NEUROPATHOLOGY

INFECTIONS OF THE NERVOUS SYSTEM
An infectious agent must use one of several routes of entry to reach the CNS & cause a disease.
1. Hematogenous spread via the arterial blood supply is the most common mode of entry. There can also be retrograde venous spread, through the anastomoses between veins of the face and the venous sinuses of the skull.
2. Direct implantation of microorganisms is almost invariably post-traumatic, with introduction of foreign material.
3. Local extension from an established infection in the skull or the bony spine can occur. The infection may originate from
   a. air sinus, most often the mastoid or frontal
   b. infected tooth
   c. surgical operation on the cranium or spine causing osteomyelitis
   d. congenital malformation, such as meningomyelocele.
4. Peripheral nerves can also serve as the path of entry for rabies and herpes zoster.

Epidural and Subdural Infections
These spaces can be involved with bacterial or fungal infections, usually as a consequence of direct local spread. Epidural abscess, commonly associated with osteomyelitis, arises from an adjacent focus of infection, such as sinusitis or a surgical procedure. When the process occurs in the spinal epidural space, it may cause spinal cord compression and constitute a neurosurgical emergency. Infections of the skull or air sinuses may also spread to the subdural space, producing subdural empyema. A large subdural empyema may produce a mass effect. In addition, thrombophlebitis may develop in the bridging veins that cross the subdural space, resulting in venous occlusion and infarction of the brain.

Meningitis
This is an inflammatory process of the leptomeninges and CSF within the subarachnoid space. Meningoencephalitis develops with spread of the infection from the meninges into the underlying brain. Infectious meningitis is broadly classified into
1. Acute pyogenic (usually bacterial),
2. Aseptic (usually viral), and
3. Chronic (usually tuberculous, spirochetal, or cryptococcal)

Acute Pyogenic Meningitis (Bacterial Meningitis) (Fig. 14-17)
While a wide range of bacteria can cause acute pyogenic meningitis, there is a relationship between the age of a patient and the most likely organisms. In neonates, common organisms are Escherichia coli and the group B streptococci; at the other extreme of life, Streptococcus pneumoniae and Listeria monocytogenes are more common. Among adolescents and in young adults, Neisseria meningitides is the most common pathogen. Regardless of the organism, patients typically show systemic signs of infection superimposed on clinical evidence of meningeal irritation and neurologic impairment-including headache, photophobia, irritability, and neck stiffness. Lumbar puncture reveals an increased pressure, abundant neutrophils, elevated protein, and reduced glucose. Bacteria may be seen on a smear stained with Gram stain or can be cultured.
Pathological features
• In acute meningitis, an exudate is evident within the leptomeninges over the surface of the brain.
• The meningeal vessels are engorged and prominent.
• When the meningitis is fulminant, the inflammatory cells infiltrate the walls of the leptomeningeal veins and may spread into the substance of the brain (focal cerebritis), or the inflammation may extend to the ventricles.

• On microscopic examination, neutrophils fill the entire subarachnoid space in severely affected areas or may be found predominantly around the leptomeningeal blood vessels in less severe cases.

Bacterial meningitis may be associated with abscesses in the brain. Phlebitis may also lead to venous occlusion and hemorrhagic infarction of the underlying brain.

Aseptic Meningitis (Viral Meningitis)
The clinical course is less fulminant than in pyogenic meningitis & is usually self-limiting. The CSF shows an increased number of lymphocytes, the protein elevation is only moderate, and glucose content is normal. The most common offending agent is an enterovirus. (Fig. 14-18)

Chronic Meningitis

Tuberculous Meningitis
There is only a moderate increase in cellularity of the CSF made up of mononuclear cells, or a mixture of neutrophils and mononuclear cells; the protein level is elevated, often strikingly so, and the glucose content typically is moderately reduced or normal. Infection with Mycobacterium tuberculosis may also result in a well-circumscribed brain mass (tuberculoma), which may be associated with meningitis. Tuberculous meningitis is a cause of arachnoid fibrosis, which may produce hydrocephalus. The subarachnoid space contains a gelatinous or fibrinous exudate, most often at the base of the brain. There may be discrete white granules scattered over the leptomeninges. Microscopically, there are well-formed granulomas, often with caseous necrosis and giant cells. Similar findings are observed in tuberculomas within the brain.

Neurosyphilis
This is a tertiary stage of syphilis and occurs in only about 10% of individuals with untreated infection. One of the major manifestations is meningeal. As with other chronic infections, there can be parenchymal disease as well that eventuates in severe dementia. Tabes dorsalis is another form of neurosyphilis, resulting from damage to the sensory nerves in the dorsal roots producing impaired joint position sense and resultant ataxia (locomotor ataxia); loss of pain sensation, leading to skin and joint damage (Charcot joints); other sensory disturbances. Individuals with HIV infection are at increased risk for neurosyphilis, and the rate of progression and severity of the disease seem to be accelerated.
TUMORS
The incidence of CNS tumors is generally low; about 50% to 75% are primary, and the rest are metastatic. In children, they constitute 20% of all tumors with a predilection for the posterior fossa (in adults they are most tumors are supratentorial).
*Tumors of the nervous system differ from neoplasms elsewhere in the body*
1. Low-grade lesions may diffusely infiltrate large areas of the brain, thus associated with poor prognosis.
2. The anatomic site of the tumor can affect the prognosis
   a. it may have lethal consequences irrespective of the histopathologic type; for example, a benign meningioma, by compressing the medulla, can cause cardiopulmonary arrest.
   b. through influencing the extent of respectability.
3. Even the most highly malignant gliomas rarely metastasize outside the CNS, however, the subarachnoid space does provide a pathway for spread so that seeding along the brain and spinal cord can occur.

GLIOMAS
Gliomas are tumors of the brain parenchyma that histologically resemble different types of glial cells. *The major types of gliomas are astrocytomas, oligodendrogliomas, and ependymomas.*

1. **Astrocytomas:** the most common of these are fibrillary and pilocytic astrocytomas.
   *Fibrillary Astrocytoma* account for 80% of adult primary brain tumors. They are most frequent in the ages of 30 to 60 years. Their usual location is the cerebral hemispheres. They show a spectrum of histologic differentiation that correlates well with clinical course and outcome. *Based on the degree of differentiation, they are classified into three groups:*
   a. Astrocytoma (infiltrating astrocytoma) (WHO grade II)
   b. Anaplastic astrocytoma (WHO grade III)
   c. Glioblastoma multiforme (WHO grade IV)
   For well-differentiated astrocytomas, which are slow growing, the mean survival is more than 5 years. Eventually, however, a more rapid growth occurs due to the appearance of anaplastic features. However, many patients present with glioblastoma from the outset. The prognosis of glioblastoma is very poor (mean survival 8 to 10 months despite treatment).

**Gross features**
- Low-grade (infiltrating) astrocytoma is a poorly defined, gray, & infiltrative mass lesion that leads to expansion and distortion of the affected regions of the brain. *(Fig. 14-22).* The cut surface of the tumor is either firm, or soft and gelatinous; cystic degeneration may be seen.
- In glioblastoma, variation in the gross appearance of the tumor from region to region is characteristic. Some areas are firm and white, others are soft and yellow (the result of tissue necrosis), and yet others show regions of cystic degeneration and hemorrhage. *(Fig. 14-23).*

**Microscopic features**
- Low-grade (infiltrating) astrocytomas are characterized by a mild to moderate increase in the number of glial cells, slight nuclear pleomorphism, and an intervening feltwork of fine, GFAP-positive astrocytic cell processes that give the background a fibrillary appearance.
- The tumor cells can be seen infiltrating surrounding normal tissue for some distance from the main lesion.
- Anaplastic astrocytomas are more densely cellular with greater nuclear pleomorphism; increased mitoses are often observed.
• Glioblastoma, have a histologic appearance similar to anaplastic astrocytoma with additional features of necrosis surrounded by pseudo-palisaded nuclei &/or prominent vascular endothelial cell proliferation.

Pilocytic Astrocytoma (WHO grade I) is a relatively benign tumor, often cystic, that typically occur in children and young adults and are usually located in the cerebellum. In the cystic variant, there is usually a mural nodule in the wall of the cyst. The tumor is composed of areas with bipolar cells with long, thin "hair-like" processes that are GFAP positive. Rosenthal fibers, eosinophilic granular bodies, and microcysts are often present. Necrosis and mitoses are absent. (Fig. 14-24)

2. Oligodendrogliomas are most common in the 30 to 50 years of age. It is mostly located in the white matter of cerebral hemispheres. The prognosis is generally better than that of astrocytoma.

Oligodendrogliomas are infiltrative gelatinous, gray tumors. Microscopically, the tumor is composed of sheets of regular cells with spherical vesicular nuclei surrounded by a clear halo of cytoplasm. It typically contains a delicate network of anastomosing capillaries (chicken wire-type vasculature). Calcifications are frequently present; these range from microscopic foci to massive depositions. (Fig. 14-25) The current WHO classification grades oligodendrogliomas into 2 different categories as WHO grade 2 and anaplastic WHO grade 3. Prominent mitotic activity and microvascular/endothelial proliferation are the 2 features that define anaplastic tumors.

3. Ependymoma most often arises next to the ependyma-lined ventricular system, including the central canal of the spinal cord. In the first two decades of life, they typically occur near the fourth ventricle. In adults, the spinal cord is their most common location. Because ependymomas usually grow within the ventricles, CSF dissemination is a common occurrence. In the fourth ventricle, ependymomas are typically solid or papillary masses projecting from the floor of the ventricle. These tumors are composed of cells with regular, round to oval nuclei. Between the nuclei there is a fibrillary background. Tumor cells may form round or elongated structures (rosettes) with long, delicate processes extending into a lumen; more frequently present are perivascular pseudo-rosettes in which tumor cells are arranged around vessels with an intervening zone consisting of thin ependymal processes. (Fig. 14-26)

NEURONAL TUMORS

Central neurocytoma is a low-grade neuronal neoplasm that is typically but not exclusively a periventricular lesion i.e., found within and adjacent to the ventricular system (most commonly the lateral or third ventricles). It is characterized by evenly spaced, round, uniform nuclei and often islands of neuropil.

Gangliogliomas are tumors with a mixture of glial elements (looking like a low-grade astrocytoma) and mature-appearing neurons. Most of these tumors are slow growing.

Medulloblastoma occurs predominantly in children and exclusively in the cerebellum. This highly malignant tumor is radiosensitive but without treatment the prognosis is poor. In children the tumor is located typically in the midline of the cerebellum. It is often well circumscribed, gray, and friable. Medulloblastomas are extremely cellular, with sheets of undifferentiated small cells with little cytoplasm and hyperchromatic nuclei; mitoses are abundant. Some tumors show differentiation along neuronal lines in the form of Homer Wright rosettes. The latter consist of tumor cell nuclei disposed in circular fashion about tangled cytoplasmic processes. (Fig. 14-27)
OTHER PARENCHYMAL TUMORS

**Primary Central Nervous System Lymphoma** are rare but are the most common CNS neoplasm in immunosuppressed individuals (including transplant recipients and persons with AIDS); under these circumstances the CNS lymphomas are nearly all driven by Epstein-Barr virus. Most of these tumors are diffuse large B-cell lymphomas.

**Germ-Cell Tumors** occur along the midline, most commonly in the pineal and the suprasellar regions. They are a tumor of the young, with 90% occurring during the first two decades. Germ-cell tumors in the pineal region show a strong male predominance. The histologic classification of brain germ-cell tumors is similar to that used in the testis, but the CNS equivalent of testicular seminoma is called a germinoma. It should be noted, however, that CNS involvement by a gonadal germ-cell tumor is not uncommon.

**MENINGIOMAS**

These predominantly benign tumors of adults arise from the meningotheelial cell of the arachnoid & are usually attached to the dura. Meningiomas may be found along any of the external surfaces of the brain as well as within the ventricular system, where they arise from the stromal arachnoid cells of the choroid plexus. They cause symptoms through compression of underlying brain. Multiple meningiomas, especially in association with eighth nerve schwannomas or glial tumors, may be a part of neurofibromatosis type 2 (NF2). About half of meningiomas not associated with NF2 still have mutations in the NF2 gene.

**Gross features** (Fig. 14-28)
- They are well-defined dural-based masses that compress underlying brain but are easily separated from it.
- On sectioning most meningiomas are grayish-tan and soft. Collagenized examples, however, have rubbery texture and whorled or trabeculated cut surface.
- Calcification may impart a gritty sensation on cutting.
- Extension into the overlying bone may be present.

**Microscopic features** (Fig. 14-28 B)
- There are many histologic patterns of meningiomas, including
  1. **Syncytial**, showing whorled clusters of tight groups of cells without visible cell membranes
  2. **Fibroblastic**, with elongated cells and abundant collagen deposition between them
  3. **Transitional**, which shares features of the syncytial and fibroblastic types
  4. **Psammomatous**, with numerous psammoma bodies (NB: psammoma bodies may also occur in the above variants but less heavily).

**Atypical meningiomas** show a higher rate of recurrence, more aggressive local growth. They are recognized by several histologic features including a higher mitotic rate.

**Anaplastic (malignant) meningiomas** are highly aggressive tumors that resemble a high-grade sarcoma.

Although most meningiomas are easily separable from underlying brain, some tumors infiltrate the brain. The presence of brain invasion is associated with increased risk of recurrence.

**METASTATIC TUMORS**

Metastatic lesions, mostly carcinomas, account for 25% to 50% of intracranial tumors. The five most common primary sites are

1. Lung
2. Breast
3. Skin (melanoma)
4. Kidney
5. GIT

The meninges are also a frequent site of involvement by metastatic disease. In the brain, metastases form sharply demarcated masses, often at the gray matter-white matter junction, usually surrounded by a zone of edema. The boundary between tumor and brain parenchyma is well defined microscopically as well, with surrounding reactive gliosis. (Fig. 14-29)
In addition to the direct and localized effects produced by metastases, paraneoplastic syndromes may involve the peripheral and central nervous systems, sometimes even preceding the clinical recognition of the malignant neoplasm. These syndromes are most commonly associated with small-cell carcinoma of the lung. There are several manifestations of paraneoplastic syndromes; some characteristic patterns include: Subacute cerebellar degeneration resulting in ataxia, Limbic encephalitis causing a subacute dementia; the pathological changes are centered in the medial temporal lobe, and Subacute sensory neuropathy leading to altered pain sensation.

**PRIMARY DISEASES OF MYELIN**

Within the CNS, axons are tightly ensheathed by myelin, which serves as an electrical insulator to allow rapid propagation of impulses. Myelin consists of multiple layers of the specialized plasma membrane of oligodendrocytes. Oligodendrocytes extend processes toward many different axons and wrap them. Myelinated axons are the dominant component in the white matter; therefore, most diseases of myelin are primarily white matter disorders. The myelin in peripheral nerves is similar to the myelin in the CNS but is made by Schwann cells, not oligodendrocytes. Therefore, most diseases of CNS myelin do not significantly involve the peripheral nerves, and vice versa.

In general, diseases involving myelin are separated into two broad groups

1. **Demyelinating diseases** of the CNS are acquired conditions characterized by preferential damage to previously normal myelin. The most common diseases in this group are multiple sclerosis (MS) and related disorders. Others are exemplified by viral infection of oligodendrocytes as in progressive multifocal leukoencephalopathy, and injury caused by drugs and toxic agents.

2. **Dysmyelinating diseases** (leukodystrophies); these are due to improperly formed myelin or to abnormal turnover kinetics of myelin. They are due to mutations affecting the proteins required for formation of normal myelin or that affect the synthesis or degradation of myelin lipids.

**Multiple Sclerosis** (MS) is an autoimmune demyelinating disorder characterized by separated episodes of neurologic deficits attributable to separated white matter lesions. It is the most common of the demyelinating disorders. The clinical onset occurs usually in adolescence or young adults, & women are affected twice as often as men. MS shows relapsing and remitting episodes of neurologic deficits. Like other autoimmune diseases, MS is caused by a combination of environmental and genetic factors that result in a loss of tolerance to self myelin antigens. A transmissible agent has been proposed. The risk of developing MS is 15-fold higher when the disease is present in a first-degree relative; this indicates a strong, but not causative, role for genes. T cell-mediated delayed type hypersensitivity reaction to myelin proteins is thought to be central to the pathogenesis, which is experimentally supported.

**Gross features** (Fig. 14-30)

- MS is a white matter disease.
- Affected areas show multiple, well-circumscribed, gray-pink, irregularly shaped plaques.
- These plaques are commonly paravenricular in location but they are also frequent in the optic nerves and chiasm, brain stem, and spinal cord.

**Microscopic features**

- The lesions have sharply defined borders.
- **In an active plaque** there is myelin breakdown with abundant macrophages containing myelin debris with perivascular lymphocytes and histiocytes infiltration. Axons are relatively preserved.
- When plaques become quiescent (inactive plaques), the inflammation mostly disappears, leaving behind little to no myelin.
The course of MS is variable, but commonly there are multiple episodes of new symptoms (relapses) followed by episodes of typically incomplete recovery (remissions). The consequence of this pattern of relapsing-remitting disease is the gradual, often stepwise, accumulation of increasing neurologic deficits. Unilateral visual impairment is a frequent initial manifestation of MS and is due to optic neuritis. Involvement of the brain stem produces cranial nerve signs and ataxia. Spinal cord lesions give rise to motor and sensory impairment, spasticity, and urinary incontinence. The CSF in MS patients shows a mildly elevated protein level with an increased proportion of γ-globulin; in one-third of cases there is moderate increase in lymphocytes.

Other Acquired Demyelinating Diseases

Immune-mediated demyelination can be found after a number of systemic infectious illnesses, including relatively mild viral diseases. It is believed that the immune response to pathogen-associated antigens cross-reacts with myelin antigens; this results in myelin damage.

Dysmyelinating diseases (Leukodystrophies) are inherited dysmyelinating diseases that result from either abnormal myelin synthesis or turnover. Some of these disorders involve lysosomal enzymes, while others involve peroxisomal enzymes; a few are associated with mutations in myelin proteins. Most are autosomal recessive. Much of the pathology is found in the white matter, which is diffusely abnormal in color (gray and translucent) and volume (decreased).

DISEASES OF THE PERIPHERAL NERVOUS SYSTEM

Neoplasms of the Peripheral Nervous System

These tumors arise from cells of the peripheral nerve, including Schwann cells, perineurial cells, and fibroblasts. In addition to arising along the peripheral course of nerve, these tumors can arise within the confines of the dura. When they do this, they may cause changes in adjacent brain or spinal cord. Schwannomas are benign tumors arising from Schwann cells. Symptoms are referable to local compression of the involved nerve, or to compression of adjacent structures (such as brain stem or spinal cord). They are often encountered in the cerebellopontine angle, where they are attached to the vestibular branch of the eighth nerve. These patients often present with tinnitus and hearing loss, and the tumor is often referred to as an acoustic neuroma. Elsewhere within the dura, sensory nerves are preferentially involved, including branches of the trigeminal nerve and dorsal roots. When extradural, schwannomas are most commonly found in association with large nerve trunks. Sporadic schwannomas are associated with mutations in the NF2 gene on chromosome 22.

Gross features (Fig. 14-35).

- These tumors are well-circumscribed encapsulated masses that are attached to the nerve.
- They form firm, gray masses sometimes with cystic change.

Microscopically

- There is a mixture of two growth patterns. In the Antoni A pattern of growth, elongated cells are arranged in fascicles with their nuclei palisade along "nuclear-free zones" forming Verocay bodies.
- In the Antoni B pattern of growth, the tumor is less densely cellular with a loose meshwork of cells along with microcysts and myxoid changes.
- In both areas, the cytology of the individual cells is similar, with elongated cell cytoplasm and regular oval nuclei.
Neurofibroma
Solitary neurofibromas are mostly cutaneous or involving a peripheral nerve. These arise sporadically or in association with type 1 neurofibromatosis (NF1). The skin lesions are evident as nodules, sometimes with overlying hyperpigmentation; they may grow to be large and become pedunculated. The risk of malignant transformation from these tumors is extremely small, and cosmetic concerns are their major morbidity. The second type is the plexiform neurofibroma, mostly arising in individuals with NF1. In the latter situation it is not only difficult to surgically remove these plexiform tumors when they involve major nerve trunks but also their potential for malignant transformation. (Fig. 14-36)

Malignant Peripheral Nerve Sheath Tumors (MPNST) are highly malignant sarcomas that are locally invasive, frequently leading to multiple recurrences and eventual metastatic spread. Despite their name, these tumors do not arise from malignant transformation of schwannomas. Instead, they arise de novo or from transformation of a plexiform neurofibroma. These tumors can also occur after radiation therapy.

FAMILIAL TUMOR SYNDROMES are inherited diseases characterized by the development of hamartomas and neoplasms throughout the body with particular involvement of the nervous system. Most of these syndromes are linked to loss of tumor suppressor genes. The following are autosomal dominant disorders.

Type 1 Neurofibromatosis (NF1) is characterized by neurofibromas (plexiform and solitary), gliomas of the optic nerve, and cutaneous hyperpigmented macules (café au lait spots). Individuals with NF1 have a propensity for the neurofibromas to undergo malignant transformation. This is especially true for plexiform neurofibromas.

Type 2 Neurofibromatosis (NF2) is characterized by the development of a range of tumors, most commonly bilateral vestibular (acoustic) schwannomas and multiple meningiomas. Ependymomas of the spinal cord also occur.

Tuberous Sclerosis is another autosomal dominant syndrome characterized by the development of hamartomas and benign neoplasms involving the brain and other tissues. Seizures, which can be difficult to control with antiepileptic drugs, are associated with the cortical lesion. Extracerebral lesions include renal angiomyolipomas, retinal glial hamartomas, and pulmonary lesions and cardiac rhabdomyomas.

von Hippel-Lindau Disease is characterized by the develop hemangioblastomas mostly within the cerebellar hemispheres, and retina. Patients may also have cysts involving the pancreas, liver, and kidneys and have a high propensity to develop renal cell carcinoma of the kidney.

Note: the text with red color is self study