

## MODULE 3: CRANIUM, VENTRICLES, & MENINGES

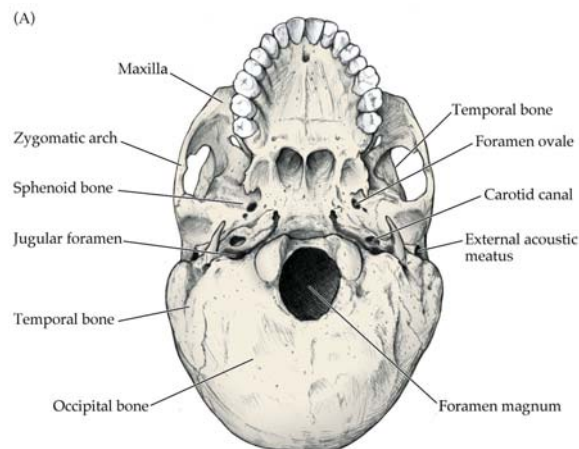
This module will be organized the same as all remaining modules. The most important anatomical facts will be presented initially. The basic neuroanatomy will be followed by a brief discussion of key clinical concepts (typical diseases and conditions associated with the anatomy). Lastly, several clinical cases will be presented to drive home the relationship between anatomy and pathology.

The anatomy in this module will include the skull, meninges, ventricles, cerebrospinal fluid circulation, and related blood vessels. The key clinical concepts will include headache, intracranial mass lesions, elevated intracranial pressure, brain herniation, intracranial hemorrhage, hydrocephalus, brain tumors and infections of the brain.

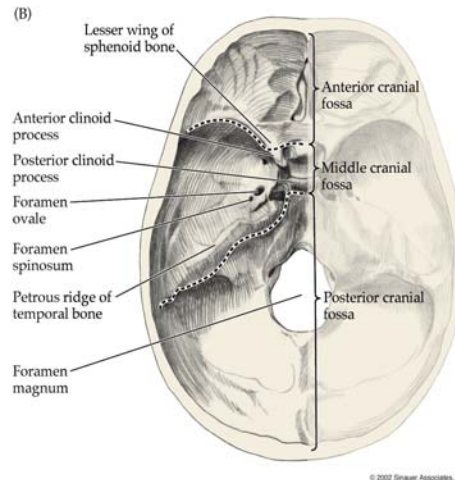
The brain is encased in several protective layers that cushion it from trauma. Most important among them are the skull and meninges. The ventricles also have a protective effect on brain. The anatomy and functions of these structures form the content of this module.

### NEUROANATOMICAL REVIEW

**SKULL AND CRANIAL VAULT.** The skull has many foramina (or holes) through which various cranial nerves, blood vessels, and the spinal cord enter and leave the cranial vault. The largest foramen is the ***foramen magnum*** which is the big hole at the base of the skull in which the spinal cord/brain stem sits. The point where the spinal cord meets the medulla, called the cervicomedullary junction, is located at the level of the foramen magnum.



On the inner surface of the skull (at the bottom) are several ridges of bone that divide the base of cranium into several compartments, or fossae. The ***anterior fossa*** on each side contains the frontal lobe. The ***middle fossa*** contains the temporal lobe. The ***posterior fossa*** contains the cerebellum and brainstem. The anterior fossa is divided from the middle fossa by the lesser wing of the sphenoid bone. The middle fossa is divided from the posterior fossa by the petrous ridge of the temporal bone and by a sheet of meninges (detailed below).



**MENINGES**. There are three protective layers called the meninges that surround the brain and cerebrospinal fluid. From the outermost layer to innermost layer they are:

- 1) Dura
- 2) Arachnoid
- 3) Pia

The term “mater” (meaning “mother”) is sometimes added to these names. The **dura mater** (dura means “hard”) is composed of two tough fibrous layers which are fused to each other except in two cases where they separate. The first is the **false cerebri** which is flat sheet of dura that is suspended from the roof of the cranium and separates the left and right cerebral hemispheres in the interhemispheric fissure. The second is the **tentorium cerebelli**, a tentlike sheet of dura that covers the upper surface of the cerebellum.

The **arachnoid** is a “spidery” meningeal layer that adheres to the inner surface of the dura. Within the arachnoid, the cerebrospinal fluid (CSF) percolates over the surface of the brain. The innermost meningeal layer, called the **pia**, is a very thin layer of cells that adheres closely to the surface of the brain and follows it along all the gyri and into the depths of the sulci.

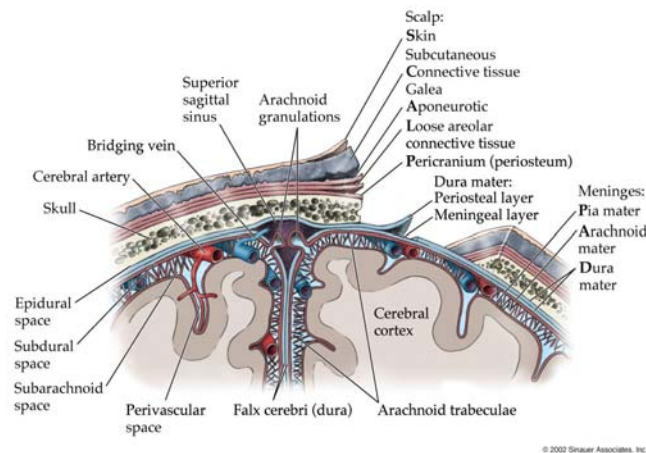
The meninges form three spaces or potential spaces that have clinical significance:

- 1) Epidural space
- 2) Subarachnoid space
- 3) Subdural space

The **epidural space** is a potential space located between the inner surface of the skull and the tightly adhered dura. The **middle meningeal artery** runs in the epidural space. The middle meningeal artery is a branch of the external carotid artery and supplies the dura mater, while the middle cerebral artery is a branch of the internal carotid artery and supplies the brain.

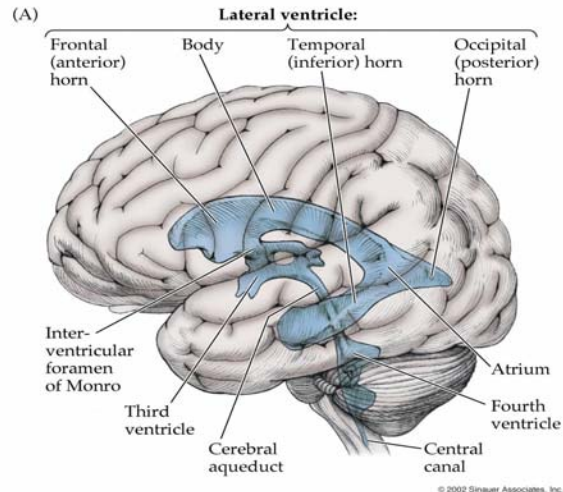
The **subdural space** is also a potential space between the inner layer of dura and the loosely adherent arachnoid. The **bridging veins** go through the subdural space. These veins drain the cerebral hemispheres and pass through the subdural space en route to several large dural venous sinuses, the largest being the **superior sagittal sinus**. The superior sagittal sinus lies between the two layers of dura and drains deoxygenated blood mainly via the sigmoid sinuses to reach the internal jugular veins.

The **subarachnoid space** is located between the arachnoid and pia and filled with cerebrospinal fluid (CSF). In addition to CSF, major arteries of the brain travel in the subarachnoid space and then send smaller penetrating branches inward through the pia.



As the spinal cord exits through the foramen magnum and continues downward through the bony spinal canal, it is enveloped by the same three meningeal layers. Thus, the entire central nervous system is surrounded by dural, arachnoid, and pial meninges.

**VENTRICLES AND CEREBROSPINAL FLUID.** The four ventricles are located deep within the brain. The ventricles contain cerebrospinal fluid (CSF) which acts as a shock absorber, bathes the brain in important chemicals, and disposes of certain biochemical waste products. The CSF is produced by a specialized vascular structure called the **choroids plexus** which lies inside the ventricles. The inner walls of the ventricles are lined with a layer of cells called **ependymal cells** which keep the CSF from leaking out into the substance of the brain. There are two lateral ventricles (one inside each cerebral hemisphere), a third ventricle located within the diencephalon, and the fourth ventricle, which is surrounded by the pons, medulla, and cerebellum.



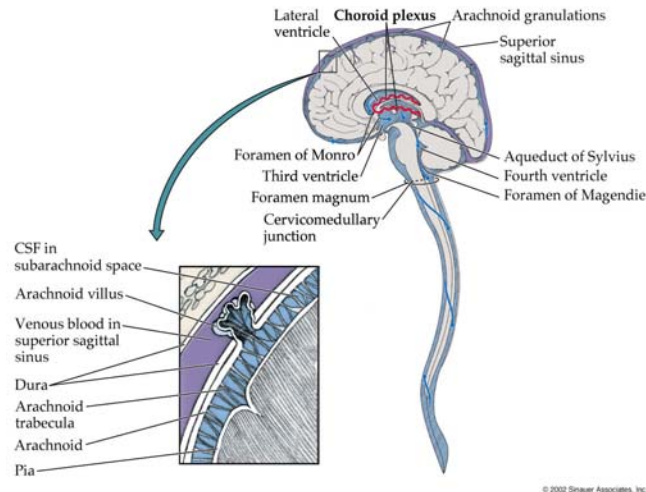
The largest ventricles are the two **lateral ventricles**. The lateral ventricles have extensions called horns that are named after the lobes in which they are located. The **frontal horn** of the lateral ventricle extends anteriorly from the **body** of the lateral ventricle into the frontal lobe. The body of the lateral ventricle merges posteriorly with the **atrium** or **trigone**. The trigone connects three parts of the lateral ventricle – the body, the **occipital horn** which extends back into the occipital lobe; and the **temporal horn** which extends inferiorly and anteriorly into the temporal lobe.

There are several “C”-shaped structures in the brain that follow the curve of the lateral ventricles. These “C”-shaped structures include the **caudate nucleus**, **corpus callosum**, **fornix**, and **stria terminalis**. The relative spatial relationships and functions of these structures will be discussed later.

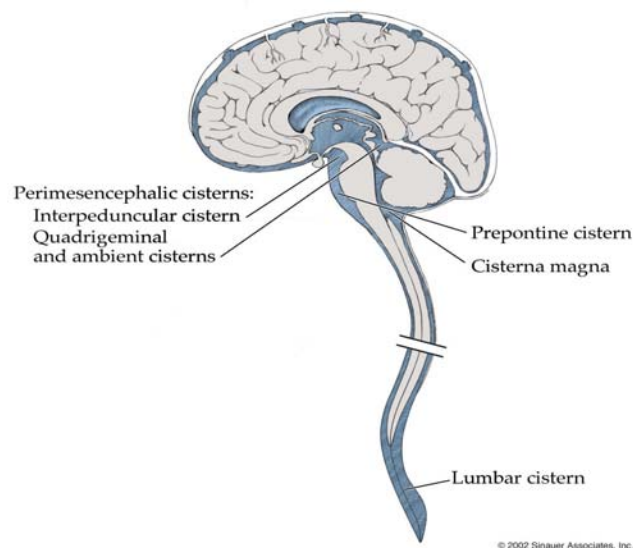
The lateral ventricles communicate into the **third ventricle** via the **intraventricular foramen** (often formally called the intraventricular foramen of Monro). The walls of the third ventricle are formed by the thalamus and hypothalamus.

The third ventricle communicates with the **fourth ventricle** via the **cerebral aqueduct** (also called the aqueduct of Sylvius) which travels through the midbrain. The roof (towards the back of the head) of the fourth ventricle is formed by the cerebellum, and the floor (towards the front) is formed by the pons and medulla.

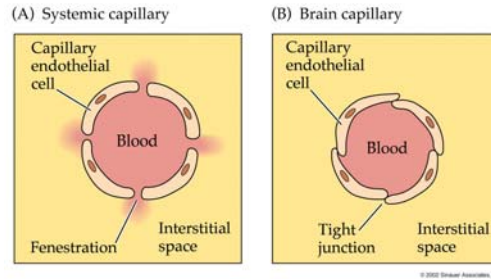
Cerebrospinal fluid circulates throughout the ventricles and then leaves the ventricular system via several foramina in the fourth ventricle – the two **lateral foramen of Luschka** and the **midline foramen of Magendie**. CSF then percolates around the outer surface of the brain and cord in the subarachnoid space until it is ultimately absorbed by the **arachnoid granulations** into the **superior sagittal sinus** (as well as other dural venous sinuses) and thus back into the bloodstream.



The subarachnoid space widens in a few areas to form larger CSF collections called **cisterns**. The largest of the cisterns is the **cisterna magna** (also sometimes called the cerebellomedullary cistern) which is located beneath the cerebellum near the foramen magnum. Another cistern that is often mentioned in clinical contexts on CT and MRI scans is the **quadrigeminal cistern** which is posterior to the midbrain (behind the superior and inferior colliculi) and beneath the posterior portion of the corpus callosum.

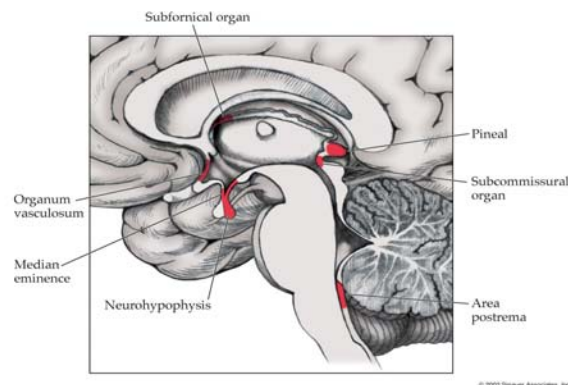


**BLOOD-BRAIN BARRIER**. The endothelial cells that form capillary walls in most of the body are separated from each other by clefts. These clefts or spaces between the endothelial cells in the body allow a relatively free passage of fluids and soluble molecules between the blood vessels and adjacent tissue. In the brain, however, capillary endothelial cells are linked by **tight junctions** so that substances entering or leaving the brain must travel through the endothelial cells, mostly by active transport mechanisms. These endothelial cells, and the tight junctions between them form the **blood-brain barrier** (see figure below).



A similar selective barrier exists between the choroid plexus and the CSF where the choroid epithelial cells form the barrier between the capillaries and the CSF, sometimes called the **blood-CSF barrier**. Lipid-soluble substances, like oxygen and carbon dioxide, readily permeate across the blood-brain barrier. However, most other substances must be conveyed in both directions through specialized transport systems.

Because neuronal synaptic transmission depends upon chemical communication between neurons, the blood-brain barrier protects the brain against almost continuous fluctuations in blood chemistry. There are, however, certain specialized brain regions known as **circumventricular organs** where the blood-brain barrier is interrupted. These brain regions may be thought of as being mostly hormonal in nature. These circumventricular organ structures need to respond to changes in the chemical milieu in the rest of the body in order to secrete modulatory neuropeptides into the bloodstream. Among the best known of these are the **median eminence** and the **neurohypophysis** of the pituitary which are involved in the regulation and release of pituitary hormones. Another is the **area postrema**, located along the caudal wall of the fourth ventricle in the medulla, which is involved in detecting circulating toxins that cause vomiting.



## KEY CLINICAL CONCEPTS

**HEADACHE**. Headache is caused by mechanical traction, inflammation, or irritation of structures other than the brain itself since there are no pain receptors in the brain parenchyma itself. The other structures will be things that have pain receptors in them such as blood vessels, meninges, scalp, and skull.

Most headaches can be classified as either a vascular headache or a tension headache. **Vascular headache** is used synonymously with migraine or cluster headaches.

The cause of **migraine** headaches is unknown but is thought to involve inflammatory, autonomic, serotonergic, and neuroendocrine influences on blood vessel caliber in the head. In migraine, about 75% of patients have a positive family history suggesting a genetic basis. Symptoms may be provoked by stress, eye strain, menstrual cycle, changes in sleep pattern, and a variety of other triggers. Migraines are often preceded by an aura (warning sign) classically involving visual blurring, shimmering or scintillating distortions. The headache pain in migraines is often throbbing and may be exacerbated by light (photophobia), sound (phonophobia), or sudden head movement. Nausea and vomiting may occur. Duration is typically between 30 minutes and up to 24 hours.

**Complicated migraines** may involve focal neurologic symptoms in the absence of headache pain. This may include such symptoms as transient motor deficits (hemiplegia), visual loss, brainstem findings (cranial nerve deficits), or impaired eye movements in ophthalmoplegic migraine. **Cluster headaches** are migraines that typically occur in clusters from one to several per day every day over a few weeks and then vanish for several months.

**Tension headache** is a steady, dull ache, sometimes described as a bandlike sensation. Although possibly related to excessive contraction of scalp and neck muscles, this has been questioned. Types and some common causes of headache are listed in the table below.

### **DIFFERENTIAL DIAGNOSIS OF HEADACHE**

- I. Vascular headache
  - a. Migraine
  - b. Cluster headache
- II. Tension headache
- III. Other causes
  - a. Acute trauma
  - b. Intracranial hemorrhage
  - c. Cerebral infarct
  - d. Hydrocephalus
  - e. Pseudotumor cerebri
  - f. Meningitis
  - g. Vasculitis
  - h. Neoplasm

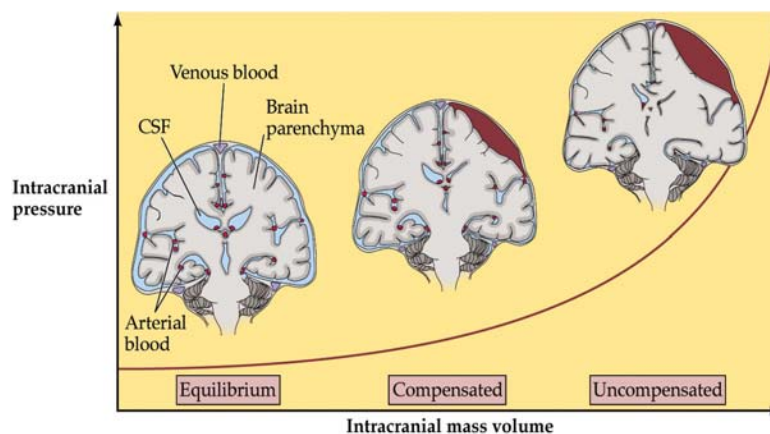
A sudden “explosive” onset of severe headache (“worst headache of my life”) should always be taken seriously as it may be due to a **subarachnoid hemorrhage**. In disorders that can increase intracranial pressure such as tumors (or **neoplasms**), the headache may be worse when lying down during the night. Thus, tumor-related headaches are often worse in the morning and get better as the day progresses. Headache accompanied by fever and signs of meningeal irritation (stiff neck, sensitivity to light) may represent infectious **meningitis**. **Pseudotumor cerebri** is a condition of unknown cause characterized by headache and elevated intracranial pressure with no mass lesion. **Temporal arteritis** is a form of vasculitis commonly seen in elderly individuals where the inflammation affects the temporal arteries and those vessel supplying the eye.

**INTRACRANIAL MASS LESIONS.** Anything that occupies volume within the cranial vault functions as a mass. Examples include tumor, hemorrhage, abscess, edema, hydrocephalus, and other disorders. Compression and destruction of adjacent regions of brain can cause neurologic symptoms. A mass located within the cranial vault will raise the **intracranial pressure** which causes characteristic signs. Mass lesions can displace nervous system structures so severely they are shifted from one compartment into another, a situation called **herniation**.

Mass lesions can cause both local tissue damage and remote effects through mechanical distortion of adjacent structures.

**Mass effect** is a term used for any distortion of normal brain geometry due to a mass lesion. If a mass distorts or irritates blood vessels or meninges, it may cause headache. Compression of blood vessels can also cause ischemic infarction. Erosion through blood vessels can cause hemorrhage. Disruption in the blood-brain barrier results in invasion of fluid into the extracellular space, producing **vasogenic edema**. Compression of the ventricular system can obstruct CSF flow, producing hydrocephalus. Large mass lesions can cause dramatic **midline shift** of brain structures away from the side of the lesion. Displacement and stretching of the upper brainstem impairs function of the reticular activating systems causing impaired consciousness and ultimately coma.

**ELEVATED INTRACRANIAL PRESSURE.** The contents of the intracranial space are confined by the hard walls of the skull. Of the three constituents of this cavity – cerebrospinal fluid (CSF), blood, and brain tissue – not one is compressible (though they can be deformed). Thus, whenever there is a space-occupying or mass lesion within the skull, something must leave the skull to accommodate the extra volume. Smaller lesions can be accommodated by a decrease in CSF and blood without causing much rise in intracranial pressure. With larger lesions, however, intracranial pressure begins to rise steeply, and can ultimately lead to herniation and death.



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It is important to recognize the signs of elevated intracranial pressure (ICP) at treatment may be started early. The headache is often worse in the morning



since brain edema increases overnight from the effects of gravity in the reclining position. Altered mental status (irritability, reduced arousal) and nausea and vomiting are common.

Increased intracranial pressure is transmitted through the subarachnoid space to the optic nerve sheath, obstructing axonal transport and venous return in the optic nerve, causing ***papilledema*** (engorgement and elevation of the optic disc seen on ophthalmologic exam). Cushing's triad is another classic sign of increased intracranial pressure. These signs of increased ICP are summarized below.

### **COMMON SYMPTOMS & SIGNS OF INCREASED INTRACRANIAL PRESSURE**

- Headache
- Altered mental status, especially irritability & depressed level of arousal & attention
- Nausea and vomiting
- Papilledema
- Visual loss
- Diplopia (double vision)
- Cushing's triad: hypertension, bradycardia, and irregular respirations

**Normal intracranial pressure (ICP)** in adults is **less than 20 cm H<sub>2</sub>O** or **less than 15 mm Hg** (mercury). ICP is often measured during lumbar puncture, but lumbar puncture should not be performed in patients suspected of having severely elevated ICP due to risk of precipitating herniation.

**BRAIN HERNIATION SYNDROMES**. Herniation occurs when mass effect is severe enough to push intracranial structures from one compartment into another. The three most important herniation syndromes are caused by herniation through the tentorial notch (transtentorial, or uncal, herniation), herniation centrally and downward (central herniation), and herniation under the falx cerebri (subfalcine herniation).

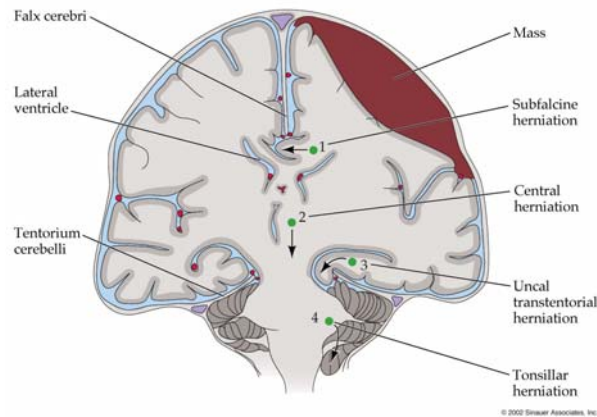
**Transtentorial herniation** is herniation of the medial temporal lobe, especially the uncus (uncal herniation), inferiorly through the tentorial notch (see #3 in figure below). **Uncal herniation** is heralded by the clinical triad of a "blown" pupil, hemiplegia, and coma. Compression of the oculomotor nerve (CN III) produces first a dilated, unresponsive ("blown") pupil. The dilated pupil is ipsilateral (on the same side) to the lesion in 85% of cases. Compression of the cerebral peduncles can cause the hemiplegia (paralysis of half the body). Distortion of the midbrain reticular formation leads to decreased level of consciousness, and ultimately, to coma.

**Central herniation** is central downward displacement of the brainstem (see #2 in figure below). With severe elevations of ICP, large supratentorial mass lesions, or mass lesions in the posterior fossa, central herniation can progress through the foramen magnum. Herniation of the cerebellar tonsils downward through the foramen magnum is called **tonsillar herniation** (see #4 in

figure). Tonsillar herniation is associated with compression of the medulla, and usually leads to respiratory arrest, blood pressure instability, and death.

**Subfalcine herniation.** Unilateral mass lesions can cause the cingulate gyrus, and other structures, to herniate under the falx cerebri from one side of the cranium to the other (see # 1 in figure below).

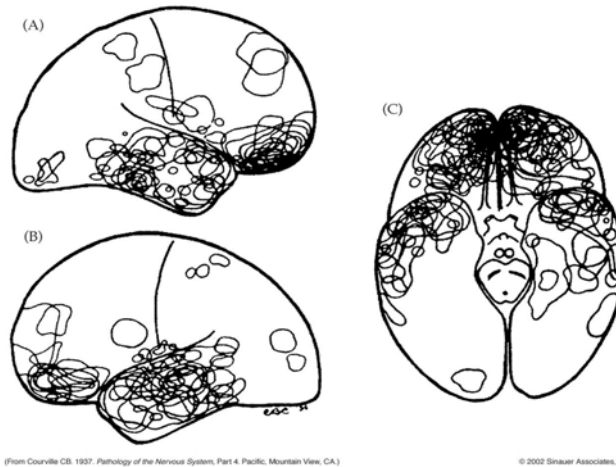
These major herniation syndromes are summarized in the diagram below.



**HEAD TRAUMA.** Head trauma is common in young adults and adolescents. Mild head trauma, also called **concussion**, is defined as a reversible impairment of neurologic function for minutes to hours following a head injury. The mechanism of concussion is unknown, but may involve transient diffuse neuronal dysfunction. Clinical features may include loss of consciousness, “seeing stars,” followed by headache, dizziness, and occasionally nausea and vomiting. Some of these symptoms may result from migraine-like phenomena triggered by head injury. Occasionally, head trauma is accompanied by anterograde and retrograde amnesia for a period of hours surrounding the injury. Recovery is usually complete, although occasional patients develop **postconcussive syndrome** with headaches, mental dullness, concentration difficulties, dizzy spells, and visual complaints.

More severe head trauma can cause permanent injury to the brain through various mechanisms, including **diffuse axonal shear injury**, which causes widespread or patchy damage to white matter; **petechial hemorrhages** (small spots of blood in white matter); larger intracranial hemorrhages; **cerebral contusion**; and direct tissue damage caused by penetrating trauma, such as gunshot wounds or open skull fracture. **Cerebral edema** may occur as well contributing to elevated ICP in head injury.

**Contusions** of the cerebral hemispheres occur in regions where cortical gyri abut the ridges of the bony skull. Thus, contusions are most common at the frontal and temporal poles (see figure below for most common sites of contusion taken from 40 cases). Severe head injuries are often accompanied by a combination of contusion, subarachnoid hemorrhage, and subdural hemorrhage.



**INTRACRANIAL HEMORRHAGE** can occur in several different compartments within the cranial vault. They are classified according to location and are often abbreviated as follows:

1. Epidural hematoma (EDH)
2. Subdural hematoma (SDH)
3. Subarachnoid hemorrhage (SAH)
4. Intracerebral or intraparenchymal hemorrhage (ICH)

**Epidural hematoma** is located in the tight potential space between the dura and the skull. It is usually caused by rupture of the **middle meningeal artery** due to fracture of the temporal bone secondary to head trauma.

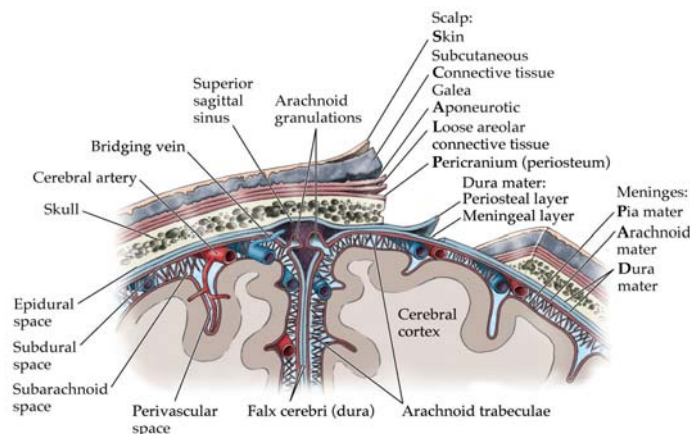
**Subdural hematoma** is located in the potential space between the dura and the loosely adherent arachnoid. It is usually caused by rupture of the bridging veins which are particularly vulnerable to shear injury as they cross from the arachnoid into the dura.

**Chronic subdural hematoma** is typically seen in the elderly where atrophy allows the brain to move more freely within the cranial vault, thus making the bridging veins more susceptible to shear injury. This type of hemorrhage may be seen with minimal or no history of trauma. Oozing slowly, venous blood collects over weeks to months, allowing the brain to accommodate and therefore causing vague symptoms such as headache, cognitive impairment and unsteady gait.

**Acute subdural hematoma**. For a significant subdural hematoma to occur immediately after an injury, the impact velocity must be quite high. Thus, acute subdural hematoma is usually associated with other serious injuries, such as traumatic subarachnoid hemorrhage and brain contusion. Prognosis for the acute form is usually worse than for chronic subdural or epidural hematomas.

**Subarachnoid hemorrhage** is located in the CSF-filled space between the arachnoid and the pia, which contains the major blood vessels of the brain. Subarachnoid hemorrhage is seen in two clinical settings: nontraumatic (spontaneous) and traumatic (discussed below).

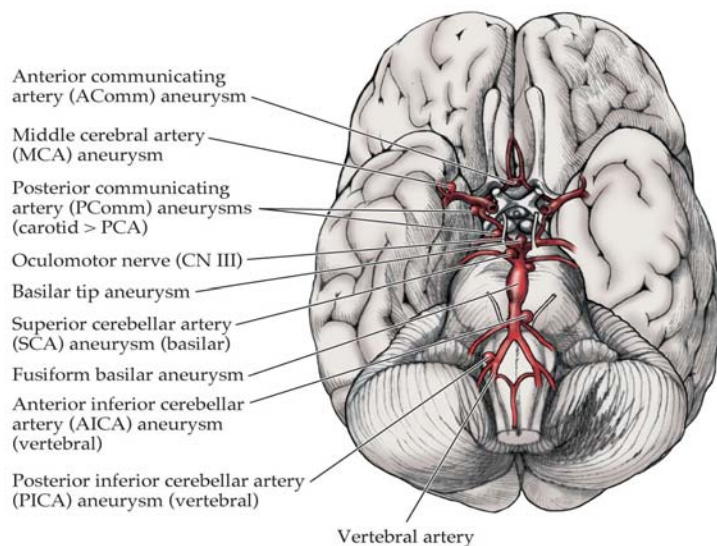
The spaces in which these hemorrhages may form can be reviewed in the figure.



### **Nontraumatic (Spontaneous) Subarachnoid Hemorrhage.**

Spontaneous subarachnoid hemorrhage usually presents with a sudden catastrophic headache (“**worst headache of my life**”) or a feeling like the head is about to explode. In the overwhelming majority of cases (75% to 80%), spontaneous subarachnoid hemorrhages occur as a result of **rupture of an arterial aneurysm** in the subarachnoid space. Less often (4% to 5% of cases) it results from bleeding of an **arteriovenous malformation**. Risk factors for intracranial aneurysm include atherosclerotic disease, congenital anomalies in cerebral blood vessels, polycystic kidney disease, and connective tissue disorders such as Marfan’s syndrome.

**Sacular, or berry, aneurysms** usually arise from arterial branch points near the circle of Willis (see figure below).



**Aneurysms** are balloon-like outpouchings of the vessel wall that typically have a neck connecting it to the parent vessel and a fragile dome that can rupture. Over 85% occur in the anterior circulation (carotid arteries and its branches). The most common locations are the anterior communicating artery (AComm, ~30%), posterior communicating artery (PComm, ~25%), and middle cerebral artery (MCA, ~20%).

Risk factors for aneurysmal rupture include hypertension, cigarette smoking, alcohol consumption, and situations causing sudden elevation in blood pressure. The overall mortality of subarachnoid hemorrhage is about 50%. The risk of a ruptured aneurysm rebleeding is 4% on the first day and 20% in the first two weeks.

**TABLE 5.5** Signs and Symptoms of Meningeal Irritation

Headache
Lethargy
Sensitivity to light (photophobia) and noise (phonophobia)
Fever
Nuchal rigidity (stiff neck): unable to touch chin to chest
Kernig's sign: pain in hamstrings when knees are straightened with hips flexed
Brudzinski's sign: flexion at neck causes hips to flex

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**Traumatic Subarachnoid Hemorrhage** is caused by bleeding into the CSF from damaged blood vessels associated with cerebral contusions and other traumatic injuries. Traumatic causes are more common than nontraumatic causes of subarachnoid hemorrhage. Similar to its nontraumatic counterpart, it is usually associated with severe headache due to meningeal irritation from blood in the CSF.

**Intracerebral or Intraparenchymal hemorrhage** is located within the brain parenchyma in the cerebral hemispheres, brainstem, cerebellum, or spinal cord. Causes may be traumatic or nontraumatic. **Traumatic** intracerebral hemorrhage may be due to brain contusions in the cortex and to small petechial or larger intraparenchymal hemorrhages caused by shearing forces producing areas of bleeding in the white matter. **Nontraumatic** intracerebral bleeds are caused by hypertension, brain tumors, secondary hemorrhage after ischemic infarction, vascular malformations, blood coagulation abnormalities, infections, vessel fragility caused by deposition of amyloid protein in the blood vessel wall (amyloid angiopathy), and vasculitis among others.

**Vascular Malformations** are another important cause of nontraumatic intracerebral hemorrhage. Vascular malformations are classified as:

- Arteriovenous malformations
- Cavernous malformations (a.k.a., cavernous angiomas, cavernous hemangiomas)
- Capillary telangiectasias (capillary angiomas)
- Venous angiomas (venous malformations, deep venous anomalies)

**Arteriovenous malformations (AVMs)** are congenital abnormalities in which there are abnormal direct connections between arteries and veins forming a tangle of abnormal blood vessels best seen on conventional cerebral angiography. AVMs can range in size from a few centimeters to half the brain. Besides intracranial hemorrhage, patients can also present with seizures or migraine-like headaches. If an AVM bleeds, the risk of rebleeding is 1% to 4% per year, much lower than in aneurysmal hemorrhage (discussed above). Treatments for AVMs include neurosurgical removal, intravascular embolization, and stereotactic radiosurgery.

**Cavernous malformations** are abnormally dilated vascular cavities lined by only one layer of vascular endothelium. They are not visible on conventional angiography, but have a characteristic appearance on MRI. Patients most often present with seizures. Risk of hemorrhage is between 0.1% and 2.7% per lesion per year. Some patients have multiple lesions. **Capillary telangiectasias** are small regions of abnormally dilated capillaries that rarely give rise to intracranial hemorrhage. **Venous angiomas** are dilated veins visible on MRI. They are usually an incidental finding and are not known to cause clinical symptoms themselves, but can be associated with cavernous malformations.

**HYDROCEPHALUS**, meaning “water on the head,” is caused by excess CSF in the intracranial cavity. This condition can result from:

1. excess CSF production
2. obstruction of flow at any point in the ventricles or subarachnoid space, or
3. decrease in reabsorption via the subarachnoid granulations.

**Excess CSF production** is a rare cause of hydrocephalus, but may be seen only in certain tumors, such as choroid plexus papilloma.

**Obstruction of CSF flow** is a common cause of hydrocephalus which may result from obstruction of the ventricular system by tumors, intraparenchymal hemorrhage, other masses, and congenital malformations. This can occur anywhere along the path of CSF flow, but is especially common at narrow points such as the intraventricular foramen (foramen of Monro), the cerebral aqueduct, or the fourth ventricle. Obstructions can also occur outside the ventricles in the subarachnoid space as a result of debris or adhesions from previous hemorrhage, infection, or inflammation.

**Decrease in CSF reabsorption** can cause hydrocephalus when the arachnoid granulations are damaged or clogged.

In clinical practice, hydrocephalus is often divided into two categories:

1. **Communicating hydrocephalus** is caused by impaired CSF reabsorption in the arachnoid granulations, obstruction in flow in the subarachnoid space, or (rarely) by excess CSF production.
2. **Noncommunicating hydrocephalus** is caused by obstruction of flow within the ventricular system.

The main symptoms of hydrocephalus are similar to those of any other cause of elevated intracranial pressure and can be acute or chronic depending upon how quickly the hydrocephalus develops.

**Symptoms of hydrocephalus** include headache, nausea, vomiting, cognitive impairment, decreased level of consciousness, papilledema, decreased vision, and VI<sup>th</sup> nerve palsies. In addition, ventricular dilation in hydrocephalus may compress descending white matter pathways from the frontal lobes, leading to frontal lobe-like abnormalities including an unsteady **magnetic gait** (feet barely leave the floor) and incontinence.

Two other forms of hydrocephalus are often encountered in clinical practice: normal-pressure hydrocephalus and hydrocephalus ex vacuo. **Normal-pressure hydrocephalus (NPH)** is characterized by chronically dilated ventricles usually seen in the elderly. Patients with NPH typically present with the clinical triad of gait difficulties, urinary incontinence, and mental decline. Measurements of CSF pressure in NPH are usually not elevated; pressure may only be increased intermittently. Although the cause is unknown, NPH is thought to be a form of communicating hydrocephalus. Some cases improve dramatically after lumbar puncture or ventriculoperitoneal shunting. **Hydrocephalus ex vacuo** is simply a descriptive term and is not itself responsible for any pathology. It refers to excess CSF in a region where brain tissue was lost as a result of stroke, surgery, atrophy, trauma, or other insult.

**BRAIN TUMORS.** The two broad categories of brain tumors are primary CNS tumors and metastatic tumors. **Primary CNS tumors** arise from abnormal proliferation of cells originating in the nervous system, while **metastatic tumors** arise from neoplasms originating elsewhere in the body that secondarily spread to the brain. The most common tumors in adults are shown in the table below.

TYPE OF TUMOR	PERCENT OF TOTAL
Glioma	40
Glioblastoma multiforme	20
Astrocytoma grades I and II	10
Ependymoma	6
Medulloblastoma	2
Oligodendroglioma	1
Choroid plexus papilloma	1
Metastases	23
Meningioma	17
Pituitary adenoma	5
Schwannoma	5
Lymphoma	3
Miscellaneous (congenital tumors, PNETs <sup>a</sup> )	7

<sup>a</sup>PNETs = primitive neuroectodermal tumors.

Source: Hochberg F, Pruitt A. Neoplastic diseases of the central nervous system. In Isselbacher ICJ, Braunwald E, Wilson JD, Martin JB, Fanci AS, Kasper DL (eds.). *Harrison's Principles of Internal Medicine*, 13th Ed, Chapter 369. McGraw-Hill, New York.

As seen in Table 5.6, the two most common brain tumors are glioblastoma and brain metastases. The next most common brain tumor is meningioma, followed by astrocytoma, pituitary adenoma, schwannoma, and ependymoma.

In adults, about 70% of tumors are supratentorial (that is, located above the tentorium cerebelli) and 30% are infratentorial. The reverse is true in children where about 70% of brain tumors are infratentorial and 30% are supratentorial.

**Symptoms of brain tumor** depend upon location, size, and rate of growth. Headache and other signs of increased intracranial pressure are common at presentation. Some tumor may present with seizures or with focal signs depending upon location. The tumors most commonly associated with seizures are oligodendrogliomas and meningiomas.

Brain tumors are **benign** if they do not infiltrate or disseminate widely through the nervous system and **malignant** if they have the potential to spread. Primary brain tumors rarely undergo metastatic spread outside of the central nervous system. As already mentioned, secondary metastases to brain from other primary sources in the body (such as lung cancer) are among the most common forms of brain tumor.

**Treatments for brain tumors** depend upon histological type, location, and size. Surgical removal of as much of tumor as possible without causing serious deficits is usually pursued. Data suggests surgical resection should be greater than 90% to have a positive effect on outcome. Next, depending upon the lesion, **radiation therapy** and/or **chemotherapy** may be beneficial. Steroids are often used to reduce edema and swelling. Small benign-looking tumors are often simply followed with serial MRI scans.

**Gliomas** are subdivided into several types (see table 5.6 above). Glial tumors arising from astrocytes are called **astrocytomas**. Gliomas are usually classified using the Daumas-Dupont grading system (I – IV) in which the most malignant is grade IV, or **glioblastoma multiforme**. Glioblastomas are relatively common and usually lead to death within one year despite maximal resection, radiation, and chemotherapy.

**Meningiomas** arise from the arachnoid villus cell and occur, in order of decreasing frequency, over the lateral convexities, in the falx, and along the basal regions of the cranium. They grow quite slowly. In females, they are associated with breast cancer. Meningiomas are treated by local excision. Only 5% of meningiomas behave in a malignant fashion.

**Pituitary adenomas** can cause endocrine disturbances and may compress the optic chiasm (usually resulting in a bitemporal visual field defect). Other tumor types may arise in this region as well including meningioma, craniopharyngioma, hypothalamic glioma, and others. Treatment with dopaminergic agonist often will shrink pituitary adenomas. If this is ineffective, transsphenoidal resection is performed.



**Lymphoma** of the CNS has been on the rise in recent years mostly attributable to the increase in human immunodeficiency virus (HIV). Lymphomas arise from B lymphocytes and commonly reside adjacent to the lateral ventricles. It can often be controlled for several years with chemotherapy and radiation therapy and currently has a median survival rate of close to 4 years.

**Schwannomas** are most commonly found on cranial nerve VIII (cochlear-vestibular nerve). **Brain metastases** can occur with numerous tumor types. The most common carcinomas are lung, breast, kidney, and gastrointestinal tract, and melanoma (skin).

The most common **pediatric brain tumors** are posterior fossa astrocytoma and medulloblastoma, followed by ependymoma. Since pediatric brain tumors are most often in the posterior fossa, they tend to cause hydrocephalus via obstruction of the fourth ventricle or the cerebral aqueduct. **Cerebellar astrocytoma** is a grade I astrocytoma that can often be cured by surgical resection. **Medulloblastoma** and **ependymoma** of the posterior fossa have worse prognoses, although long-term survival does occur following a combination of surgery, radiation, and chemotherapy. Medulloblastoma occurs before the age of 10 about 90% of the time. Similarly, it is very uncommon for cerebellar astrocytoma to occur after age 10.

**INFECTIOUS DISORDERS OF THE NERVOUS SYSTEM.** Similar to the rest of the body, the brain and spinal cord can be affected by a variety of infectious pathogens, including bacteria, viruses, parasites, fungi, and prions. Some of the more common or important infections will be reviewed below.

**Bacterial Infections** of the CNS caused by ***cocci*** and ***bacilli*** include bacterial meningitis, brain abscess, and epidural abscess. Bacteria most often gain access to the CNS via the bloodstream, and they frequently arise from infections elsewhere in the body, such as the respiratory tract or heart valves (endocarditis). Other routes of bacterial infections into the nervous system include spread from the oral-nasal passages or in trauma or surgery where direct contact can be made.

**Infectious meningitis** is an infection of the cerebrospinal fluid (CSF) in the subarachnoid space. It can be caused by bacteria, viruses, fungi, or parasites. First symptoms are typically signs of **meningeal irritation** or **meningismus**.

These signs of **meningeal irritation** include:

1. headache
2. lethargy
3. sensitivity to light (photophobia)
4. sensitivity to noise (phonophobia)
5. fever, and
6. nuchal rigidity

In **nuchal rigidity**, the neck muscles contract involuntarily, resulting in resistance to active or passive neck flexion, accompanied by neck pain.



**Treatment of brain abscess.** If the patient is clinically stable and have abscesses less than ~2.5 cm in diameter, they are usually treated with antibiotics (ceftriaxone plus metronidazole). Patients with larger abscesses (at risk for catastrophic rupture), or with signs of mass effect or progressive deterioration, should be treated with stereotactic needle aspiration as well as antibiotics.

**Epidural abscess** can occasionally occur especially in the spinal canal. It requires prompt diagnosis and treatment. Common presenting features include back pain, fever, elevated white blood cell count, headache, and signs of nerve root or spinal cord compression. Common organisms are *Staphylococcus aureus*, streptococci, Gram-negative bacilli, and anaerobes.

**Subdural empyema** is a collection of pus in the subarachnoid space, usually resulting from direct extension from an infection of the nasal sinuses or inner ear. This condition is treated by urgent surgical drainage and antibiotics (ceftriaxone plus metronidazole).

**Infections caused by Spirochetes.** The two most important spirochetal infections of the CNS are neurosyphilis and Lyme disease.

**Neurosyphilis** was common in the pre-penicillin days and has had a resurgence in recent years, possibly related to HIV. Syphilis is caused by the spirochete *Treponema pallidum*. It is sexually transmitted and has various stages after primary infection. In primary syphilis, painless skin lesions appear at sites of infection about 1 month after exposure. In secondary syphilis, more diffuse skin lesions appear within approximately 6 months, often on the palms and soles. In tertiary syphilis, neurologic manifestations are often present.

The later stages of syphilis, after about 4 to 15 years, typically follow a progressive of neurologic involvement from meningovascular syphilis to general paresis, and finally to tabes dorsalis. In **meningovascular syphilis**, chronic meningeal involvement causes an arteritis that results in diffuse white matter infarcts. If untreated, this condition eventually leads to **general paresis**, in which the accumulation of lesions causes dementia, behavioral changes, psychosis, delusions of grandeur, and diffuse upper motor neuron-type weakness. In another variant that often coexists with general paresis, patients with **tabes dorsalis** have involvement of the spinal cord dorsal roots, especially in the lumbosacral region, resulting in degeneration of the dorsal columns. These patients therefore have sensory loss in the lower extremities, sensory ataxia, and incontinence.

Diagnosis of neurosyphilis is based on blood tests for treponemes together with CSF from lumbar puncture showing lymphocyte-predominant meningitis (also called "aseptic meningitis"). Treatment of neurosyphilis consists of intravenous penicillin G and serial lumbar punctures to monitor response to therapy.

**Lyme disease** is caused by the spirochete *Borrelia burgdorferi*, carried by *Ixodes* species of deer tick which are common in certain areas of the U.S., Europe, and Australia. Primary infection is often heralded by a characteristic raised rash which gradually shifts its location and enlarges over days to weeks.

In some cases, neurological manifestations are seen, including aseptic meningitis or mild meningoencephalitis, characterized by meningeal irritation signs, cognitive and emotional changes. Lyme disease is diagnosed by typical clinical features, lumbar puncture, and serological testing. Untreated cases can eventually show white matter abnormalities on MRI scan. Lyme disease with neurological involvement is treated with intravenous ceftriaxone.

**Viral Infections.** **Viral meningitis** is less severe and less deadly than bacterial meningitis, and recovery usually occurs spontaneously within 1 to 2 weeks. Patients present with signs of meningeal irritation (e.g., headache, fever, lethargy, nuchal rigidity). Common causes are enteroviruses such as echovirus, coxsackievirus, and mumps virus. Often the causative agent is not identified. There is no specific treatment for most viral infections of the nervous system, except for herpes and HIV.

When viral infections involve the brain parenchyma, they are called **viral encephalitis**. Unlike viral meningitis, the clinical manifestations of viral encephalitis are often quite severe. Patients often present with bizarre psychotic behavior, confusion, lethargy, headache, fever, meningeal signs, and seizures. The most common cause is herpes simplex virus type 1 (type 2 also occasionally causes encephalitis). The herpes simplex virus has a tropism for limbic cortex and often causes necrosis of the undersurface of the anterior temporal lobes and ventral frontal cortices frequently seen on MRI. Focal signs such as anosmia, hemiparesis, memory loss, and aphasia may be seen in some cases. Untreated, it usually progresses within days to coma and death. Therefore, it is essential to initiate therapy promptly with acyclovir.

**HIV-Associated Disorders of the Nervous System.** Human immunodeficiency virus (HIV) can increase susceptibility to numerous infectious disorders of the CNS including viral, bacterial, fungal, and parasitic infections. HIV itself can cause aseptic meningitis at the time of seroconversion. AIDS dementia complex is the most common neurologic manifestation of HIV, with increased frequency late in the course of the illness. Treatment with the antiretroviral agent azidothymidine (AZT) often used in combination therapy (e.g., AZT + 3TC + protease inhibitor = highly active antiretroviral therapy, or HAART) can cause improvement in AIDS-related dementia.

Other viral infections in patients with HIV include encephalitis caused by herpes simplex virus, **varicella-zoster virus**, or **cytomegalovirus**. Important bacterial infections of the CNS in patients with HIV include tuberculous meningitis and neurosyphilis. The most common fungal infection in HIV patients is **cryptococcal meningitis**. A common parasitic infection of the CNS in patients with HIV is **toxoplasmosis**. CNS toxoplasmosis is caused by reactivation of infection with the parasite *Toxoplasma gondii*. Initial exposure is from cysts in cat feces or undercooked meat and is usually asymptomatic. In patients with AIDS the toxoplasma infection spreads to the CNS forming brain abscesses visible on MRI as ring-enhancing lesions: a nonenhancing center (dark on T1) surrounded by a ring of enhancement. Common presenting features are seizures, headache, fever, lymphocytic predominant (“aseptic”) meningitis, and focal signs that

depend upon the location of the abscesses. Toxoplasmosis is the most common cause of intracranial mass lesions in HIV patients.

**Parasitic Infections** that involve the CNS include cysticercosis, toxoplasmosis, malaria, African sleeping sickness, amebiasis, rickettsial illnesses, and schistosomiasis. Toxoplasmosis was discussed above under the section on HIV. Cysticercosis will be described here.

**Cysticercosis** is caused by ingestion of the eggs of the pork tapeworm *Taenia solium*, found predominantly in Latin America and certain regions of Africa, Asia, and Europe. The organism migrates through the bloodstream to the whole body forming multiple small cysts in the muscles, eyes, and CNS. Seizures are a common result. Other common symptoms include headache, nausea, vomiting, aseptic meningitis, and focal deficits depending upon cyst location. CT scans in active infection typically show multiple small, 1 to 2 cm cysts in brain parenchyma, with surrounding edema. The organisms eventually die leaving numerous 1 to 3 cm calcifications scattered throughout the brain. Diagnosis is made by history in appropriate populations, by typical radiologic appearance, and by antibody tests of serum and CSF. The condition is treated with albendazole.

**Fungal Infections** of CNS are uncommon in immuno-competent hosts. Cryptococcal meningitis was discussed above in the section on HIV. Aspergillosis and candidiasis can involve brain parenchyma and are usually accompanied by intense inflammatory response. Other fungi that can affect brain include *Histoplasma*, *Coccidioides*, and *Blastomyces*. An important fungal infection to be aware of is **mucormycosis**, which occurs mainly in diabetics in the rhinocerebral form causing ophthalmoplegia, facial numbness, visual loss, and facial weakness, with a typical violet coloration of the tips of the eyelids.

Most fungal infections can be diagnosed only by biopsy, which is pursued aggressively because early treatment is essential. Mucormycosis is treated with amphotericin B. Steroids can exacerbate fungal infections and should be avoided when a fungal infection is suspected.

**Prion-Related Illnesses**. In recent years, a new protein-based infectious agent called the **prion** has been identified in certain neurologic disorders. Prions can transmit disease from one animal to other despite the fact that they contain no DNA or RNA. Pathologically, diffuse degeneration of the brain and spinal cord occurs with multiple vacuoles resulting in a spongiform appearance. Human prion-related illnesses include **Creutzfeldt-Jacob disease**, **kuru**, and **fatal familial insomnia**. These disorders are all relatively rare. The most common is Creutzfeldt-Jacob disease which has an incidence of approximately one new case per million individuals per year.

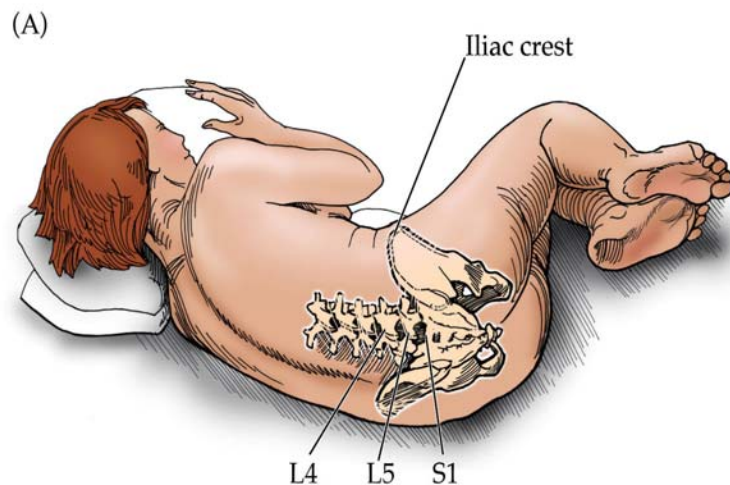
Typical presenting features of **Creutzfeldt-Jacob disease** are rapidly progressive dementia, an exaggerated startle response, myoclonus, visual distortions, and ataxia. EEG often shows periodic sharp wave complexes. There is currently no treatment. Progressive neurologic deterioration and death usually occur within 6 to 12 months. Prion-related illnesses can occur in an inherited

pattern, or they can be transmitted by exposure to infected tissues with an incubation period of 2 to 25 years. A cluster of atypical cases of Creutzfeldt-Jacob disease may have been caused by ingestion of cattle infected with bovine spongiform encephalopathy (“mad cow disease”) in Britain.

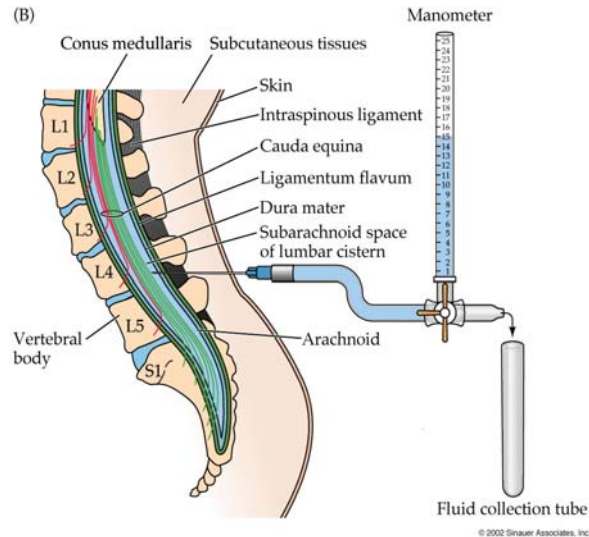
**LUMBAR PUNCTURE** is an important procedure that provides direct access to the subarachnoid space of the lumbar cistern. It can be used to obtain samples of CSF, measure CSF pressure, to remove CSF in cases of suspected normal-pressure hydrocephalus (NPH), and occasionally to introduce drugs (such as antibiotics or cancer chemotherapy) or radiological contrast material into the CSF.

Before a lumbar puncture (LP) is performed, the patient should be evaluated for evidence of increased intracranial pressure because rapid decompression of an closed hydrodynamic system under pressure (from intracranial mass lesions for example) may result in brain herniation. The LP is performed with a sterile technique under local anesthesia. A hollow spinal needle is introduced through the skin and passes through subcutaneous tissues, ligaments of the spinal column, dura, and arachnoid, to finally encounter CSF in the subarachnoid space.

Note that the spinal cord ends at about the L1 or L2 level of the vertebral bones, and the nerve roots continue downward to form the **cauda equine** meaning horses tail. To avoid hitting the spinal cord, the spinal needle is inserted at the space between the L4 or L5 vertebral bones (see figure below).



Note that the lumbar cistern is normally in direct communication with CSF in the ventricles and CSF flowing over the surface of the brain. A manometer tube is used to measure CSF pressure. Pressure measurements are more reliable in the lying position. Normal CSF pressure in adults is less than 20 cm H<sub>2</sub>O (refer to the figure below).



After opening pressure has been measured and recorded, CSF samples are collected and sent for numerous studies including cell count, protein, glucose, and microbiological testing. Normally, red blood cells are not present in CSF. Red blood cells can indicate subarachnoid hemorrhage, hemorrhagic herpes encephalitis, or they may simply have been introduced by damage to blood vessels by the spinal needle at the time of lumbar puncture, referred to as a **traumatic tap**.

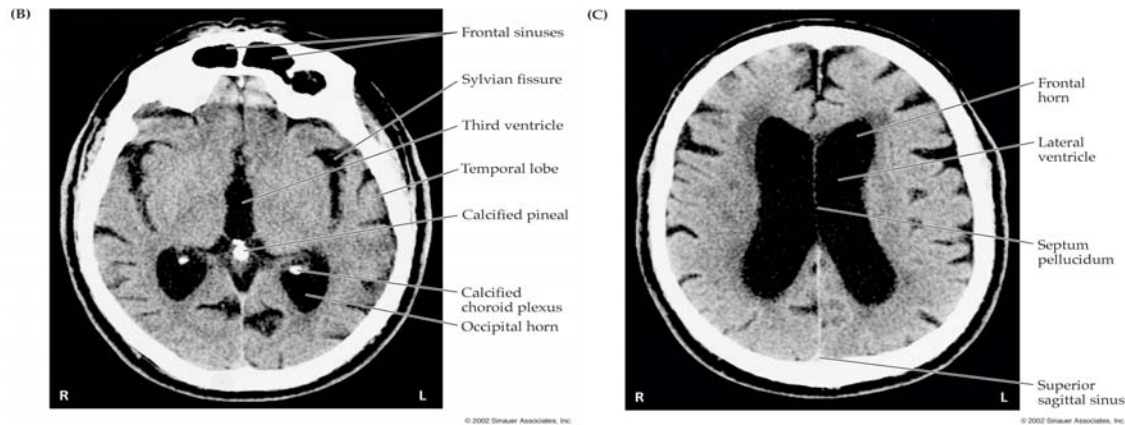
In addition to diagnosing infection or hemorrhage, lumbar puncture can be useful for obtaining cytological specimens for the diagnosis of **neoplastic meningitis**, and it can be useful for immunologic testing such as detection of **oligoclonal bands** in suspected multiple sclerosis.

## CLINICAL CASE EXAMPLES

**CASE 1.** A 76 year-old man was admitted to the hospital because of progressive gait unsteadiness, memory difficulty, and incontinence. His gait unsteadiness developed over the course of 1 year, beginning with a shuffling stride and difficulty rising from a chair. This unsteadiness progressed until he required a cane, and eventually assistance from another person, in order to ambulate.

Urinary incontinence began 4 months prior to admission, and his family noted the onset of memory problems around the same time. Examination on admission was notable for recall of only 1 of 3 objects at 5 minutes during mental status exam, and an unsteady, shuffling gait, the patient barely lifting his feet off the floor.

Head CT scans shown below reveal the third ventricle, the occipital horns of the lateral ventricles, and the lateral ventricles appear enlarged. Note that in patients with brain atrophy, both the sulci and the ventricles are proportionately increased in size. In hydrocephalus, however, the ventricles are increased out of proportion to the amount of sulcal prominence.



In this patient's CT scans, the sulci are slightly prominent, while the ventricles are markedly enlarged, making this hydrocephalus.

### FINAL DIAGNOSIS

Normal pressure hydrocephalus

### OUTCOME

Treated with insertion of a right ventriculoperitoneal shunt. Incontinence ceased, and gait markedly improved. Memory did not improve, but did not decline further at 7-month follow-up.

**CASE 2.** An 11 year-old girl was brought to the pediatrician's office because of **worsening headaches, nausea, and diplopia** during the past week.

The patient was healthy until 1 week ago, when she developed persistent bifrontal headaches (worse in the mornings) and nausea.

Both symptoms gradually worsened, and for the past 2 days she had multiple episodes of **vomiting**. Four days ago, she also noticed horizontal diplopia (double vision where images overlap side-by-side horizontally) when looking to the left. History was otherwise normal.

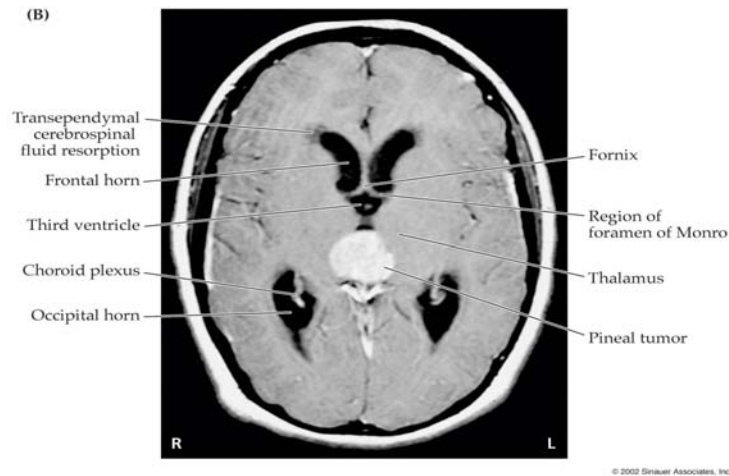
Neurologic examination showed the left eye did not fully abduct upon left lateral gaze and ophthalmoscopic exam revealed **bilateral papilledema**. Physical and neurologic exam (including other cranial nerves, motor, sensory, reflexes, coordination, and gait) were otherwise normal.

Dysfunction of the left abducens nerve (CN VI) (which controls the left lateral rectus muscle) could cause incomplete abduction of the left eye upon left lateral gaze.

The patient also shows worsening signs of elevated intracranial pressure which in this patient could be caused by a mass lesion such as a brain tumor, hydrocephalus, or pseudotumor cerebri. Other, less likely possibilities include a slowly developing intracranial infection or perhaps a coagulation disorder causing sagittal sinus thrombosis.



MRI with radiologic dye (gadolinium) was given intravenously and showed a large pineal tumor obstructing the cerebral aqueduct and causing noncommunicating hydrocephalus.



The hydrocephalus was treated immediately with placement of a ventriculoperitoneal shunt. One week later she was taken back to the operating room for a biopsy of the mass lesion. Because of its deep location within the brain adjacent to the midbrain, open surgical resection was not feasible.

### FINAL DIAGNOSIS

Results of the biopsy showed she had a primitive neuroectodermal tumor (PNET also called a DNET for developmental NET) of the pineal region, also called a pineoblastoma.

### OUTCOME

This is an uncommon brain tumor which often responds well to treatment although it can be fatal. Patient was treated with radiation and chemotherapy. She recovered fully and had no evidence of recurrence at 3-year follow-up.