cells characterized by enlarged nuclei and cell body.

The enlarged nucleus has an “owls-eye” appearance with a basophilic inclusion containing viral particles surrounded by a clear nucleoplasm. Eosinophilic cytoplasmic viral inclusions are also present in CMV infected cells.

ID-11. HIV SUBACUTE ENCEPHALITIS WITH MULTINUCLEATED CELLS. Centrum semiovale. Multinucleated giant cell (center) in white matter showing relatively little pathologic abnormality. These cells are frequently seen in relation to blood vessels and in areas of inflammatory changes.

ID-12. TOXOPLASMOSIS. Cerebral cortex. An acute abscess with a central necrotic zone, associated with macrophages, neutrophils and necrotic debris. There are several pseudocysts containing bradyzoites of toxoplasma gondii.

ID-13. PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML). **Cerebral gray-white junction. Heidenhain.** Multifocal demyelination of white and deep gray matter

Grossly, these lesions will appear granular to cystic. They are asymmetric and they are usually restricted to cerebrum or cerebellum.

ID-14. PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY. **Centrum semiovale. H&E (A) and (C); SV40 immunostain (C).** Massive destruction of the white matter with infiltration by numerous macrophages (A&B). Bizarre astrocytes with large nuclei and eosinophilic cytoplasm (B). Enlarged oligodendroglial nuclei with a smudged, eosinophilic intranuclear viral inclusion (A). Immunostain to SV40 antigen (B) [SV40 is a related papova virus] cross-reacts with JC viral antigen and facilitates detection of intranuclear viral inclusions

The papova virus ("JC" after the patient in Wisconsin from whom it was isolated) is thought to lyse oligodendrocytes by direct invasion, with demyelination secondary to oligodendroglial loss.

ID-15. STATUS SPONGIOSIS. **Cerebral Cortex. (A)** Numerous clear vacuoles in the neuropil of two adjacent gyri. This spongy change in gray matter is highly specific. It is seen in Creutzfeldt-Jakob disease and other transmissible spongiform encephalopathies. The vacuoles are swollen neurites and glial processes. This cortex is very severely involved. **(B)** Higher magnification image of an earlier stage of CJD where the spongiform change is far less severe. Vacuoles may indent the nucleus of adjacent neurons and glia.

The definitive diagnosis of CJD is established by Western blot and immunohistochemical analysis of biopsy (and/or autopsy) brain tissue to identify prion proteins.

DEGENERATIVE DISEASES AND DEMENTIA

DDD-1. ALZHEIMER'S DISEASE. **Lateral view of left hemisphere.** Marked atrophy (narrow gyri, wide sulci) of frontal, temporal, and parietal lobes. Relative sparing of occipital lobe.

DDD-2. SENILE PLAQUE WITH NEURITIC COMPONENTS. **Cerebral cortex. Modified Bielschowsky silver stain.** Many silver-positive (black), abnormally thickened, neuronal processes (dystrophic neurites) arranged radially at the periphery of the senile plaque. The central amyloid core is brown and immediately surrounded by a clear zone.

DDD-3. NEUROFIBRILLARY TANGLES. **Hippocampus. Modified Bielschowsky silver stain.** Neurofibrillary tangles appear brown to black in color and have a distinct fibrillar morphology. The neuron at the top (right of center) shows granulovacuolar degeneration with characteristic argyrophilic core and surrounding clear halo.

The major component of tangles are paired helical filaments. These contain the microtubule associated protein, tau, which is hyperphosphorylated and apparently polymerized in an abnormal fashion.

DDD-4. **AMYLOID ANGIOPATHY. Cerebral cortex. Thioflavin S.**
Fluorescent, amyloid-containing blood vessels.

DDD-5. **PARKINSON'S DISEASE. Transverse sections of normal (left) and Parkinson (right) midbrain.** Loss of pigment in the substantia nigra of the Parkinson brain.

The pallor reflects the disappearance of the normal nigral neurons containing neuromelanin.

DDD-6. **LEWY BODY. Substantia nigral neurons. H&E.** Intracytoplasmic, eosinophilic inclusions.

Lewy bodies are inclusions made up in part of disorganized neurofilaments, which are arranged peripherally in a radial fashion, and a granular core.

DDD-7. **PICK'S DISEASE. Hippocampus. Modified Bielschowsky silver stain.** Round, so-called 'globose', intracytoplasmic Pick body inclusions in pyramidal neurons.

Pick bodies are composed of abnormally polymerized tau protein similar in some ways to the neurofibrillary tangles seen in Alzheimer's disease.

DDD-8. **HUNTINGTON'S DISEASE. Coronal sections of cerebral hemispheres.** Marked atrophy of caudate nucleus bilaterally with secondary enlargement of lateral ventricles.

Neocortical atrophy can be seen in Huntington's disease, but this was not notable in this particular brain.

DDD-9. **HUNTINGTON'S DISEASE. Immunohistochemistry to ubiquitin.**

The neuronal inclusions in Huntington's disease are not seen on routine histologic stains (e.g. H&E). When antibodies to ubiquitinated proteins became available, ubiquitinated inclusions were identified in the nucleus of striatal neurons. Immunostaining is also seen in dystrophic neurites.

METABOLIC DISEASES

MBD-1. HYPOXIC ENCEPHALOPATHY. **Coronal section of hippocampus.** Necrosis in Sommer's sector (curved band in hippocampus)

Sommer's sector (CA1 of the hippocampus) is one of the most sensitive areas of the CNS to hypoxia or ischemia. The thin, discolored band reflects neuronal death and tissue atrophy with glial scarring.

MBD-2. CHRONIC WERNICKE'S DISEASE (WERNICKE-KORSAKOFF DISEASE). **Coronal section of cerebral hemispheres.** Atrophy and discoloration of mammillary bodies (arrows). Atrophy of thalamus and hypothalamus with secondary enlargement of third ventricle

This picture represents a chronic case of Wernicke's disease. Acute Wernicke's often shows hemorrhages in the mammillary bodies, thalamus, and hypothalamus.

MBD-3. SUBACUTE COMBINED DEGENERATION. **Cross section of spinal cord (Dorsal at top). Phosphotungstic acid hematoxylin.** Spongy change in posterior columns (top) and postero-lateral funiculi

This is due to Vitamin B12 deficiency. The changes are seen mainly in posterior and postero-lateral tracts, but are not restricted to specific spinal tracts. Demyelination and axonal loss are primary, with a gliosis seen in chronic cases.

MBD-4. SUBACUTE NECROTIZING ENCEPHALOMYELOPATHY (SNE, LEIGH'S DISEASE). **Cross section of pons.** Bilateral, symmetrical discoloration and softening in the pontine tegmentum

MBD-5. SNE. **Affected area in pons.** Vascular hyperplasia and proliferation. Pallor and spongy change in gray matter

These histologic changes are typical of both Leigh's disease and Wernicke's encephalopathy.

MBD-6. GANGLIOSIDOSIS GM2. **Retina.** Cherry-red spot (top left)

The spot itself is a normal, aganglionic fovea, but it is surrounded by a pale retina due to lipid accumulation in retinal ganglion cells. This spot is found in a variety of lipid and mucopolysaccharide storage diseases. This particular child had an infantile form of GM2 gangliosidosis known as Tay-Sachs disease.

MBD-7. GANGLIOSIDOSIS GM2. Cerebral cortical neuron. Electron micrograph. Lamellated inclusions in the neuronal cytoplasm (membranous cytoplasmic bodies)

These are composed mostly of lipids, with a small amount of protein. Present in perikarya, dendrites, and meganeurites, they are found in many of the lipidoses.

MBD-8. GANGLIOSIDOSIS GM2. Cerebral cortical neuron. Golgi stain. Cell body at top, with basilar dendrites Meganeurite (center) arising from proximal axon || Abnormal processes on meganeurite

This bizarre distortion of neuronal geometry is seen in many lipid and mucopolysaccharide storage diseases. The meganeurite may subvert the normal physiological properties of the axon hillock region and alter neuronal output.

MBD-9. NEURONAL CEROID-LIPOFUSCINOSIS. Retina. Pigmentary degeneration

These are a group of disorders characterized by the accumulation of autofluorescent pigment in neurons and other cells.

MBD-10. NEURONAL CEROID-LIPOFUSCINOSIS. Cerebral cortex. Enlarged neurons with vacuolated cytoplasm.

Neuronal enlargement and distortion of geometry are seen in ceroid-lipofuscinosis, mucopolysaccharidoses and other lysosomal storage disorders.

MBD-11. KERNICTERUS (NUCLEAR JAUNDICE). Unfixed coronal section of cerebral hemispheres. Yellow discoloration of hippocampus, globus pallidus, subthalamic nucleus

This is due to the penetration of high levels of unconjugated bilirubin into the brain. The hemolytic anemia of Rh incompatibility was a major cause of kernicterus.

MBD-12. WILSON'S DISEASE. Coronal section of cerebral hemispheres. Cystic necrosis in the ventral putamen (arrow). Cerebral atrophy

MBD-13. HEPATIC ENCEPHALOPATHY (NON-WILSONIAN). **Globus pallidus.** Astrocytes with enlarged, lucent, nuclei (Alzheimer Type II glia)

This change in astrocytes is seen in many diseases of the liver, including hepatitis, cirrhosis, and urea cycle enzyme deficiencies. Alzheimer type II glia have nothing to do with Alzheimer's disease. Dr. Alzheimer managed to have his name associated with several clinical and neuropathological entities.

MBD-14. SUBACUTE CEREBELLAR DEGENERATION, NUTRITIONAL TYPE. **Sagittal section of cerebellum.** Atrophy of anterior-superior sector of the vermis (top)

This is seen in chronic nutritional deficiencies, often in alcoholics.

MBD-15. SUBACUTE CEREBELLAR DEGENERATION, NUTRITION TYPE. **Cerebellum.** Atrophy of the cerebellar folia with narrow molecular layer

Marked loss of both Purkinje and granule neurons. Cellularity of Purkinje cell layer due to proliferation of astrocytes (Bergmann glia)

DEVELOPMENTAL DISEASES

DD-1. ANENCEPHALY. **Top view of newborn head.** Absence of skin and cranial bones. Vascular and glial tissues (cerebro-vasculosa) replacing the hemispheres. Prominent orbital ridges (top)

A fringe of scalp with hair can be seen peripherally, but the large extent of the cranial contents are uncovered and the hemispheres are missing.

DD-2. SPINA BIFIDA AND LARGE MYELOMENINGOCELE. **Posterior view of lumbo-sacral region.** Midline defect. Disorganized mixture of nerve roots, abnormal vessels, meninges, spinal cord tissue. Absence of posterior elements of vertebrae

DD-3. SPINA BIFIDA WITH SPINAL CORD MALFORMATION. **Coronal section, Hematoxylin-Eosin stain.** The posterior spinal vertebral processes are not properly fused at the midline. Meninges from the underlying spinal cord extended between them and formed a fluid filled sac in the overlying skin (meningocele; not shown). The spinal cord is split into two halves by a fibrous septa (diplomyelia = split cord). Each half of the spinal cord has separate and multiple spinal canals. The neuronal organization in the cord is also abnormal.

Spinal cord abnormalities often underly both meningoceles and myelomeningoceles.

DD-4. ARNOLD-CHARI MALFORMATION. **Medial surface of right hemisphere.** Hydrocephalus (enlarged right lateral ventricle). "Beaking" deformity of inferior colliculus (center right). Dorso-ventral flattening and elongation of pons and medulla (bottom). Finger-like elongation and downward displacement (herniation) of the cerebellar vermis (bottom right)

DD-5. LISSENCEPHALY. **(A) Coronal section of cerebral hemispheres.** The cerebral surface is largely without gyri; only a few small few gyri are present. The Sylvian fissure is evident on the left side. The cortex is markedly thickened, reflecting the incomplete migration of neurons to form the cortex and abnormalities in neuronal positioning. **(B) Myelin stain of lissencephalic brain.** This brain is predominantly agyric; a few gyri are present in the cingulate and temporal cortices. Note the markedly thickened cortex but apparently normal formation of deep gray nuclei (caudate, putamen and globus pallidus). **(C) Axial T2 FLAIR MRI image.** The thickened cortical layer shows only a few shallow gyri and the underlying white matter is reduced; the Sylvian fissure is present bilaterally.

Lissencephaly represents a spectrum of gyral abnormalities, from agyria (no gyri) to pachgyria (large gyri, fewer in number). There are abnormalities in cortical layering and neuronal heterotopias near the ventricles, reflecting defects in neuronal migration. Lissencephaly is not a specific disease but is associated with sporadic or familial inheritance patterns and may be caused by teratogens (e.g. alcohol).

DD-6. GERMINAL MATRIX HEMORRHAGE. **Coronal section of cerebral hemispheres.** Lateral ventricles filled with blood by extension of a germinal matrix hemorrhage.

These hemorrhages are often seen in premature infants. They arise in the germinal zone in the lateral wall of the lateral ventricles, and sometimes extend into the ventricles or into subcortical brain tissue.

DD-7. PORENCEPHALY. **Lateral surface of left hemisphere.** Large defect in hemispheric wall covered by leptomeninges. Defect in continuity with the lateral ventricle, leading to communication between subarachnoid space and lateral ventricle.

This lesion is the result of severe hypoxic or ischemic injury in the distribution of a major arterial division during early development.

DD-8. MULTICYSTIC ENCEPHALOPATHY. **Coronal section of cerebral hemispheres.** Cavities in hemispheric gray and white matter (the largest beneath the medial convolutions on right)

This picture is usually the result of hypoxic or ischemic injury well into the last trimester of gestation.

DD-9. TUBEROUS SCLEROSIS. **Coronal sections.** Numerous subependymal gliomas [arrows] (so called "candle gutterings") on the surfaces of the lateral ventricles

These lesions are benign astrocytic proliferations (hamartomas). They often calcify, thus becoming radiographically visible.

DD-10. TUBEROUS SCLEROSIS. **Coronal section of parieto-occipital lobe.** Whitish "tubers" replacing gray bands of cortex

The tubers in this inherited disease are composed of abnormal, disorganized mixtures of bizarre neurons and glial cells.

NEOPLASTIC DISEASES

ND-1. DIFFUSE ASTROCYTOMA. **Coronal section of cerebral hemispheres.** Enlargement of thalamus and infiltration of adjacent white matter (left)

The infiltrative quality of this tumor and, in this example, its relatively inaccessible location (to surgery) are well-demonstrated here.

ND-2. FIBRILLARY ASTROCYTOMA. **Centrum semiovale.** Uniform nuclei, low cellularity, characteristic fibrillary background.

The thalamic astrocytoma in #104 would have a similar appearance but would also reveal entrapped neurons. The white matter version is the most frequent cerebral neoplasm in adults, and it inevitably undergoes malignant change.

ND-3. CYSTIC ASTROCYTOMA. **Cerebellum.** Tan neoplasm with cysts

In spite of the posterior fossa location of this neoplasm, which is usually seen in childhood, the prognosis is favorable - even with incomplete removal.

Note: The tumor is relatively well circumscribed.

ND-4. JUVENILE PILOCYTIC ASTROCYTOMA. **III ventricle.** Dense areas, usually with Rosenthal fibers around blood vessels, alternating with loose protoplasmic areas

In spite of the benign histologic pattern of this neoplasm and its slow progression, its location may render it largely inoperable and thus fatal (e.g. when in III ventricle or brainstem). These tumors occur in other regions (cerebellum and cerebral cortex) where it is surgically accessible and thus carries a more favorable prognosis.

ND-5. ANAPLASTIC ASTROCYTOMA. **Centrum semiovale.** Moderate pleomorphism and cellularity with vascular proliferation. WHO grade III.

This is the usual intermediate stage of fibrillary astrocytomas in the cerebrum of adults. Its prognosis is intermediate between that of the fibrillary astrocytoma (WHO grade II) and the higher grade IV lesion that follows, glioblastoma multiforme.

ND-6. GLIOBLASTOMA MULTIFORME. **Unfixed coronal section of cerebral hemispheres.** Variegated appearance due to hemorrhages (red) and necrosis (white, top left). Fairly well-demarcated, in part, with invasion of corpus callosum (center), midbrain (bottom center), and cingulum. Cingulate herniation and compression of lateral ventricle

Involvement of the corpus callosum is highly distinctive of glioblastoma, infiltrative astrocytoma, or lymphoma and is highly unusual in metastatic neoplasms.

ND-7. GLIOBLASTOMA MULTIFORME. **Centrum semiovale.** Increased cellularity and pseudopalisades around foci of tumor necrosis (serpiginous areas with pink interior). WHO grade IV astrocytic tumor.

In addition to increased cellularity and vascular proliferation, the diagnostic feature of glioblastoma multiforme on microscopic examination is necrosis. When the cell nuclei line up around small areas of necrosis (palisades or pseudopalisades), this is said to be pathognomonic of glioblastoma. Vascular proliferation (glomeruloid type, not shown) is characteristically quite prominent in these tumors.

ND-8. OLIGODENDROGLIOMA. **Frontal lobe.** Characteristic "fried-egg" appearance of the cells due to artifactual cytoplasmic swelling

Although usually slow-growing, oligodendrogliomas may also be malignant and are then designated as anaplastic oligodendroglioma. In common with their astrocytic counterparts, increased pleomorphism, mitotic activity, endothelial proliferation, and tumor necrosis are the histologic hallmarks of the malignant or anaplastic form. However, these histologic-biologic correlations are not as good as those seen in the cerebral fibrillary astrocytoma.

ND-9. EPENDYMOMA. **Fourth ventricle.** Characteristic perivascular pseudorosettes (top center, bottom right, left)

Malignant histologic features in these lesions seem to be less important than the location and the age of the patient. For example, fourth ventricular ependymomas in children under the age of 2 are highly aggressive lesions, while the spinal cord ependymomas, especially those of the filum terminale, grow slowly.

ND-10. MEDULLOBLASTOMA. **Cerebellum.** (A) Densely packed undifferentiated small cells with little cytoplasm and high mitotic rate. Tumor cells may form neuroblastic rosettes (Homer Wright) where they are circumferentially arranged and send processes towards the center without forming a lumen (note rounded neuropil areas surrounded by tumor cells). (B) Several Homer Wright rosettes are shown. Note also mitotic figures and apoptotic tumor cells.

The undifferentiated quality of these cells had prompted their designation as primitive neuroepithelial or neuroectodermal tumors (PNET). Indistinguishable cells may be seen in neoplasms elsewhere, such as the pineoblastoma in the pineal gland.

ND-11. MENINGIOMA. **Coronal section of cerebral hemispheres.** Falcine attachment (top center) of encapsulated neoplasm with compression of adjacent parietal lobe and sharp demarcation

These slow growing, discrete, and firm lesions frequently invade dura and bone but rarely the brain. When they do, their biologic behavior is distinctly more aggressive.

ND-12. MENINGIOMA. **Parasagittal location.** Characteristic whorls with variable degrees of central calcification (psammoma bodies)

This represents the most diagnostic histologic pattern of meningiomas.

ND-13. SCHWANNOMA (NEURINOMA, NEURILEMMOMA). **Transverse section of medulla.** Well encapsulated, yellowish neoplasm of VIII cranial nerve (center right) [See also ND-14]

This lesion is the most common neoplasm of the cerebellopontine angle. It must be distinguished from exophytic astrocytomas, metastatic lesions, and meningiomas.

ND-14. SCHWANNOMA. **Peripheral nerve.** Dense collections or fascicles of spindle cells. Palisades at edge of eosinophilic fibrillar material (Verocay bodies)

This neoplasm is composed exclusively of Schwann cells, whether located in peripheral, cranial, or spinal nerves (see ND-16]. The other major nerve sheath neoplasm, the neurofibroma, has a more loosely packed, fibromyxomatous histologic appearance and contains a mixed proliferation of fibroblasts and perineurial cells in addition to the Schwann cell.

ND-15. METASTATIC MELANOMA. **Unfixed coronal section of cerebral hemispheres.** Two foci of sharply demarcated neoplasm at gray-white junction with central tumor necrosis or "umbilication" and hemorrhage (bottom left and right).

By the time of death patients with skin melanoma almost invariably present with metastatic lesions in CNS. The characteristic location of metastatic lesions at the gray-white junction and at multiple sites are well demonstrated in this image.

DISEASES OF MYELIN

DM-1. MULTIPLE SCLEROSIS. **Cerebral cortex and white matter, parieto-occipital region. Heidenhain.** Several "punched out" lesions of total loss of myelin in subcortical white matter (classical plaques). Between them, a relatively large area of mild pallor of myelin staining ("shadow" plaques). Several other irregular foci of demyelination. Very-faintly-gray bands of cortex without lesions. (Numerous tiny clear "holes" are retraction artifact of blood vessels).

While some cases of allergic encephalomyelitis can resemble the classical plaques of multiple sclerosis, shadow plaques, which reflect incomplete remyelinative activity, are characteristic of MS.

DM-2. MULTIPLE SCLEROSIS (MS). **Coronal section of cerebral hemispheres.** Chronic demyelination plaques around superior-lateral angle of lateral ventricles, around temporal horns, in putamen-internal capsule (left), and elsewhere.

Except for preferential sites like the angles of the ventricles, the asymmetry and multiplicity of plaques of different ages is virtually diagnostic of MS.

DM-3. MULTIPLE SCLEROSIS. **Centrum semiovale.** Active demyelinating lesion (acute plaque) with perivascular collections of mononuclear cells (mostly small lymphocytes). Marked hyperplasia and hypertrophy of astrocytes (reactive astrocytosis). Scattered lipid-laden macrophages. Loss of oligodendrocytes (Selective breakdown of myelin difficult to appreciate by H&E)

Oligodendroglial loss appears to follow closely upon the inflammatory infiltration and breakdown of myelin in MS.

DM-4. MULTIPLE SCLEROSIS. **Centrum semiovale. LFB-PAS (A) and Bielschowsky (B).** LFB-PAS stain demonstrates marked loss of myelin (blue) in this acute plaque; note normal parenchyma at top of section. Bielschowsky stain demonstrates the relative preservation of axons (black) in the region of demyelination

The relative preservation of axons in MS indicates that the loss of myelin is the primary pathology in these lesions. This distinguishes these lesions from infarctions in which both axons and myelin are similarly destroyed.

DM-5. MULTIPLE SCLEROSIS. **Centrum semiovale.** Chronic Plaque with loss of myelin staining, loss of oligodendrocytes and isomorphic gliosis. Inflammatory infiltrates are no longer prominent.

Isomorphic gliosis usually reflects loss of myelin within myelinated fiber tracts where the astrocytes are believed to be physically forced into this parallel arrangement.

DM-6. ACUTE DISSEMINATED (POSTINFECTIOUS) ENCEPHALOMYELITIS **Centrum semiovale. LFB-PAS.** Small perivenous foci of complete demyelination with sparse mononuclear cells

The perivenular localization is the hallmark of this monophasic disease following vaccinations or viral infections. The pathogenesis is not believed to be direct infection of the nervous system by the virus but an allergic cross-reaction between myelin proteins and homologous viral proteins.

DM-7. GLOBOID CELL (KRABBE'S) LEUKODYSTROPHY (GLD). **Coronal section of cerebral hemispheres.** Diffuse or confluent loss of myelin in almost entire centrum semiovale. Frequent sparing of arcuate or "U" fibers

This gross appearance is characteristic of many leukodystrophies; they differ from each other in their microscopic and ultrastructural features.

DM-8. METACHROMATIC LEUKODYSTROPHY (MLD). **Peripheral nerve. Acid cresyl violet.** Abnormal myelin breakdown products staining metachromatically (reddish brown) and decrease of myelinated nerve fibers

This leukodystrophy in particular also affects the peripheral nerve severely. Peripheral nerve biopsy and demonstration of metachromasia is diagnostic.

DM-9. GLOBOID CELL LEUKODYSTROPHY. **Centrum semiovale.** Clusters of multinucleated and uninucleated globose or globoid cells (top center and bottom left)

Instead of metachromasia or inflammation, this leukodystrophy is characterized by the accumulation of globoid cells. The galactocerebrosidase deficiency results in the accumulation of psychosine rather than the expected galactocerebroside. GLD may also affect the peripheral nervous system.

DM-10. ADRENO-LEUKODYSTROPHY (ALD). **Centrum semiovale. LFB.** Perivascular collections of mononuclear cells (left) with loss of myelin, reactive astrocytosis and macrophages, similar to acute MS. The diffuse distribution of white matter demyelination and clinical history distinguish this disease from MS.

DM-11. CENTRAL PONTINE MYELINOLYSIS. **Transverse section of pons.** Demyelination in mid-central basis pontis

This lesion is most commonly seen after too rapid correction of hyponatremia. It entered our world of medicine when parenteral administration of solutions became available. The lesion is largely one of intramyelinic edema and thus appears to be another example of cytotoxic edema.

DM-12. SPONGY DEGENERATION . Cerebral gray-white junction. Vacuolar appearance of intramyelinic edema involving deep cortex and arcuate fibers (bottom) with a barely perceptible increase in cortical astrocytes.

This fatal disease of infancy (Canavan's disease) is usually seen in a localized population (Ashkenazi Jews) and is now known to be due to deficiency of aspartoacylase. In addition to intramyelinic edema, there is also Alzheimer type II astrocytosis in deep cortex. In contrast to most leukodystrophies, the cortical arcuate fibers are preferentially involved in this disease.

NEUROMUSCULAR DISEASES

NM-1. SEGMENTAL DEMYELINATION AND REMYELINATION. **Peripheral nerve.** Top: Nodes of Ranvier demarcate normal internodes, each with a single Schwann cell nucleus. Next: Early myelin breakdown in two of three internodes, axon intact. Next: Complete demyelination. Bottom: Remyelinated internodes shorter than normal, and thinner (not shown)

Conduction block of action potentials appears early with subsequent breakdown of internodal myelin. Macrophages recruited from the blood stream are the chief removers of myelin sheath. Conduction reappears at reduced velocity as Schwann cell forms new thinner myelin sheaths.

NM-2. NORMAL MYELINATED FIBER AND SEGMENTAL REMYELINATION. **Teased myelinated fibers following osmication.** Top: Normal myelinated fiber with uniformly spaced nodes of Ranvier (arrows). Bottom: Short and thin remyelinated internodes flanked by residual internodes of normal length and caliber

The combined length of the three new internodes equals the length of the normal internode on the left. This implies that the original internode was replaced by three internodes (and three Schwann cells).

NM-3. ONION BULB. **Remyelinated nerve fiber.** Thinly-myelinated nerve fiber surrounded by concentric processes of Schwann cell cytoplasm, resembling a sliced onion (bottom). Between Schwann cell processes, collagen fibers in cross section (dots). Longitudinal section of an onion bulb next to normal internodes (top)

Onion bulb formation reflects repeated episodes of demyelination and remyelination over a period of months or years, each round producing Schwann cells and redundant cell processes.

NM-4. ONION BULBS IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY. **Peripheral nerve, semithin section, toluidine blue.** Most bulbs with one or more thinly remyelinated nerve fibers. Some bulbs without a visible myelin sheath, presumably containing a naked axon with insufficient remyelination. Schwann cell processes identifiable by nuclei, not cytoplasm, in this section

This CIDP patient had a relapsing polyneuropathy for ten years. The neuropathy in this disease is thought to be caused by T cells and/or autoantibodies acting on the surface membrane of Schwann cells, but target antigens have not been identified in most instances.

NM-5. ONION BULB. **Sural nerve of a similar patient, electron micrograph.** Disproportionately thin myelin sheath, an indication of remyelination. Concentric extensions of Schwann cell cytoplasm. Collagen fibrils in transverse section (dark dots) among the cells. Indistinct basal lamina around each Schwann cell process.

The diagnostic features of a chronic demyelinating neuropathy are: 1) Segmental demyelination of teased nerve myelinated fibers. 2) Segmental remyelination of teased nerve fibers. 3) Onion bulb formation in nerve sections.

NM-6. WALLERIAN DEGENERATION AND REGENERATION. **Peripheral nerve.** Top: Transected nerve fiber. Next: Retraction of paranodal myelin sheath distal to point of transection. Next: Axons and myelin breaking down and blood-borne macrophages appearing to remove debris. Next: Proliferation of Schwann cells within tube of basal lamina (Bungner's band); axon growing from proximal stump into Bungner's band; branching of regenerating axon. Bottom: Regenerated nerve fiber with short and (not shown) abnormally thin myelin sheaths

NM-7. WALLERIAN DEGENERATION. **Teased myelinated fiber following osmication.** Myelin breakdown into a linear train of myelin ovoids (debris) secondary to axonal degeneration.

All myelin sheaths distal to the point of transection of the axon have broken down simultaneously to form a series of globules of phagocytosed myelin debris within macrophages, known as myelin ovoids.

NM-8. ALS. **Spinal cord, ventral horn.** Loss of large (alpha) motor neurons with a few survivors (bottom center) and astrocytosis

NM-9. AMYOTROPHIC LATERAL SCLEROSIS (ALS). **Thoracic spinal cord, Mahon.** Pallor and atrophy of crossed (lateral) corticospinal tracts

In ALS, axons and myelin degenerate both in the corticospinal tracts and in the ventral spinal nerve roots. In the upper motor neuron system, the fiber degeneration is much more severe in the spinal cord than at brain stem or cerebral levels, suggesting a CNS version of distal axonopathy. In the ventral nerve roots, loss of fibers mostly reflects loss of lower motor neurons in the ventral horn, but peripherally motor nerves demonstrate a minor distal axonopathy that may antedate death of the nerve cell.

NM-10. ALS. **Spinal cord, ventral horn. Immunoperoxidase-ubiquitin.**
Haphazardly arranged fibrils within a surviving motor neuron

Surviving motor neurons in ALS have distinctive intracytoplasmic ubiquitin-containing fibrillar inclusions, first reported in 1988. The structure of the inclusion often resembles a ball or skein of yarn. Ubiquitin is a small protein that forms covalent bonds to other proteins and marks them for degradation through the ATP-dependent, non-lysosomal proteolytic system. This protein is expressed in several different inclusions of neurodegenerative diseases including neurofibrillary tangles and Lewy bodies. In ALS, skein-like inclusions are nearly invisible in H&E stained sections and are not argentophilic. Ubiquitin is presumably linked to protein, but the composition of the inclusion has not been elucidated yet.

NM-11. ALS. **Spinal cord, ventral horn. Immunoperoxidase-neurofilament.**
Remaining large motor neuron and a proximal axonal swelling or "spheroid" (center)

"Spheroids" or swollen axons occur in a wide variety of conditions, including certain toxic distal axonopathies. In lower motor neuron disease they occur in the proximal segment of the axon before the cell body is clearly affected. Candidate toxins have been intensively investigated in ALS, but the etiology of ALS remains obscure.

NM-12. NORMAL SKELETAL MUSCLE. **Transverse cryostat sections stained by H&E (left) and myofibrillar (myosin) ATPase (right).** Polygonal fibers with nuclei at the margin and uniform, finely textured sarcoplasm (left). Very thin layer of connective tissue (endomysium) between fibers and a thicker layer (perimysium) around bundles or fascicles of fibers (left). Random mosaic of type I (pale slow-twitch) fibers and type II (dark, fast-twitch) fibers (right)

NM-13. NORMAL SKELETAL MUSCLE. **Transverse cryostat sections stained by modified Gomori trichrome (left) and NADH-tetrazolium reductase (right).** Myofibrils green; mitochondria and sarcotubular system as darker, slightly reddish, fine granules (left). Admixture of dark mitochondria-rich, slow-twitch, type I fibers and pale, mitochondria-poor, fast-twitch, type II fibers

NM-14. NEUROGENIC ATROPHY. WERDNIG-HOFFMANN DISEASE. **H&E.** Clustering of atrophic fibers (group atrophy). A group of hypertrophic fibers (right center). Thickened perimysial septa between muscle fascicles

Werdnig-Hoffman disease is a fatal hereditary, autosomal recessive, infantile spinal muscular atrophy. Muscle biopsy distinguishes this disease from infantile myopathies with hypotonia as a major symptom.

NM-15. NEUROGENIC DISORDER WITH FIBER TYPE GROUPING. PERIPHERAL NEUROPATHY. **Cryostat section, myofibrillar ATPase.** Clustering of fibers of the same histochemical type.

A single motor neuron unaffected by the disease is thought to act through collateral reinnervation to eventually supply all fibers of a group. Because the nerve cell can determine fiber type, it can convert fibers of a group to produce fiber type grouping. In this patient, reinnervation has apparently kept pace with muscle denervation because few, if any, muscle fibers are atrophic.

NM-16. NEUROGENIC ATROPHY. **Cryostat section, NADH-TR.** "Target" fibers

The central zone of pallor reflects absence or reduction of mitochondria. Why target fibers develop in muscle degeneration is not clear, but in experimental models they form when nerve regeneration and reinnervation of muscle fibers takes place.

NM-17. FIBER TYPE GROUPING AND GROUP ATROPHY. **Schematic sequence.** **Top left:** Normal motor units. **Bottom left:** One denervated motor unit and atrophy of denervated muscle fibers. **Top right:** Sprouting axons of a surviving motor unit and reinnervation of muscle fibers with the formation of type grouping. **Bottom right:** As the motor neuron or axon in the previous panel is affected by disease, the muscle fibers become atrophic, forming group atrophy

NM-18. MYOPATHY. DUCHENNE DYSTROPHY. **Cryostat section, H&E.** Increased variation in fiber size. Dark eosinophilia and hyaline textured fibers. Necrotic fibers (top right) with breakdown of normal myofibrillar texture. Small, basophilic fibers with large nuclei undergoing regeneration (top left). Endomysial fibrosis (pale pink collagen) between muscle fibers

Both necrosis and regeneration in a single muscle fiber (cell) is typically segmental, leaving intact portions of muscle fibers (not shown). The rest of the length of the fiber is more or less normal at the same time. Necrotic sarcoplasm is removed by macrophages. Simultaneously, satellite cells become activated and proliferate as individual myoblastic cells. Subsequently, the myoblasts fuse with each other and with the surviving segments of muscle fiber to form a regenerating fiber with basophilic sarcoplasm. In normal muscle, the satellite cells remain dormant as reserve cells for muscle fiber regeneration.

NM-19. MYOPATHY. DUCHENNE DYSTROPHY. **Cryostat section, immunofluorescence-dystrophin.** Dystrophin at periphery of fibers in normal muscle (1a). Anti-serum for dystrophin omitted as control (1b). Loss of immunoreactive dystrophin in Duchenne dystrophy (2a, 2b)

In Duchenne dystrophy, an X-linked recessive disorder, the gene that encodes for dystrophin (a large protein of about 410 kD) is defective. The normal protein is thought to stabilize the muscle fiber sarcolemma.

NM-20. INCLUSION BODY MYOSITIS. Increase variation in fiber size. Rimmed vacuoles in two myofibers (left side of field). Centrally located myonuclei. Endomysial fibrosis and one large lymphocytic infiltrate.

Inclusion body myositis is the most common myopathy in adults over the age of 50 years. Cytotoxic T cells invade muscle fibers (not shown), but the patients usually do not respond to immunosuppressive therapy.

NM-21. MITOCHONDRIAL MYOPATHY. CYTOCHROME C OXIDASE DEFICIENCY. **Cryostat sections, modified Gomori trichrome stain (left) and succinate dehydrogenase (SDH, right).** Ragged red fibers (left). Hyperstaining fibers (right)

Hereditary disorders of the electron transport chain are often attended by excessive numbers of mitochondria which, in muscle, appear as aggregates of finely granular material with a dark reddish color in the modified Gomori trichrome. Enzymes unaffected by the abnormal gene often show increased activity, as in the SDH stain in this case. Increased staining is particularly common in the histochemical reaction for SDH in disorders caused by mutations of mitochondrial DNA, because this electron transport carrier (complex II) is entirely encoded by nuclear DNA.

NM-22. CENTRAL CORE DISEASE. **Paraffin section, trichrome (left); Cryostat section, NADH-TR (right).** Core lesions with abnormal myofibrils (left). Core lesions with loss of mitochondrial staining and a thin margin of increased staining (right)

Central core disease is a rare congenital myopathy with an autosomal dominant pattern of inheritance. The central cores closely resemble target fibers, but no disorder of motor neurons or axons has been found. Patients with this disorder are at risk for malignant hyperthermia, a potentially fatal reaction to halothane and other anesthetic agents. Both disorders have been linked to mutations of the gene for the ryanodine receptor, a calcium-release channel of the sarcoplasmic reticulum.

TRAUMATIC DISEASES

TD-1. SKULL FRACTURE, FLOOR OF ANTERIOR FOSSA. **Face.**
Orbital ecchymoses

The hemorrhage from the fracture pools in the orbital soft tissues. A similar appearance could result from direct trauma to the orbits, but the absence of other evidence of facial trauma makes this unlikely.

TD-2. EPIDURAL HEMATOMA. **Head at autopsy, scalp reflected and calvarium removed.** Localized accumulation of fresh blood, external to the dura mater

A temporal location is most common for this lesion, which usually results from fracture of the squamous portion of the temporal bone with laceration of the middle meningeal artery, which passes along a groove in this bone.

TD-3. SUBDURAL HEMATOMA, FRESH: **Dorsal surface of unfixed brain.**
Bilateral parasagittal accumulation of fresh blood

The hemorrhage is due to rupture of bridging veins coursing from the surface of the brain to the superior sagittal sinus.

TD-4. SUBDURAL HEMATOMA, OLD, BILATERAL. **Floor of cranial cavity after removal of brain.**

Outer membrane, adherent to dura. Well-formed inner membrane, best appreciated at frontal poles of blood clot. Liquefaction and partial resorption and retraction of blood clot. Brownish tones secondary to hemosiderin.

TD-5. SUBDURAL HEMATOMA, SOME 2 WEEKS AFTER INJURY.
Dura mater and subdural space at low magnification. Well-formed outer membrane of granulation tissue between dura mater (above) and blood clot. Thin inner membrane on free surface of clot.

TD-6. SUBDURAL HEMATOMA, ALMOST RESOLVED. **Inner aspect of calvarial dura with falx cerebri and portion of tentorium cerebelli (right).**
Hematoma completely resorbed over the left cerebral hemisphere (top), less so over the right. Inner and outer membranes fused. Hemosiderin remaining in neomembranes

TD-7. HEMISPHERIC COMPRESSION BY CHRONIC SUBDURAL HEMATOMA. **Coronal section of cerebral hemispheres at posterior horns of lateral ventricles.** Flattened convexity of right cerebral hemisphere, both above and below equatorial plane. Small right lateral ventricle. Absence of midline shift

A subdural hematoma is free to spread out over the surface of the brain and commonly produces a flat deformity of the underlying brain. In contrast, an epidural hematoma is restricted by the dura matter and produces a concave deformity. An acute subdural hematoma of comparable size would probably cause a midline shift.

TD-8. CEREBRAL CONTUSIONS, RECENT. **Coronal section of frontal lobes, anterior to lateral ventricles.** Superficial hemorrhagic areas on ventral surface of brain

The orbital surface of the brain is a common site of cortical contusions, along with the temporal poles, frontal poles, and the cortical banks of the Sylvian fissure.

TD-9. CEREBRAL CONTUSION, ANCIENT. **Anterior view of temporal poles and coronal section of frontal lobes.** Superficial cavity of left temporal pole. Communication with subarachnoid space. Brown discoloration due to hemosiderin.

TD-10. DIFFUSE AXONAL INJURY. **Coronal section at level of head of caudate nucleus.** Bilateral, slit-shaped hemorrhages in white matter of superior frontal gyri

Slit-shaped hemorrhages in the white matter, presumably due to shearing forces on blood vessels, are a gross hallmark of diffuse axonal injury, which itself can be appreciated only by microscopic examination. The hemorrhages shown here are frequently referred to as "gliding contusions," although they are not true contusions.

TD-11. ATLANTO-OCCIPITAL DISLOCATION. **Base of skull.** Odontoid process, still covered by dura mater, displaced posteriorly into foramen magnum. Spinal cord not compressed, but nearly so.

Cervical spinal injury should be suspected in all cases of serious head or facial trauma. Dislocation of the odontoid process can occur with or without odontoid fracture (not present in this case). Note that movement of the head would result in severe compression of cervical spinal cord, it is essential to immobilize the spine whenever the possibility of a spinal injury exists.

NEUROPATHOLOGY CLINICAL EXERCISES

FOR

SMALL GROUP DISCUSSIONS

Case 1: Vertigo

Chief Complaint: A 58-year old diabetic man developed nausea and dizziness.

History of present illness: On the day of admission, a 58-year old left-handed pastry chef awoke with a dull headache, nausea, and a sense of spinning. When he attempted to stand, he felt himself tending to fall to the right, although did not lose balance. He initially attributed the symptoms to a migraine headache, triggered by a glass of red wine before bed. As the morning progressed, his dizziness increased, and he noted slurred speech and clumsiness with the right hand. A friend drove him to the Emergency Room.

Review of systems: There was no history of vomiting, diplopia, blurred vision, hearing loss, weakness, or numbness. There was no recent history of head or neck trauma, chest pain, palpitations, dyspnea, or other symptoms.

Past medical history:

1. Type II diabetes of 5 years' duration, treated using glipizide [Glucotrol]
2. Hypertension of ten years' duration, treated using enalapril [Vasotec]
3. Hypercholesterolemia, treated using atorvastatin [Lipitor]
4. Occasional headaches

Family history: His mother was alive at age 88, but had hypertension, diabetes and dementia. His father had died at age 66, following a myocardial infarction. His only sibling, a brother, underwent a triple CABG at age 50. His brother suffered from migraine headaches.

Personal history: He was a former 1 pack per day smoker for 15 years, having quit at age 31. He drank up to two glasses of wine most evenings, and had a fondness for single malt whiskey.

Examination: The patient was a heavy-set 58 year old man who looked anxious. His blood pressure was 190/100 and his heart rate was 76 and regular. His weight was estimated at 230 pounds. He was alert with normal cognition and language function, but his speech was slightly dysarthric, with an irregular cadence. Visual fields were full and the fundoscopic exam was normal. His right pupil was small and reactive, with a slightly drooped upper eyelid. He had right-directed horizontal nystagmus when looking to the right, accompanied by a rotatory component. He had decreased hearing in the right ear. His facial sensation was decreased over the right side, and there was absent perception of pinprick and temperature over the left body. Bulk, tone and power were normal in all muscles. He had impaired coordination in the right hand, with dysmetria and past-pointing in a target-following test. His right coordination was impaired on the heel-to-shin maneuver. He was unable to stand, tending to topple to the right.

Course in hospital:

Within one hour after arriving in the ER, he suddenly complained of being unable to see. He then became unable to speak or move, and seemed unable to move his eyes. His blood pressure was

210/120 and the heart rate 60. He breathing became shallow and irregular, and he made gurgling noises. He was intubated, and placed on a ventilator. On neurological examination he was unresponsive. His pupils were small, but remained slightly reactive to light. The fundoscopic exam was difficult to perform due to pupillary miosis. Using oculocephalic maneuvers, his eyes could not be deviated horizontally or vertically. His corneal reflexes produced no response. His motor exam showed a flaccid paralysis of all limbs, with no withdrawal responses or localization to pain. His deep tendon reflexes were hypoactive, and the plantar responses were indifferent.

The patient underwent a cranial imaging study before transfer to the NICU. On arrival to the NICU, approximately 12 hours after his initial symptoms, he was unresponsive, apneic, with no brainstem reflexes. His pupils were 6 mm, dilated and unreactive.

Issues to discuss:

1. What is the localization of this patient's initial exam findings? What neurological structures are involved in his disease process? In which vascular territory are the patient's initial symptoms and signs?
2. What are the hallmarks of brainstem localization? What is a Horner syndrome?
3. What happened to this patient after arrival in the ER? What additional neurological structures were affected by his deterioration?
4. What are the clinical criteria for brain death?
5. What were this patient's risk factors for cerebrovascular disease?

Case 2: Forgetfulness

Chief complaint: The patient was an 81-year old man with slowly progressive memory loss.

History of present illness: The patient was a retired electrical engineer who worked until the age of 70. In the years following his retirement, the patient gradually became forgetful, often losing objects or missing appointments. He became slower at decision-making, and had difficulties with recall of small details. Formerly a fastidious hobbyist, the patient could no longer assemble model airplanes, which now made him frustrated and irritable. Gradually, he became unable to manage the household finances, complete a shopping list, or set the table for dinner. He tended to wander around his neighborhood without knowing how to find his way home. On one occasion, he got into the subway, and was brought back by the police. When he was subsequently confined to his house, he insisted that people were plotting to kidnap him. His sleep was disturbed with frequent awakenings during which he would call out to his wife for help. During the day, he slept for 3 hours, and often sat in his chair looking out of the window.

Review of systems: There was no history of systemic illness, seizures, myoclonus, headaches, visual deficits, hearing loss, weakness, tremor, dysarthria, or bladder impairment. He did not have hypertension, diabetes, tobacco use, toxin exposure or excessive alcohol intake.

Family history: Negative for dementia or other neurological disorders. A son suffered from schizophrenia.

Examination: On examination, he was slightly disheveled, but pleasant, alert and cooperative. He did not seem to know why he was being examined, and could not give the date or location. He tended to cover up his errors, stating, "Why do you ask me these silly questions?" His speech was fluent and articulate, but he often lost track of his train of thought. Sometimes, his speech was laden with technical terms from his engineering background, but did not make sense. His repetition was intact. When asked to write a sentence, he wrote his first name. He could not copy a cube. He could read aloud, but not follow a written command, or perform a two-step command. He had difficulty imprinting 3 objects, and could remember none subsequently. When shown a standard series of pictures, he named a wristwatch a "clock", and a dolphin a "pluke". When asked to list the past five Presidents, he could name only Kennedy and "the peanut farmer." He could not subtract serial 3s from 20. The digit span was 4 forwards, but he could not repeat the sequence backwards. He tended to persevere on performing tasks of the neurological exam. When asked to pantomime simple actions, he performed adequately.

The cranial nerve exam was normal. The motor exam showed active resistance to passive movement, but no weakness or spasticity. Bilateral grasp reflexes, palmomental reflexes, and a snout reflex were elicited. Sensory exam, reflexes, coordination and gait were all completely normal.

Laboratory:

Neuropsychological testing - The patient had undergone neuropsychological testing at age 76 and 81. Over this interval, the full scale IQ declined from 125 to 99. Prominent deterioration was seen in short-term recall, verbal memory, language skills, spatial perception and executive function.

Electroencephalogram [EEG] – Mild, diffuse, nonfocal background disorganization and slowing.

Cranial MRI - Mild cortical and subcortical atrophy.

Questions for discussion:

1. How is a diagnosis of dementia made?
2. Differentiate between dementia, delirium and pseudodementia.
3. What cognitive deficits are revealed by the neurological exam, and to what parts of the cerebrum do they localize?
4. What is dysphasia? What is a paraphasic error?
5. List some causes of dementia, and describe how you would diagnose and treat them.
4. What is the most likely cause of dementia in this individual?

Case 3: Seizures

Chief complaint: The patient is a 39-year old right-handed accountant who experienced a seizure at work.

History of present illness: The patient was in his usual state of good health until 1 month before admission, when he first developed recurring episodes of tingling over the left side of his face and left hand, up to three per week. At least two of the episodes were associated with single, synchronized jerks in the left arm. On the day of admission, he was at work giving a presentation that had taken him most of the previous night to prepare, when he suddenly experienced a generalized seizure. A witness observed that he was standing at the lectern and in mid-sentence became silent. He developed a strange, twisted expression and had some jerking in the left face. He stiffened up, toppled to the floor, and experienced a generalized tonic-clonic seizure, lasting about 2 minutes. After the episode, he gradually became aware of his surroundings, and had no recollection for the event. He was exhausted, complained of mild headache, and had a left facial droop with weakness in his left arm and leg. He was taken to the hospital by ambulance, and experienced no further events.

Review of systems: Over the past several weeks, the patient had remarked to co-workers that he had headaches, and felt himself under a lot of pressure. His colleagues noticed that he was distracted, and vague; one co-worker wondered if he might be depressed. He had lost 5 pounds in the past month, attributed to poor eating habits.

Past medical history:

Migraine headaches, sometimes preceded by a visual aura of jagged peripheral lines, followed by a steady, throbbing headaches, often lasting for hours, and accompanied by nausea and phonophobia.

Personal history: The patient was unmarried and lived alone. His social history was unknown. There was no family history of neurological problems, including brain tumors, peripheral neuropathies or demyelinating disease.

Examination: Physical examination revealed a thin, pale well-developed man with normal blood pressure and respirations. The general exam was entirely within normal limits, including fundoscopic exam. On neurological exam, the patient was quiet, cooperative, and withdrawn. His answers to questions were slow, but always accurate. He had difficulty drawing a clock and copying a cube, requiring two tries for each task. When asked to pantomime a sequence of three actions, he perseverated on the first element. There was a grasp reflex on the left. On cranial nerve exam, his visual acuity and visual fields were normal. Extraocular movements were full but he had a preference to gaze to the right. On left gaze, he had left-directed horizontal nystagmus. Facial sensation was normal, but the corneal reflex was slow on the left. He had weakness of left eye closure, a flattened left nasolabial fissure, and weakness in the left lower face. The rest of the cranial nerve exam was normal, including olfaction, hearing, palate, tongue, and phonation. On motor exam, he had increased tone on the left side of his body, with three beats of clonus at the left ankle. He had mild weakness over the left side. Sensation appeared normal when the modalities were tested individually, but he had persistent extinction of left-sided sensation when both sides were stimulated simultaneously. The deep tendon reflexes were hyperactive on the left, but the plantar responses were flexor. Tests of

coordination and gait were slightly limited by the mild left hemiparesis, but otherwise revealed no additional deficits.

Laboratory:

Brain MRI - Large, minimally contrast-enhancing mass lesion in the right frontal lobe, surrounded by edema, and exerting considerable mass effect, including midline shift and compression of the lateral ventricle.

Clinical course: The patient underwent a frontal craniotomy with gross-total resection of the lesion. He did well post-operatively and had no further seizures on phenytoin, followed by carbamazepine, followed by phenobarbital therapy (the first two medications were not tolerated). His brain tumor was closely followed by serial MRI scans. Four years after his initial presentation, his headaches returned and increased in severity. He experienced another generalized seizure. A repeat brain MRI scan was obtained, and he underwent a craniotomy for further surgical resection.

Issues for discussion:

1. What type of seizure did this man experience? Provide a brief classification of seizures.
2. What is the differential diagnosis of seizures in an adult?
3. What is a Todd's paralysis?
4. How does the neurological exam correspond to the neuroimaging in this case? What aspects of the exam relate to a disturbance in the frontal lobe?
5. What is the differential diagnosis of a solitary mass lesion in a 39-year-old man? What additional testing would you request?
6. What is the typical treatment regimen for this patient? Did the surgeon successfully remove the entire lesion?
7. What eventually happened to the lesion in his brain?

Case 4 – Weakness and numbness

Chief complaint: The patient is a 34-year old woman with weakness and numbness in the legs.

History of present illness: The patient, a research assistant at Columbia University, was in her usual state of health when she awoke with a vague feeling of numbness over the entire side of her left leg. She attributed the numbness to having slept in an uncomfortable position. She described the leg numbness as “prickly and burning”, but stated that she could feel sensation over the involved region. Over the next day, her left leg felt increasingly “heavy” and “clumsy”, with a tendency to give out when attempting to weight-bear; she decided to skip her daily jog along Riverside Park. On the second day, her prickly numbness sensation persisted, and she fell in the shower when her left leg gave out. At this point, she decided to seek medical attention.

There was no recent history of back pain, trauma, headache, weakness or numbness in other extremities, or problem with vision, hearing, speech, swallowing or bladder function.

Past medical history: Five years ago, at age 29, the patient developed blurred vision in her right eye while canoeing in the Adirondacks. Her visual loss lasted 4 days, with gradual resolution over the next two weeks. She did not seek medical attention, or undergo testing after this event.

Family history: Her father died of a myocardial infarction at age 65, and mother, now 72, has hypertension under good control with medication. Two older male siblings were alive and well. A maternal aunt was in a wheelchair, diagnosis unknown.

Examination: The general examination revealed a thin, athletic-appearing female in no apparent distress. Her blood pressure was 133/84 and her pulse was 68. She weighed 124 pounds. The rest of the general exam was within normal limits.

On neurological examination, she was bright, cheerful, and articulate, with normal language and cognition. Her visual fields were full but she complained that colors did not seem as bright when viewed with the right eye. Her right optic disc was small and pale. The pupillary light reflex was brisk directly and consensually when light was shined into the left eye. However, when light was shined into the right eye, both pupils reacted sluggishly. The pupillary reaction was normal to convergence. The rest of the cranial nerve exam was normal, including olfaction, extra-ocular movements, sensation, strength and hearing. On motor exam, there was moderate weakness in the left leg, graded 4/5. She had increased tone in the left leg, with clonus at the ankle. Stretch reflexes were pathologically active in the arms and legs, and she had extensor plantar responses bilaterally. She had decreased perception of light touch sensation over the left leg and flank. Over the same area, sensory testing using a pin produced a heightened, unpleasant sensation. On tests of coordination, she had slowness and clumsiness with the left arm, giving a tendency to overshoot the target. Gait was mildly unstable, with a stiff, awkward tendency to circumduct the left leg. She was unable to tandem walk.

Laboratory:

CSF - 10 cells/mm³; 100% lymphocytes [normal = 0-5 cells]; protein 35 mg/dl [normal < 45mg/dl]; glucose 60 mg/dl [normal]; IgG made up 19% of total CSF protein [normal 3-12%]; two oligoclonal bands were in CSF that were not seen on serum electrophoresis.

Brain MRI - Multiple white matter lesions, involving the centrum semiovale and periventricular white matter, as well as the corpus callosum.

Issues for discussion:

1. What is the differential diagnosis of the patient's presenting symptoms: left leg weakness and numbness? How can these symptoms be localized to the central or peripheral nervous system?
2. What is the significance of the visual symptoms? To where in the visual system do the patient's findings localize? What is a relative afferent pupillary defect [Marcus-Gunn pupil]?
3. What is the differential diagnosis of multiple white matter lesions?
4. What is the most likely cause of the neurological problems in this individual? What is the treatment and prognosis for this disorder?

Case 5 – Trouble walking

Chief complaint: The patient was a 62-year old ballroom dancing instructor with an eight month history of troubling walking.

History of present illness: One year before presentation, the patient gradually became aware of clumsiness and difficulty while dancing. With time, she felt that her legs would give out with exertion. Attributing the problem to her busy schedule, she decided to take a two-month vacation in the south of France. She found herself progressively unable to climb hills, ascend stairs, or rise from a seated position due to leg weakness. Due to vigilance, she did not fall or trip, but had some close calls. Over two weeks before admission, she developed difficulty reaching and lifting objects. She found herself unable to brush her hair. There was no weakness referable to the bulbar musculature, but she complained of shortness of breath. There was no muscle pain or aching, back pain, sensory symptoms, or bladder or bowel impairment. She returned to New York, and took a taxi directly from the airport to the Emergency Room at Columbia University Medical Center.

Review of systems:

There was no history of dysphagia or dysarthria. She did not experience systemic symptoms, such as anorexia, weight loss, joint pains, neck pain, rashes, night sweats, myoglobinuria or other medical symptoms.

Past medical history:

Hypertension, treated using propranolol

Family history:

Her parents died in their eighties of unknown cause. Her younger sister had severe rheumatoid arthritis.

Examination: On exam, she was a vivacious, somewhat stocky 62-year old woman. Her blood pressure was 200/120 and her pulse was 84. She weighed 158 pounds. The general examination was within normal limits. On neurological exam, she was alert with normal language and cognition. The cranial nerve exam was normal, including visual system, eye movements, facial strength, sensation, hearing, and lower cranial nerves. On motor exam, muscle tone was normal. There was no muscle wasting, tenderness or fasciculations. She had moderately severe weakness of neck flexion and proximal arm extension; wrist and finger extensors were slightly weak. She had moderately severe proximal leg weakness, and was unable to arise from a low chair without assistance. She could not rise from a squat, or get up off the floor. On sensory testing, there were no abnormalities. Her deep tendon reflexes were diffusely hypoactive and the planter responses were flexor. On coordination testing, there was limb ataxia, attributed to weakness. Her gait was narrow-based and slow. She could perform tandem gait, and the Romberg test was negative.

Laboratory:

CBC, WBC, platelets, routine chemistry tests, liver function tests, serum protein electrophoresis [SPEP], rheumatoid factor [RF], ANA antibodies, serum cortisol, thyroid function tests, and angiotensin converting enzyme [ACE] levels were all negative or normal. The serum creatine kinase [CK] level was 923 [normal <50].

Nerve conduction studies – normal

Electromyogram [EMG] - diffuse spontaneous activity in the form of fibrillation potentials and positive sharp waves in all muscles sampled, including deltoid, biceps, and quadriceps. The motor unit potentials [MUPs] were polyphasic and of short duration, most consistent with a myopathic process.

Pathology - a muscle biopsy was taken from left quadriceps.

Course in hospital: The patient was treated with intravenous corticosteroids, an antacid, a H₂-blocker, and her anti-hypertensive agent. Over two weeks, the serum CK activity decreased to the range of 100-300, and her strength improved. She was discharged on prednisone 50 mg daily, and over two months gained weight and developed glucose intolerance. The steroid was slowly tapered and another immunosuppressive agent, azathioprine [Imuran] 50 mg twice daily, was added. This regimen, in combination with light physical therapy, produced a gradual return to normal strength. One year after discharge from hospital, she was seen socially in her high heels by her neurologist at a hospital fund raising gala.

Issues for discussion:

1. What are the signs of upper motor neuron weakness? What are the signs of lower motor neuron weakness? Based on the history and exam, what is the localization of this patient's progressive weakness?
2. How can myelopathy, radiculopathy, neuropathy, myopathy, and neuromuscular junction disorders be distinguished clinically, and by using electrodiagnostic studies?
3. What is the differential diagnosis of myopathy?