- Increases in the volume of intracranial contents (as a result of increased CSF volume, edema, hemorrhage, or tumor) raise the pressure inside the fixed capacity of the skull.
- Increases in pressure may result in decreased perfusion (leading to ischemia). The increased pressure may also result in displacement of tissue past the edges of dural partitions inside the skull or through openings in the skull (herniations).

Malformations and Developmental Disorders

Although the pathogenesis and etiology of many CNS malformations remain unknown, both genetic and environmental influences appear to be involved. Newer genetic methods, including whole exome and whole genome sequencing, have begun to uncover a range of alterations that may cause many of these malformations. The causal relationship between the genetic alterations and the pathogenesis of the malformations is the subject of active research. Besides genetic factors, many toxic compounds and infectious agents also have teratogenic effects and may cause brain malformations.

Neural Tube Defects

Failure of a portion of the neural tube to close, or reopening of a region of the tube after successful closure, may lead to malformations involving some combination of neural tissue, meninges, and overlying bone or soft tissues. Collectively, neural tube defects account for most CNS malformations, with the most common neural tube defects involving the spinal cord.

- *Spinal dysraphism* or *spina bifida* may be an asymptomatic bony defect (spina bifida occulta) or a severe malformation with a flattened, disorganized segment of spinal cord, associated with an overlying meningeal outpouching.
- *Myelomeningocele* (or meningomyelocele) refers to extension of CNS tissue through a defect in the vertebral column; the term *meningocele* applies when there is only a meningeal extrusion. Myelomeningoceles occur most commonly in the lumbosacral region. Affected individuals have motor and sensory deficits in the lower extremities as well as disturbances of bowel and bladder control. These are often complicated by superimposed infection that extends into the cord from the thin, overlying skin.
- *Encephalocele* refers to a diverticulum of malformed brain tissue extending through a defect in the cranium. It most often occurs in the posterior fossa, although comparable extensions of brain occur through the cribriform plate in the anterior fossa (sometimes misleadingly referred to as a "nasal glioma").

The frequency of neural tube defects varies widely among different ethnic groups. Evidence for a genetic basis includes the high concordance rate among monozygotic twins. The overall recurrence rate for a neural tube defect in subsequent pregnancies has been estimated at 4% to 5%. Folate deficiency during the first several weeks of gestation is a well established risk factor; differences in rates of neural tube defects between populations can be attributed in part to polymorphisms in enzymes involved in folic acid metabolism. Folate supplementation can lower the risk of neural tube defects, but because neural tube closure is normally complete by day 28 of embryonic development (before most pregnancies are recognized), it must be given to women throughout their reproductive years to be fully effective. Precisely how folate deficiency increases the risk is uncertain; defects in the timing of DNA synthesis and effects on DNA methylation (an important epigenetic mode of gene regulation) are suspected.

Anencephaly is a malformation of the anterior end of the neural tube, with absence of most of the brain and calvarium. Forebrain development is disrupted at approximately 28 days of gestation, and all that remains in its place is the *area cerebrovasculosa*, a flattened remnant of disorganized brain tissue with admixed ependyma, choroid plexus, and meningothelial cells. The posterior fossa structures may be spared, depending on the extent of the skull deficit; descending tracts associated with disrupted structures are, as expected, absent.

Forebrain Anomalies

Abnormalities in the generation and migration of neurons result in malformations of the forebrain that may be focal or involve entire structures. The pool of proliferating precursor cells in the developing brain lies adjacent to the ventricular system. Overall neuronal number is determined by the fraction of proliferating cells that undergo transition into migrating cells with each cell cycle. Early on, most cell divisions yield two more progenitor cells, while as development progresses there are more asymmetric divisions yielding both a progenitor cell and a cell directed to the developing cortex. If excess cells exit the proliferating pool too early, then the overall generation of neurons is reduced; if too few exit during early rounds of division, then the geometric expansion of the proliferating population results in an overproduction of neurons. The migration of neurons from the germinal matrix zone to the cerebral cortex follows two paths: a radial migration for neuronal progenitor cells destined to become excitatory neurons and a tangential migration course for those which will become inhibitory interneurons. The signaling that governs radial migration is better understood than the corresponding mechanisms for tangential migration. For radial migration, a secreted protein (reelin) signals to migrating neuroblasts through a surface receptor; the ability of these cells to respond appropriately is dependent on cytoskeletal proteins that propel the migrating neuroblasts.

A range of malformation patterns have been defined, initially by focusing on the region of the brain that is involved and what changes are present. With genetic advances, it has become clear that many of these patterns can be caused by mutations in several genes that are required for proper cerebral development. Changes may be seen from the surface of the brain, with either too few or too many gyri, in the organization of the brain into normal lobes, in the structure of the cerebral cortex or in the distribution of neurons within the brain.