Development of the nervous system is a very complex process which can be adversely affected by many disorders – genetic, infectious, hypoxic/ischemic, toxic, or nutritional. These may exert their effects by preventing or distorting normal development or by damaging already-formed structures. Generally, the earlier in development an abnormality occurs, the more severe the malformation will be.

In most cases, malformations produce functional impairment that cannot be restored. Therefore, it is important to understand their pathogenesis for purposes of genetic counseling or possible prevention. Examples of preventive measures that have resulted from such studies include maternal vaccinations, nutritional supplements, avoidance of X-rays, and the identification and avoidance of teratogenic substances.

Various factors confound our study of CNS malformations. For example, a particular malformation (e.g. micropolygyria) may be caused by a variety of agents or perhaps may be a non-specific accompaniment of another lesion. Also, the time of exposure of the fetus to a particular noxious agent will often determine the type of malformation seen.

Most major anomalies can be considered morphologically in broad categories:

1. Abnormal closure of the neural tube, either failure to close or re-opening (dysraphism; spina bifida)

Several specific lesions are associated with spina bifida. All of them involve a combination of neural tissue, meninges, and overlying bone or soft tissue. Spina bifida is the most common CNS malformation, and most frequently occurs in the lumbosacral area. It has been related to folate deficiency early in pregnancy, and genetic influences have also been noted, particularly with genes that control glucose metabolism. There is a wide range of severity, from asymptomatic failure of bony closure (spina bifida occulta) to a completely open segment in which the disorganized neural tissue merges with the adjacent soft tissue, skin and vascular elements (spina bifida aperta). Intermediate lesions include:

   **Congenital dermal sinus**, in which there may be a connection between the subarachnoid space and the body surface. This may be a portal of entry for infection, and should be closed as early as possible.

   **Meningocele**, which comprises a protrusion of arachnoid and subarachnoid space through the bony defect. The underlying nervous tissue of the spinal cord may be malformed or nearly normal.

   **Meningomyelocele (or myelomeningocele)**. A more severe form, in which the protruding meningeal sac also contains a portion of malformed spinal cord and nerves.

   **Encephalocele** is the brain's analogue of meningomyelocele; it is usually found in the occipital region or posterior fossa.

   **Anencephaly** is the brain's analogue of spina bifida aperta, with absence of brain and calvarium at the anterior end of the neural tube. The disruption in development happens at ~28 days gestational age. All that is left is a jumble of disorganized tissue including neural elements, meninges, vessels, choroid plexus and ependymal which is referred to as the **area cerebrovasculosa**.
2. **Disorders of forebrain formation**, usually with abnormalities of neuronal population and/or migration:

The brain as a whole may be abnormally large ("megalencephaly") or small ("microencephaly"). Megalencephaly is sometimes associated with autism. Microencephaly is much more common and is accompanied by small head circumference ("microcephaly"). It may be caused by chromosomal abnormalities, fetal alcohol syndrome, intrauterine HIV infection and other infections (see below). It is postulated that the initial abnormality is a decrease in the number of neurons that reach the neocortex, which leads to a simplification of the gyral folding.

**Holoprosencephaly** - defective separation of the prosencephalon into two cerebral hemispheres, thus a single ("holo") prosencephalon. There are varying degrees of severity, usually associated with severe midline facial defects. Holoprosencephaly has been associated with trisomy 13 and trisomy 18, and has been caused in animals by maternal ingestion of cyclopamine which inhibits Sonic Hedgehog (Shh) signaling during embryogenesis.

**Arhinencephaly** (absence of the "smell brain") - loss of the olfactory bulbs and tracts, often associated with midline facial defects, such as cleft lip and palate.

**Agenesis of the corpus callosum** – may accompany holoprosencephaly or be an isolated defect.
3. **Cortical anomalies due to abnormal neuronal migration.**

- **Lissencephaly/ agyria/ pachygyria** - these terms all refer to a lack of gyral folding and sulcus formation. Different forms of lissencephaly have been attributed to specific genetic abnormalities, such as mutations in the gene encoding the microtubule-associated protein LIS-1.

- **Microgyria** and **polymicrogyria** - little tiny folds that mimic gyri.

- **Heterotopias** - clusters of neurons that didn’t make it all the way to their appropriate destinations. They are often associated with epilepsy and are frequently seen along the ventricular cavities, where the germinal matrix is located. At least two genes on the X chromosome have been associated with abnormal neural migration and heterotopias. Mutations in these genes affect males and females differently. One gene codes for an actin-binding protein called filamin-A. Mutation of this gene is lethal in males. In females, the random inactivation of one X chromosome results in two populations of neurons: those with the normal allele, which reach their correct location, and those with the mutant allele, which are in the heterotopia. A second gene codes for a microtubule-associated protein called doublecortin (DCX). Males with mutations develop lissencephaly, while females develop laminar rows of heterotopias beneath the cortex (“doublecortex”).

Cortical anomalies may also be caused by intrauterine infections, particularly with cytomegalovirus or rubella. For instance, CMV infection is typically in the periventricular regions, where it can interfere with neuronal proliferation or migration, resulting in any of the anomalies listed above. The newly emerging Zika virus outbreak is also associated with infection of cortical neural progenitor cells, resulting in microcephaly. The earlier in a pregnancy that these infections occur, the greater the damage.

4. **Posterior Fossa Anomalies**

   a. **The Arnold-Chiari malformation.** This complex malformation is associated with several of the previously considered neural tube and forebrain lesions. Its main features are:
      1. elongation of the medulla and 4th ventricle
      2. protrusion of the posterior portion of the cerebellar vermis through the foramen magnum, thus lying dorsal to the elongated medulla.
      3. flattening and “beaking” of the quadrigeminal plate.

   The Arnold-Chiari malformation is almost always associated with spina bifida, typically
accompanied by a lumbosacral meningomyelocele. Most cases develop hydrocephalus.

b. The Dandy-Walker malformation. Is characterized by an enlarged posterior fossa. The cerebellar vermis is absent or rudimentary, and in its place is a midline cyst lined by ependyma. The cyst represents the expanded 4th ventricle.

5. Syringomyelia - a dilated, glial-lined (not ependymal) fluid-filled (not CSF) cavity in the spinal cord, that does not communicate with the central canal. It is often at the junction of alar and basal plates. Hydromyelia is dilation of the central canal filled with CSF. It is the spinal cord analog of hydrocephalus.

Cerebral palsy is a term used to describe neurologic deficits which are noted soon after birth and don’t progress. It has no unifying neuropathologic correlate, and may be caused by malformations or destructive lesions, including many of the disorders mentioned above. It may also follow perinatal hypoxia/ischemia. An important aspect of these disorders is that they are discrete and non-progressive. Therefore, the neurologic deficits are also non-progressive. If an infant has neurologic symptoms that become worse, look for another explanation.

Other forms of perinatal brain injury that cause non-progressive symptoms (cerebral palsy) include:
   a) periventricular hemorrhage – especially in very premature infants. This occurs in the germinal matrix and may rupture into the ventricular cavities.
   b) periventricular leukomalacia due to focal infarcts in the white matter.
   c) status marmoratus, an abnormal “marbling” of the deep gray matter due to hypoxic destruction of neurons in the perinatal period.

OBJECTIVES FOR MALFORMATIONS OF THE NERVOUS SYSTEM

1. Know the spectrum of disorders that may be associated with abnormal closure of the neural groove, both in the spinal cord and the brain.

2. Know the structural and pathogenetic features of forebrain and posterior fossa anomalies and complex malformations and abnormalities, including:
   a) holoprosencephaly
   b) Arnold-Chiari malformation
   c) polymicrogyria
   d) heterotopic cortex
   e) anencephaly
   f) porencephaly
   g) hydranencephaly
   h) lissencephaly
   i) Dandy-Walker malformation
   j) “Cerebral palsy”
   k) Syringomyelia

Reading: Robbins & Cotran, 9th edition, pp 1256-59