# Prematurity, postmaturity, and destructive lesions in utero.

L B Rorke and R A Zimmerman

*AJNR Am J Neuroradiol* 1992, 13 (2) 517-536
http://www.ajnr.org/content/13/2/517.citation

# Prematurity, Postmaturity, and Destructive Lesions in Utero

*Lucy B. Rorke*[1] *and Robert A. Zimmerman*

From the Departments of Neuropathology (LBR) and Neuroradiology (RAZ), the Children's Hospital of Philadelphia

Central nervous system (CNS) lesions resulting from hypoxia-ischemia (H-I) during gestation and the perinatal period, and from intrapartum trauma form the subjects of this review. Whereas mechanical factors are primarily responsible for the traumatic lesions, a wide spectrum of complex physiologic disturbances and pathologic sequelae are associated with H-I. CNS damage most commonly occurs among infants born prematurely, term infants of high risk mothers, and those who suffer severe cardiorespiratory problems. Since brain damage can occur in utero, a newborn may harbor already well-established brain lesions at a time when adverse circumstances again produce additional insults. Thus, lesions of various ages may coexist. Moreover, intrapartum complications tend to be more common in brain-damaged fetuses whether such damage is of a developmental or acquired etiology (1). The clinician, therefore, should resist the strong but simplistic temptation to assume that neurologic impairment in the newborn is necessarily a consequence of intrapartum H-I.

The current imaging methods of evaluating the brain of the pediatric patient injured by a H-I or intrapartum traumatic event are: ultrasound (2–4); computed tomography (CT) (5–8); and magnetic resonance (MR) imaging (9–15). The imaging findings of representative examples of the major brain insults are shown in the figures.

[1] Address reprint requests to Dr Rorke, The Children's Hospital of Philadelphia, 3400 Civic Center Boulevard, Philadelphia, PA 19104.

**Index terms:** Fetus, abnormalities and anomalies; Infants, newborn; Pediatric neuroradiology

AJNR 13:517–536, Mar/Apr 1992 0195-6108/92/1302-0517



## The Intrauterine Period

Optimal fetal development requires a healthy mother and a normally functioning placenta. The fetus receives nutrients and excretes waste products by exchange through the trophoblastic membrane of the placental villi. These contain the fetal capillaries and are bathed in maternal blood circulating in the intervillous spaces. As gestation advances, there is an increase in the number of vessels within a given villus. The vessels establish a more intimate relationship with the trophoblastic membrane, since the two layers of trophoblastic cells present during the first trimester are partially shed by the third trimester. Attenuation of this cellular barrier thus allows for a more efficient exchange between the mother and fetus. Interposition of the placenta between mother and fetus requires a unique mechanism to provide for circulatory communication between them. The fetal capillary bed within chorionic villi is interposed between the larger arteries and veins. In contrast to the arrangement in the organs of the body wherein oxygenated blood is delivered through the arterial system, it is the single umbilical vein that carries oxygenated blood to the fetus. Blood flows into the ductus venosus, then into the inferior vena cava and right heart. The largest proportion crosses to the left atrium through the foramen ovale, enters the ventricle, and then the ascending aorta and cephalic arteries. A small proportion is diverted to the lungs and the lower half of the body. There is preferential flow of the well-oxygenated blood to the liver, heart, and brain.

The poorly oxygenated blood leaves the fetus through the two umbilical arteries, the entire circulation requiring exactly four heartbeats (16).

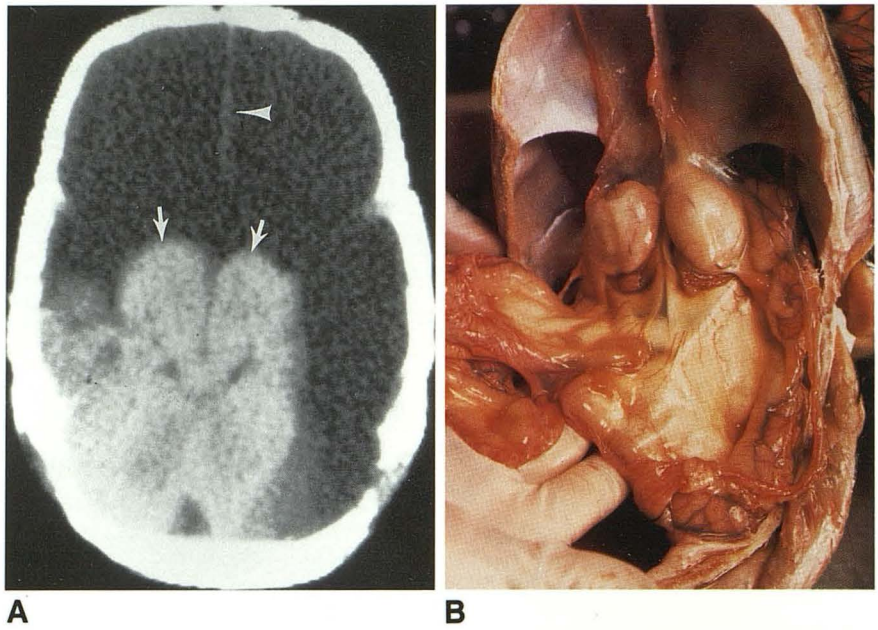



Fig. 1. Hydranencephaly.

*A*, Noncontrast axial CT shows preservation of the thalami (*arrows*) and supratentorial brain within the vascular distribution of the posterior cerebral arteries. There is an absence of cerebral tissue in the vascular distribution of the anterior and middle cerebral arteries. The falx cerebri (*arrowhead*) is present.

*B*, Typical hydranencephalic brain within elongated skull (anteroposterior diameter). The fluid-filled cavities have collapsed, leaving residual thalami-deep gray matter and some temporal and occipital tissue.

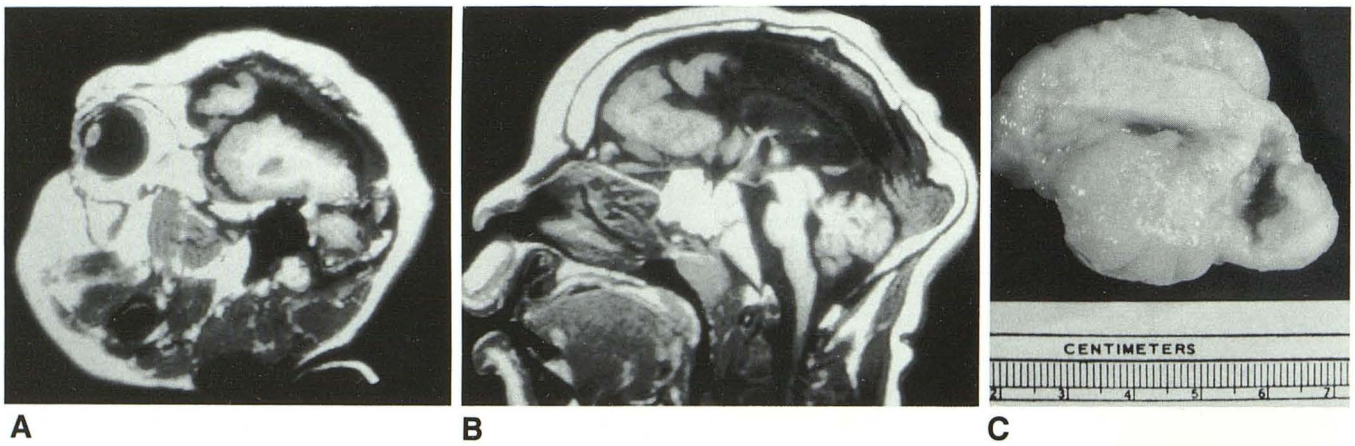



Fig. 2. Twin-twin transfusion resulting in in utero H-I event.

*A*, Sagittal T1-weighted image shows severe microcephaly.

*B*, Midline section shows marked diminution in brain size with evidence of tissue necrosis.

*C*, Lateral view of severely micrencephalic brain of twin, victim of twin-twin transfusion syndrome. The basic configuration is preserved, but the tissues were diffusely gliotic and partially calcified.

While the normal condition of the fetus is one of hypoxemia, a significant drop in oxygen concentration leads to vasoconstriction of special arteriovenous anastomoses of epithelial type in muscle, skin, lungs, kidneys, and intestine to allow maximal flow to liver, heart and brain (17). If oxygen deprivation is severe and/or prolonged, the infant may die or sustain significant brain damage, along with dysfunction of other organs.

Under some circumstances, the likely cause of intrauterine damage may be known such as fetal-maternal bleeding, severe eclampsia with placental infarction, premature separation of the placenta, twin-twin transfusion, maternal drug addiction (most commonly heroin or cocaine) and maternal suicide attempts. In other instances, the etiology of the damage remains speculative.

Hydranencephaly, an uncommon but dramatic lesion, for example, is thought to result from inadequate blood flow through the internal carotid arteries sometime after the basic structure of the brain has developed, ie, during the early or middle second trimester. However, identification of thromboses, vascular kinking, or other carotid anomalies is often lacking. Rarely, hypoplasia of these vessels may be observed. In this condition, those portions of the cerebral hemispheres supplied by the internal carotid arteries are replaced by fluid-filled cystic cavities (Fig. 1).

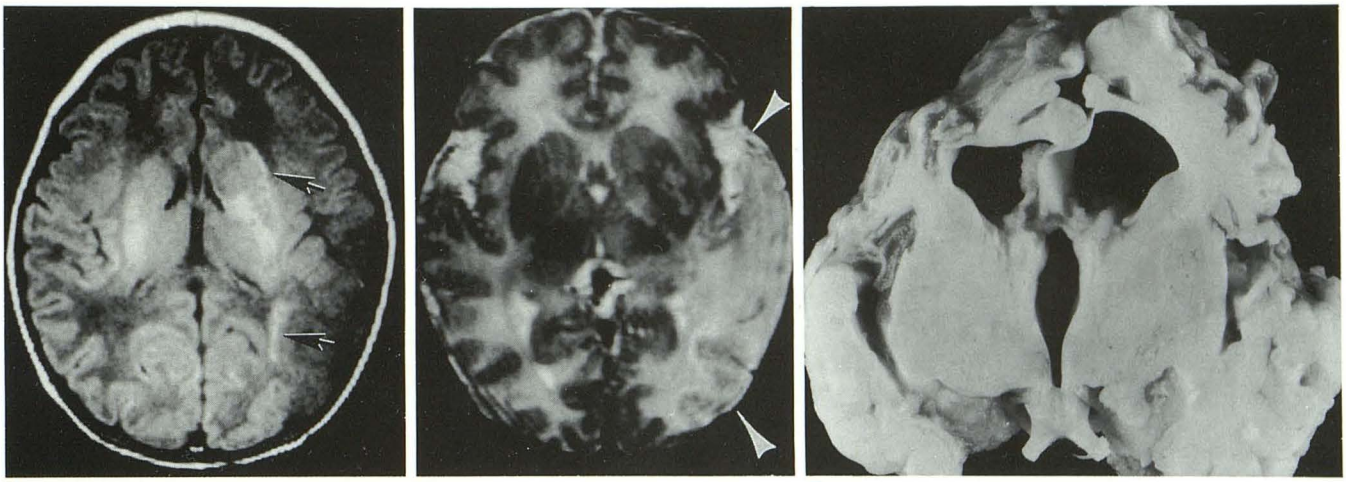



Fig. 3. Newborn infant with multiple left-sided hemorrhagic infarcts secondary to placental emboli.

*A*, Axial T1-weighted MR shows high signal intensity methemoglobin (*arrows*) in the left basal ganglionic region and periatrial region.

*B*, Axial T2-weighted MR shows loss of the normal gray/white interface, and high signal intensity in the gray and white matter of the left middle cerebral artery vascular distribution (*arrowheads*).

*C*, Bilateral infarctions in cortical branches of major cerebral arteries secondary to thrombi from placental infarctions. Note the severe sclerosis of the cortical ribbon with marked reduction in the volume of white matter, more severe on the left than on the right side. On the left, infarction affects tissue in the distribution of the anterior and middle cerebral arteries, whereas the middle cerebral artery distribution is primarily affected on the right. There is atrophic (passive) dilatation of the ventricles.

In the twin-twin transfusion syndrome, one twin in a monochorionic placenta receives the bulk of the blood flow. The deprived twin remains small overall. Its brain is also smaller than normal and may contain foci of necrosis (18) (Fig. 2). Micrencephaly, however, may occur in singleton births for other known or obscure reasons.

Foci of infarction in the newborn brain in a specific vascular distribution such as the middle cerebral artery have been associated with thromboemboli from the placental veins (19–21) (Fig. 3).

Many brain lesions arising during gestation do not fall into one of these specific categories. They are characterized instead by foci of hemorrhage, hemorrhagic or ischemic cystic or noncystic necrosis of limited or widespread distribution. In contrast to lesions in the perinatal period that are often hemorrhagic (especially in low birth weight infants), those arising during gestation are more likely to be ischemic in nature. However, matrix zone hemorrhages, a common affliction of the small, premature infant, do occur in utero.

In general,those portions of the brain containing mature neurons are most vulnerable to H-I injury, ie, brain stem tegmentum, nodulofloccular lobe of cerebellum, pallidum, and thalamus. Unless the ictus is severe, the cerebral cortex often escapes damage, largely because it is populated with primitive cells with low metabolic activity.

The insult may be a single, catastrophic event or may involve suboptimal perfusion over a longer period of time. A simple catastrophic episode of H-I, for example, occurs in abruptio placenta, life-threatening maternal cardiorespiratory collapse as in drug overdose, or suicidal attempt. Prolonged suboptimal perfusion is, among other things, characteristic of fetal-maternal bleeding, preeclampsia and premature aging of the placenta.

It may not be possible to predict the precise distribution and severity of the lesion even if the basic pathophysiology is known, because similar patterns of tissue destruction result from quite different intrauterine disorders. These are illustrated in Figures 4 and 5. The brain in Figure 4 was partially destroyed in utero consequent to fetal-maternal transfusion syndrome; at birth the infant had a hemoglobin of 2 g. Although the lesion pictured in Figure 5 is basically similar to that shown in Figure 4, damage resulted from severe preeclampsia.

## The Intrapartum Period

The brief journey from an intrauterine existence to the vagaries of earthly life is sometimes hazardous. Of all the organs of the body, the brain is at greatest risk for damage. Damage to

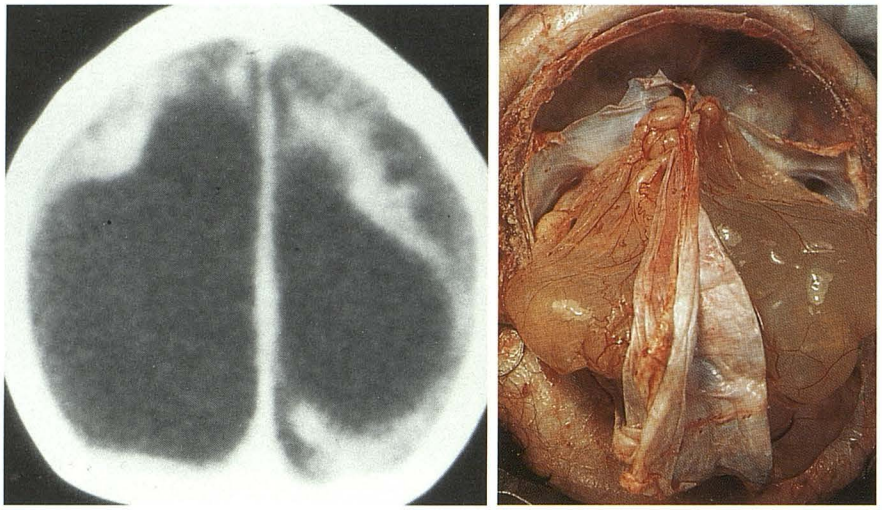



Fig. 4. In utero disruption of placental function; subsequent birth with microcephaly and cerebral H-I insult.

*A*, Axial CT shows marked ventricular dilatation, with decreased brain tissue.

*B*, Brain in situ of 17-year-old boy who sustained bilateral destruction of the frontal lobes with cystic replacement consequent to fetal-maternal transfusion syndrome. The falx cerebri and a small portion of the parasagittal dura remain in place. Note the retraction of the cystic frontal lobes with better preservation of the posterior portions of the hemispheres.

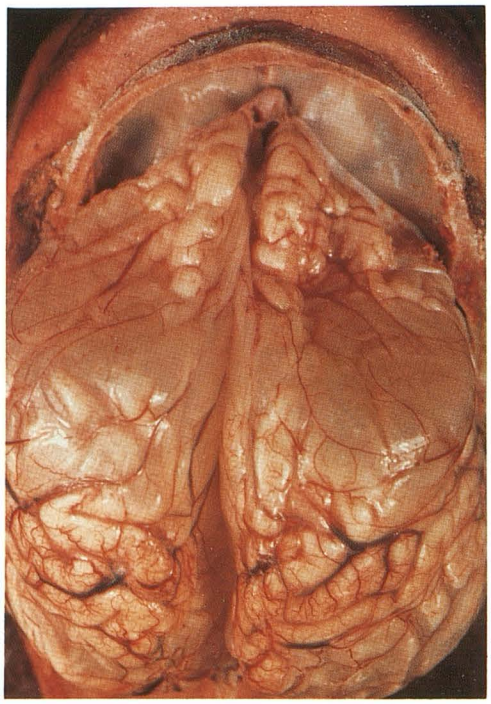


Fig. 5. Brain in situ of 18-year-old boy who sustained damage in utero because of severe maternal preeclampsia. Note the partial cystic replacement of the frontal lobes with relative preservation of the posterior half of the brain.

the CNS is generally inflicted either through mechanical injury or as a consequence of H-I.

### *Birth Injury Secondary to Trauma*

Although a rare fetus is traumatized in utero, mechanical trauma is generally an intrapartum event associated with cephalopelvic disproportion or an abnormal presentation. The most common injury is subdural hematoma (22, 23). Typically, the head and brain are injured by forceps or vacuum suction in an effort (1) to assist egress through a channel that is too small to allow easy passage or (2) to facilitate birth of an infant who has become distressed because of cord prolapse or other problems. Infants who present a single or double footling, frank breech, or face are at particular risk for damage to both brain and spinal cord.

Lesions that may be seen under these circumstances include soft-tissue edema or hemorrhages (caput succedaneum), subgaleal hematoma, subperiosteal hemorrhage (cephalhematoma) (Fig. 6), skull fracture, epidural hemorrhage (Fig. 7), and subdural hemorrhage (Fig. 8). The subdural hemorrhage is usually secondary to tears of the falx or tentorium and of the venous sinuses contained therein (Fig. 9). Hemorrhage within the leaves of the falx is relatively common and, in isolation, is unassociated with significant problems. Subarachnoid bleeding and contusions/laceration injury of brain or spinal cord are less common.

Whereas soft-tissue edema and hemorrhage are generally resorbed leaving no permanent sequelae, large cephalhematomas require drainage, since these have a tendency to calcify and disfigure the head. Cephalhematoma is typically located in the parietal bone (Fig. 6) and may be associated with skull fracture.

Epidural hemorrhage is rare, but accumulation of blood in the subdural space secondary to tearing of bridging veins (Fig. 8) or sinuses (Fig. 9) is a common feature of traumatic delivery.

Parenchymal damage of brain and/or spinal cord may also occur but is fortunately rare. The

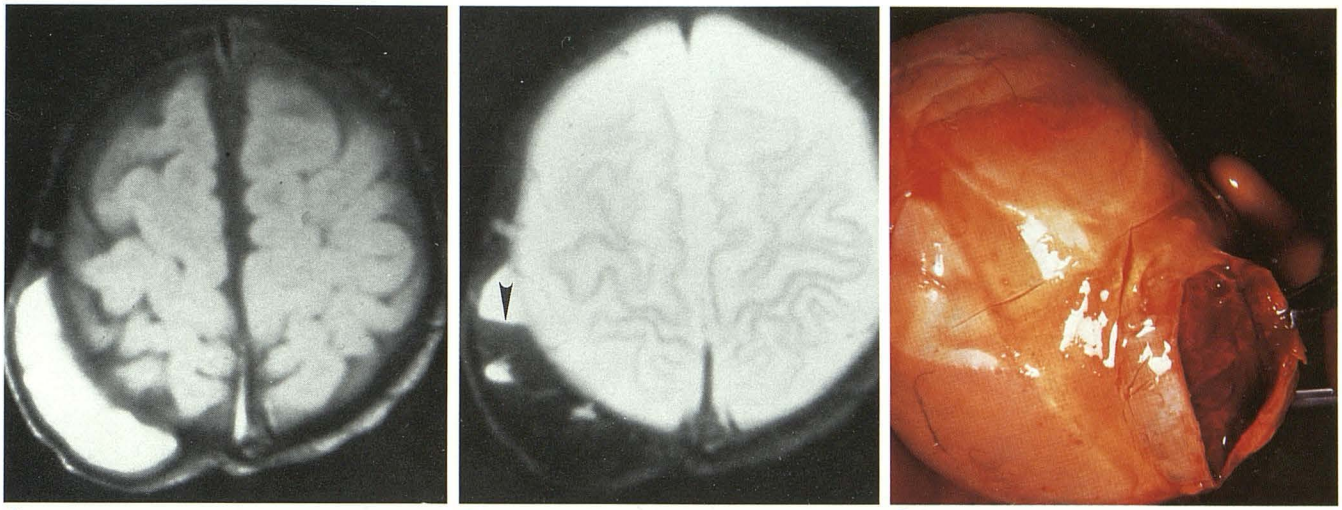



Fig. 6. Cephalhematoma.

*A*, Axial T1-weighted MR shows high signal intensity methemoglobin in a subperiosteal collection bound down by the sutures.

*B*, Axial T2-weighted MR shows a blood fluid level (*arrowhead*) within the collection. Hypointense intracellular methemoglobin is pooled inferiorly, with more hyperintense extracellular methemoglobin superiorly.

*C*, Right parietal cephalhematoma which has undergone partial organization.

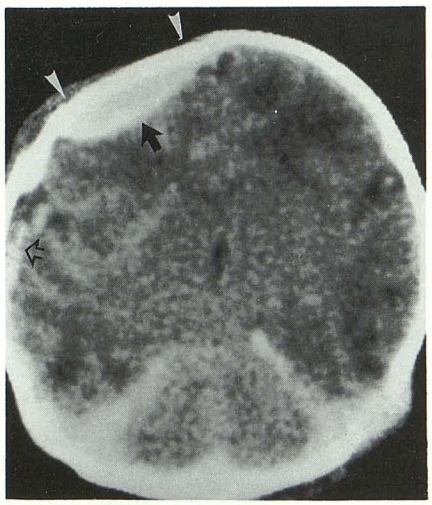


Fig. 7. Birth trauma; depressed fracture with epidural hematoma, contusion, and subdural hemorrhage along tentorium. There is depression of the right frontal bone (*arrowheads*) secondary to misapplication of forceps. The calvarium was fractured. Underlying the depressed fracture there is a biconvex, high signal intensity mass (*arrow*) representing an acute epidural hematoma. High density outlining the edges of the tentorium represents subdural hemorrhage.

spinal cord (Fig. 10) and brain stem are at particular risk in breech or face presentation.

### *Intrapartum H-I Injury*

Labor may commence at or before term for a normal fetus or one who has already sustained damage in utero. A number of catastrophes may accentuate previous problems or create new ones, including placental abruption, placenta previa, prolapse of the umbilical cord or other cord abnormalities, uterine tetany, or, rarely, accidents in the labor or delivery room such as administration of nitrous oxide instead of oxygen to the mother, or attempts to delay progress of a normal delivery by an inexperienced attendant. Tissue necrosis may be massive and lethal or more selective, damaging sensitive areas such as the hippocampus.

H-I lesions occurring during the intrapartum period tend to be ischemic rather than hemorrhagic in nature, although areas of necrosis may be transformed into hemorrhagic infarction when blood flow is reestablished.

Morphologic and radiographic features of these lesions are discussed in the following section.

## The Perinatal Period

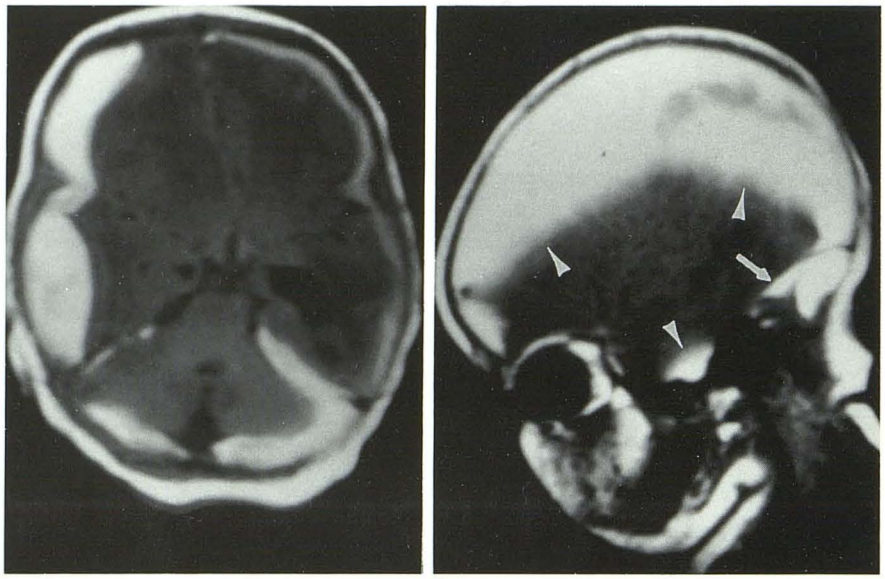
The newborn may enter the world before, at, or after the appointed time. Its nervous system may be normal or may already have been damaged in utero and/or intrapartum. The newborn faces the additional risk of damage during the perinatal period. Although humans are never immune from CNS injury, the possibility is especially great during the developmental period.

Radiographic assessment of the fetus before birth by use of ultrasound, or by CT, MR, or ultrasound study within the first day (Figs. 11 and 12) provides crucial documentation of the age and extent of the CNS abnormalities that the

Fig. 8. Birth trauma supra- and infratentorial subdural hamatomas.

*A*, Axial T1-weighted MR shows high signal intensity methemoglobin in the subdural space of the supra- and infratentorial brain. The subdural collection adjacent to the right frontal and temporal lobes is large, as is the collection adjacent to the left cerebellum.

*B*, Sagittal T1-weighted MR shows a large right subdural hematoma of high signal intensity blood (*arrowheads*). There is a posterior fossa subdural hematoma (*arrow*).



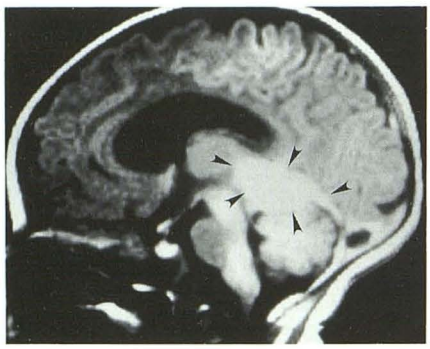



Fig. 9. Birth trauma; tentorial bleeding from dural venous sinuses fills the quadrigeminal plate cistern, compressing the cerebellum. Sagittal T1-weighted MR shows high signal intensity methemoglobin (*arrowheads*) outlining the quadrigeminal plate cistern and superior cerebellar cistern, compressing the anterior superior vermis and quadrigeminal plate. Bleeding arose from dural sinuses in the tentorium.

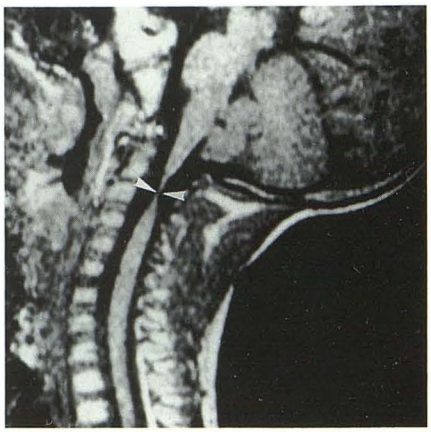


Fig. 10. Birth trauma; cervical cord stretch injury. Sagittal T1-weighted MR shows focal marked narrowing (*arrowheads*) of the upper cervical cord at the C2 level.

newborn sustained in utero or during delivery.

A small number of lesions are unique to the developing brain. These include the matrix zone hemorrhages, cysts of the matrix zone, cystic sclerosis, status marmoratus, brain stem injury selectively involving cranial nerve nuclei or neurons of the basis pontis (so-called "ponto-subicular necrosis"), and cerebellar hemorrhages. Necrosis of cerebral white matter, generally referred to as "periventricular leukomalacia," while most common in infants of low birth weight, also occurs in term neonates.

Although some lesions are more common among low birth weight infants in contrast to those born at term, essentially all the lesions arising during the perinatal period may affect infants of all body weights. Before commenting about the specific lesions, a brief discussion of the pathophysiology of H-I encephalopathy is in order.

### *Pathophysiology of H-I Encephalopathy in the Neonate*

Observations of the response of both humans and animals to asphyxia have established that asphyxic lesions are highly variable and dependent upon many factors. Detailed discussion of them is far beyond the scope of this paper, although a number of important points require comment. Whereas many of the specific variables can be isolated and studied in the laboratory, the problem is often so complex as to defy precise analysis in a specific situation.

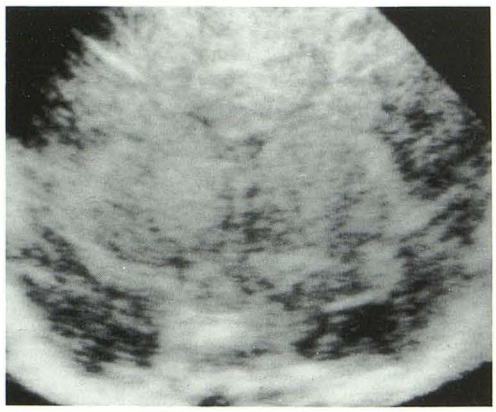


Fig. 11. Diffuse H-I insult. Coronal ultrasound examination shows diffuse increased echogenicity of the brain with compression of the ventricular system. (Courtesy of Dr Henrietta Rosenberg, The Children's Hospital of Philadelphia, PA.)

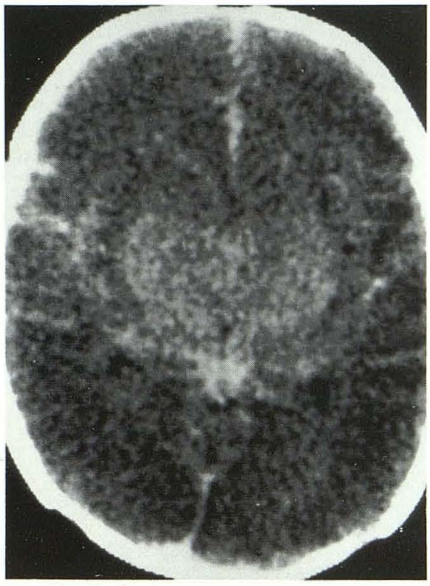


Fig. 12. Diffuse H-I injury in a 1-day-old infant. Axial noncontrast CT shows complete obliteration of ventricular, sulcal, and cisternal cerebrospinal fluid spaces, a loss of the gray/white differentiation between cortex and subjacent white matter, and preservation of the density in the central ganglionic structures.

There are five major areas of concern: cerebral blood flow, concentration of glucose in the blood, concentration of oxygen and carbon dioxide in the blood, selective vulnerability of various regions of the brain to injury, and the length and severity of insult.

1. In the normal mature individual, autoregulation maintains the cerebral blood flow (CBF) relatively constant over a wide range of variation of arterial blood pressure. Normal CBF is much lower in preterm than term newborns—20 mL/100g·min versus 50–60 mL/100g·min brain weight (24, 25). There is disagreement concerning the critical rate of CBF below which the infant is at risk to develop brain damage.

Abnormalities of CBF occur in a variety of circumstances. Prematurity is a major risk factor in distressed infants who cannot autoregulate efficiently (26). Hypoxia, hypoglycemia, and hypercarbia increase CBF, whereas CBF falls when $O_2$ concentration and blood glucose are elevated and when carbon dioxide is decreased (27, 28). Aside from these general biochemical changes that influence CBF, it has also been established that CBF normally varies in different regions of the brain. Flow is greater in the brain stem, lower in white matter, somewhat higher in cortex, and intermediate in the subcortical nuclei in both normal and hypoxic conditions (29, 30).

2. The precise relationships between glucose concentration and brain damage are complex and controversial. Normally the metabolic activity of oxygen and glucose tend to be parallel. However, lesions that occur secondary to inadequate supplies of one or the other are not necessarily similar (31). Moreover, there is no consensus on the levels of glucose below which the brain is at significant risk. Beyond that problem is a paradox that suggests that hyperglycemia may even enhance the damaging effects of H-I (32). Even here, however, the data are conflicting (33–35).

3. There is an absolute relationship between the need for an adequate supply of oxygen and maintenance of optimal brain function; without oxygen, the brain is damaged or dies. However, the precise biochemical and physical aspects of tissue oxygenation and factors involved in tissue damage and death are multifactorial. Because the fetus normally develops in a hypoxic environment, it can tolerate this state within narrow limits. However, at birth, it must make a rapid adjustment to extrauterine existence.

For a detailed discussion of the numerous factors involved, the reader is referred to the excellent work of Versmold and Linderkamp (36) and Versmold et al (37). A brief outline of the important issues will provide an indication of the physiologic complexities.

Utilization of oxygen requires transport to the tissues which is dependent upon several factors: 1) cardiovascular function; 2) cerebral microcirculation; 3) oxygen unloading capacity of the blood; and 4) tissue respiration (36). The oxygen unloading capacity is a function of hemoglobin concentration and oxygen affinity of the blood that, in turn, is dependent on five other variables: 1) type of hemoglobin (HbA, HbF); 2) concentra-

tion of 2-3 diphosphoglycerate; 3) pH; 4) $pCO_2$; and 5) base excess.

Consideration of physical principles governing blood flow are also important and are summarized by Poiseuille's law:

$$V = \frac{\Pi\ r^4}{8\ l}\ n$$

where V is the volume escaping per second, p the difference of pressure at the ends, r the radius, l the length of the tube, and n the coefficient of viscosity. If autoregulation is set aside for the moment, there are two variables of major importance in this context. First, a decrease in vessel radius increases its resistance to flow, so the small arterioles and capillaries of the infant brain offer considerable resistance. Second, resistance also increases with increases in viscosity, and viscosity is relatively high in the newborn because of the normally high hematocrit.

4. The concept of selective vulnerability has been utilized for many years to explain the pattern and distribution of CNS lesions in different disease states. Patterns of injury secondary to H-I in adults are relatively stereotyped, the earliest targets being the pyramidal neurons in $CA_1$ of the hippocampus, the neurons in layer 3 of the neocortex, and the Purkinje cells of the cerebellum. In the immature nervous system, however, only the neurons of $CA_1$ are especially vulnerable. The others are relatively resistant to injury because of their immaturity. In general, the tissues that are most susceptible to damage in the infant CNS are those CNS neurons that are mature, and the white matter. An exception to this are the brainstem neurons, which mature early in fetal life and are resistant to inadequate oxygen supply because of the increased CBF that occurs in this circumstance. However, if perfusion pressure falls significantly, these neurons are also subject to damage.

Vulnerability of the white matter to injury is partly a function of inadequacy of autoregulation and the fact that CBF, especially in the distressed infant, is pressure passive. According to Poiseuille's law, the volume of flow is inversely related to the length of the tube. The terminal branches of penetrating cortical vessels are not only end arteries, but they are also the furthest away from the source of power, which in humans is the heart. A drop in pressure compromises flow in those vessels perfusing the deep white matter before other regions are affected. In addition, the deep white matter is poorly vascularized, especially in infants of less than 34 weeks of gestation.

5. Finally, there remains the issue of the length and severity of the insult. A catastrophic interruption of well-oxygenated blood will naturally lead to irreversible tissue destruction. Situations that are less severe are not necessarily life-threatening, even if they produce permanent damage. These concepts are based upon the premise that body temperature and glucose remain in a normal range.

Experimental studies indicate that the upper limit of total ischemia that might allow complete neurologic recovery is between 10–16 minutes (38–41). However, repetitive shorter episodes of ischemia may produce significant neuronal damage (42). Postischemic disturbances leading to the "no-reflow" phenomenon often accentuate the damage and remain a serious problem (43–45).

### *The Lesions*

**Hemorrhages.** A major proportion of H-I damage in the infant brain is hemorrhagic rather than ischemic, especially in infants of low birth weight. Hemorrhages are most commonly located in the subarachnoid space, the matrix zone, and the subpial regions but occur in other parenchymal regions less frequently.

1. Subarachnoid hemorrhages—A small proportion of subarachnoid hemorrhages are typically found along the lateral aspect of one or both temporal lobes or along the posterior vertex and convexities of the cerebral hemispheres. These collections are more appropriately called subarachnoid hematomas when the volume of blood is large (Fig. 13). A small fraction are associated with venous thromboses but the etiology of the majority has been attributed to diverse factors.

Most commonly, the blood is located in the basal cisterns, having arrived there via the cerebrospinal fluid. In term infants, the blood typically originates within the lateral ventricles from rupture of choroid plexus vasculature. In low birth weight infants, especially those weighing 1500 g or less, the hemorrhage originates from ruptured vessels in the matrix zone. Rarely, the basal subarachnoid hemorrhage is the result of a coagulopathy, ruptured vascular malformation, or hemorrhage into a congenital tumor.

2. Matrix zone hemorrhages—Hemorrhage within the germinal matrix is the most common lesion in the brain of high-risk low birth weight infants. In fact, these lesions are unique to the

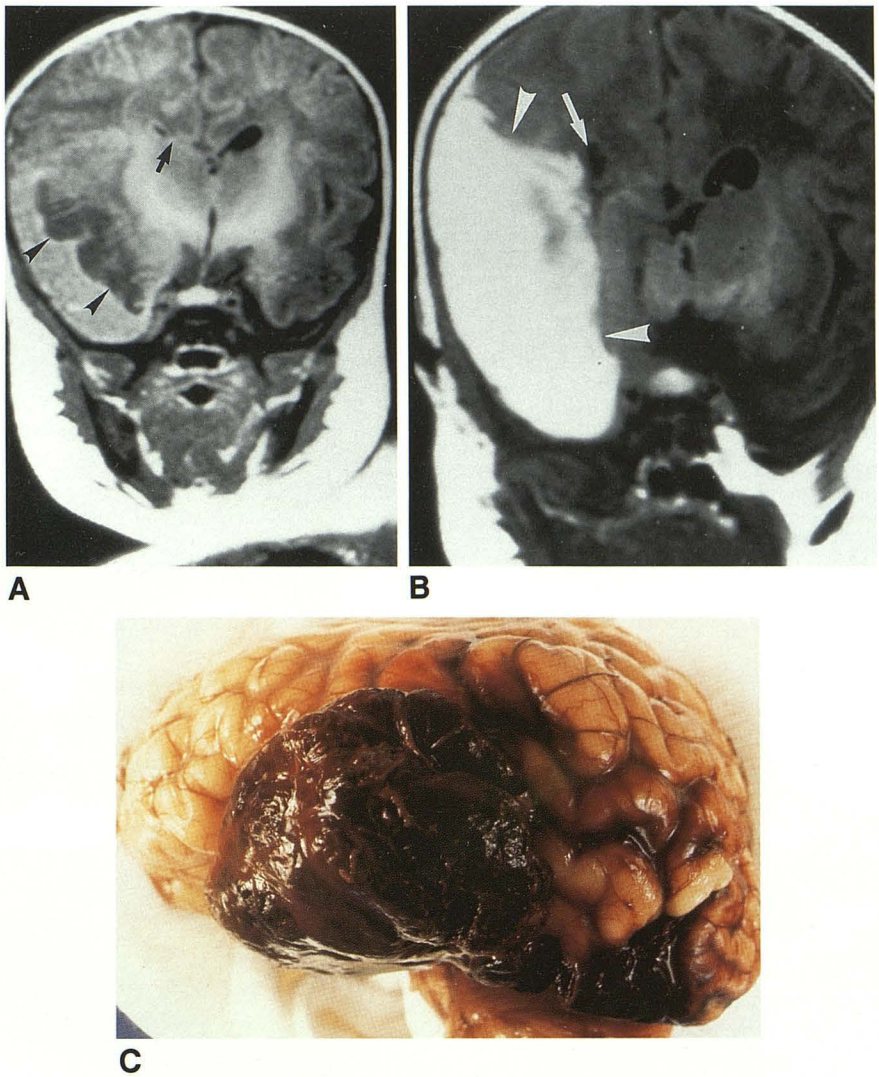



Fig. 13. Hemorrhagic cerebral venous infarct with extracerebral rupture of clot.

*A*, Coronal T1-weighted MR shows an extracerebral collection of blood, consistent with deoxyhemoglobin compressing inward the cerebral cortex (*arrowheads*). Note that the right lateral ventricle (*arrow*) is compressed, and there is subfalaceal displacement of the midline structures.

*B*, Coronal T1-weighted MR, 7 days later, 10 days after birth, shows high signal intensity methemoglobin (*arrowheads*) within both the cortex and the extracerebral space. The left lateral ventricle (*arrow*) is compressed.

*C*, Brain of a 3-day-old infant showing a large frontotemporal subarachnoid hematoma. Incarcerated veins contained thrombi.

immature brain. They occur rarely in utero (46, 47) and almost never beyond the first 28 days of life. Most frequently they arise within the first 3 days of extrauterine existence. These hemorrhages are of major clinical importance since all infants who sustain them do not die. Organization of the blood within the ventricles and subarachnoid space may lead to hydrocephalus. If the hemorrhage has dissected into the centrum ovale on one or both sides, permanent neurologic deficits remain.

A combination of developmental and anatomic factors coupled with pathophysiology of the low birth weight infant account for the frequent occurrence of the hemorrhages.

The telencephalic germinal zone is unique to the mammalian brain and consists of a second population of germinal cells that arise after mitotic activity in the embryonic ventricular zone has ceased between the 13–15th fetal week (47, 48). The deep cerebral venous system is located within this transient cell population that consists of neuronal precursors of thalamic nuclei and immature glia that will contribute to myelination (48). The majority of cells from this zone have almost all migrated by 40 weeks of gestation.

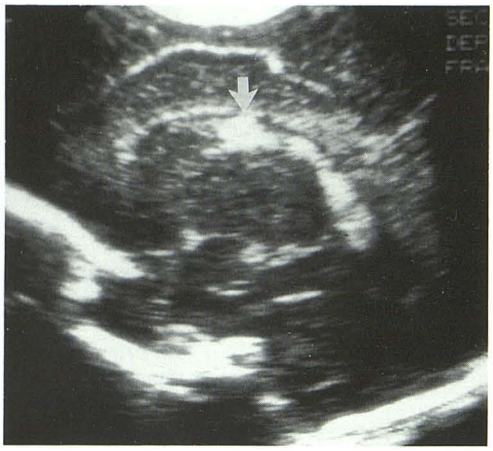


Fig. 14. Grade I germinal matrix hemorrhage. Sagittal ultrasound study shows hyperechoic hematoma (*arrow*) in the striothalamic sulcus. (Courtesy of Dr Henrietta Rosenberg, The Children's Hospital of Philadelphia, PA.)

This transient cell population does not have an accompanying stroma, and the walls of the veins within it are little more than a single layer of endothelial cells. Their proximity to the ventricular cavity, absence of the subependymal glial barrier, which develops closer to term, and the unusual configuration of the deep veins (49) all conspire to make this portion of the infant brain a *locus minoris resistentae.*

Superimposed upon these unique anatomical features are the pathophysiologic changes that plague the low birth weight infant and act in concert to produce the hemorrhages. These include disturbances in cardiorespiratory function such as apneic episodes, hypoxia, acidosis, bradycardia, instability of blood pressure, pneumothorax, and impaired autoregulation of CBF (25, 26, 49–52).

The preferred method of clinical diagnosis is by ultrasonography (Figs. 14–16), CT, or MR (Figs. 17 and 18).

Pathological correlates of these hemorrhages are pictured and described in Figures 14B, C, 15B and 16B.

3. Intraventricular hemorrhages—Blood from matrix zone hemorrhages often ruptures into the ventricular system, especially if the baby weighs less than 1500 g. Blood may also enter the ventricles secondarily from primary parenchymal hemorrhages in other sites or from other causes, eg, ruptured vascular malformations, coagulopathy, or, rarely, tumors. In most term infants, intraventricular hemorrhage results from ruptured choroid plexus blood vessels (Fig. 19). These infants usually have severe disturbance of cardi-

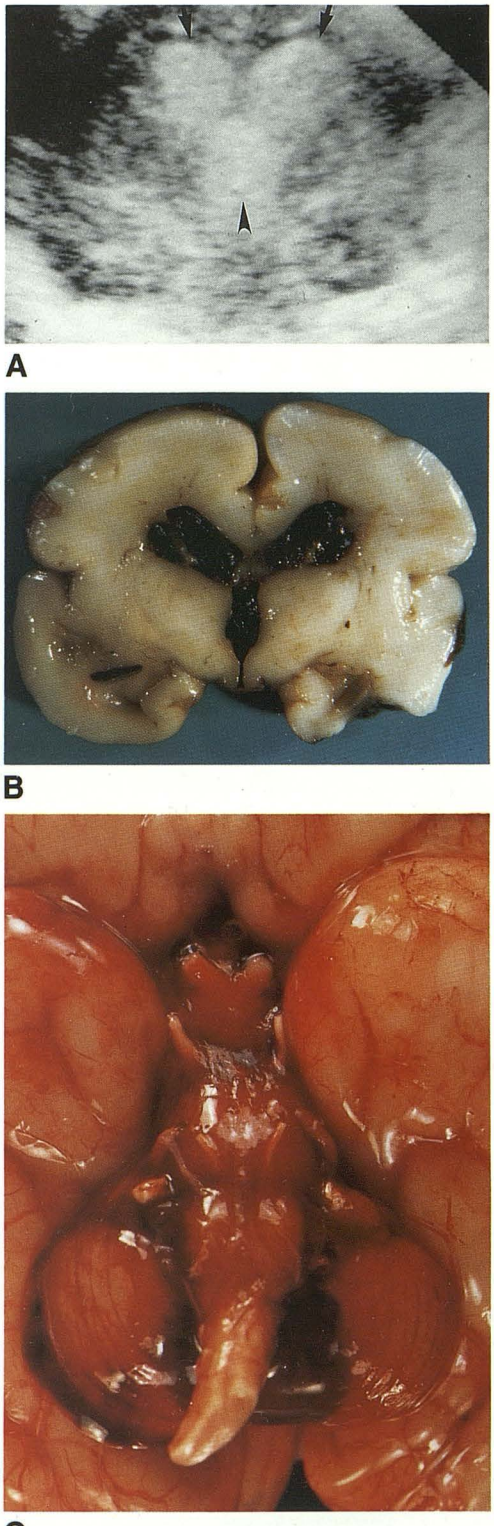


Fig. 15. Grade 3 intraventricular hemorrhage.

*A*, Coronal ultrasound examination shows hyperechoic clot filling both lateral ventricles (*arrows*) and the third ventricle (*arrowhead*). (Courtesy of Dr Henrietta Rosenberg, The Children's Hospital of Philadelphia. PA.)

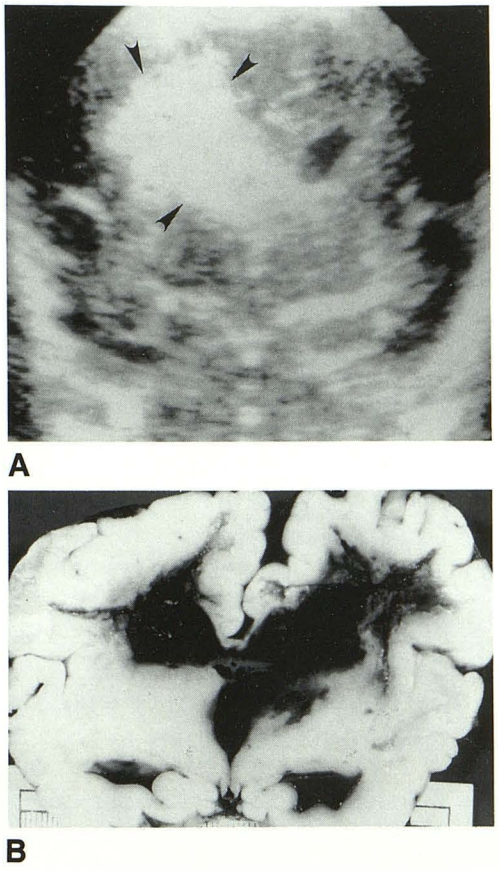


Fig. 16. Grade 4 germinal matrix hemorrhage.

*A*, Coronal ultrasound study shows a hyperechoic hematoma involving the lateral ventricle, extending into the white matter on the right (*arrowheads*). (Courtesy of Dr Henrietta Rosenberg, The Children's Hospital of Philadelphia, PA.)

*B*, Coronal section of brain from infant who sustained bilateral matrix zone hemorrhage that subsequently ruptured into the ventricles and dissected into the cerebral white matter, more extensively on one side than the other.

orespiratory function secondary to cardiac malformations, persistent fetal circulation, and diaphragmatic hernia.

4. Parenchymal hemorrhage—Small or microscopic parenchymal hemorrhages are common in the newborn brain, probably consequent to fragility of incompletely developed blood vessels. These are generally of no major clinical import. The larger bleeds are of diverse pathogenesis, including those already listed above, as well as trauma, sepsis, venous thrombosis, or other vascular disorders (53).

Hemorrhages are most common in the cerebrum but are also found in the cerebellum (Fig. 20), usually accompanied by overlying subarachnoid hemorrhage. They often arise in a subpial location. Although their pathogenesis has been disputed, particularly in the cerebellum, it is partly, at least, related to the presence of a rich fetal vasculature in the subarachnoid space and vulnerability to damage in H-I and its attendant acidosis (54).

**Cysts of the Ganglionic Eminence.** Subependymal uni- or multiloculated cysts are sometimes found in the matrix zone. A proportion of these represent the residue of organized hemorrhages, but the pathogenesis of the others remains conjectural (54).

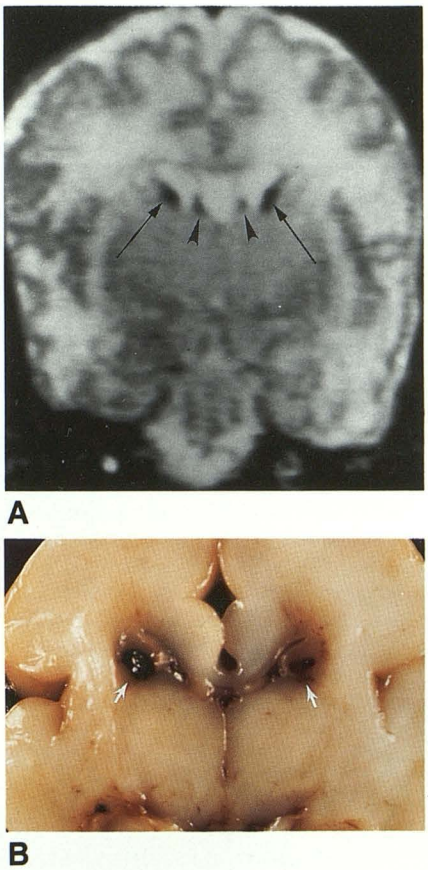


Fig. 17. Bilateral grade I germinal matrix hemorrhages.

*A*, Coronal T2-weighted MR shows hypointense hematomas (*arrows*) in the germinal matrix. Note medial extension (*arrowheads*) adjacent to the two leaves of the septum pellucidum, separated by a cavum septum pellucidum.

*B*, Coronal section of brain of 2-day-old, 1380-g infant with bilateral, localized matrix zone hemorrhages (grade 1). Note diffusely pale, swollen brain. (See also Figure 15B).

Fig. 15—*Continued.*

*B*, Brain of a 1380-g infant with bilateral matrix zone hemorrhages that have ruptured into the lateral and third ventricles (grade 3). Note the focal subependymal hemorrhage adjacent to the left inferior horn.

*C*, Basal view of brain from infant with subarachnoid hemorrhage resulting from intraventricular accumulation of blood as shown in *B*.

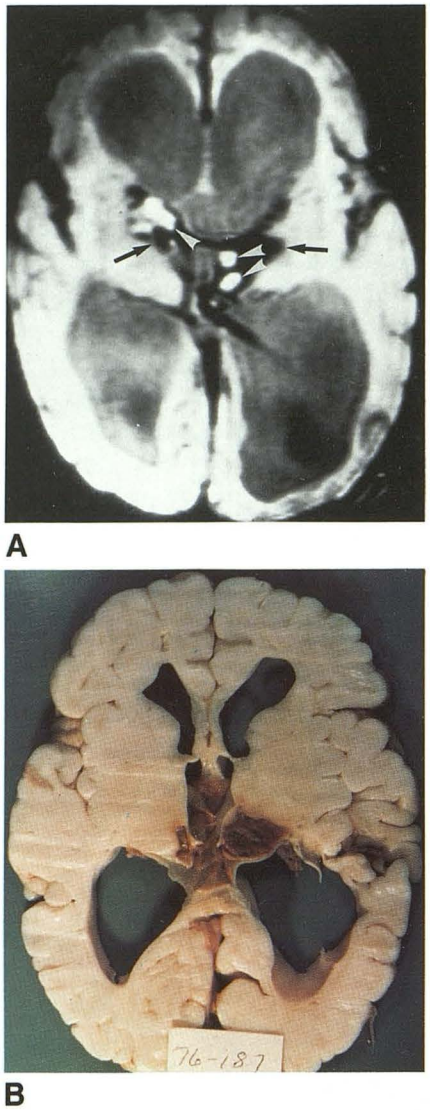



Fig. 18. Postbilateral germinal matrix hemorrhage with residual hemorrhage, hydrocephalus, and superficial siderosis.

*A*, Axial proton density MR shows hypointense hemosiderin (*arrows*) surrounding hyperintense pockets of methemoglobin within the germinal matrix. The lateral ventricles are enlarged, consistent with hydrocephalus. Subarachnoid space is darker along the pial margin because of deposition of hemosiderin.

*B*, Axial section of brain from prematurely born infant who survived for 4 months. Note the rust-colored, organized subependymal hemorrhages, larger on one side than the other, and ventricular dilatation.

**Infarctions.** The developing brain contains several types of parenchymal lesions that are unique and essentially never occur in older individuals. These include selective damage of thalamus and basal ganglia (so-called "status marmoratus"), white matter gliosis, and necrosis of basal pontine neurons. Although white matter necrosis, ie, periventricular leukomalacia is most common in neonates, elderly individuals, typically those with hypertension, may also sustain selective damage to white matter. However, the pathologic features of these lesions occurring at the two extremes of life are quite different, except for their similarity of location.

While there are obvious differences in distribution and histologic features in infants with H-I lesions in contrast to adults, many are similar to those occurring in the mature brain.

Several points of vascular anatomy and physiology require brief mention, the first of which deals with the phenomena commonly referred to as "border zone" and "terminal field of supply" lesions.

Vascular anatomy of the brain differs from that of other organs (except the heart) in that there are few effective anastomoses between the major cortical arteries and none at all between the deep branches of the cortical vessels and the terminal branches of the basal penetrating vessels serving the depths of the hemispheres.

The concepts of "border zone" and "terminal field of supply" are best regarded in combination. The border zones are those regions where the branches of each of the cortical arteries, ie, anterior, middle, and posterior cerebral vessels, terminate. In other words, the terminal field of supply is at the border zone. The most important border zones are in the parasagittal portion of the cerebral hemispheres between the anterior and middle cerebral arteries (Figs. 21 and 22), along the posterior convexity between the anterior, middle, and posterior cerebral arteries (Fig. 22),

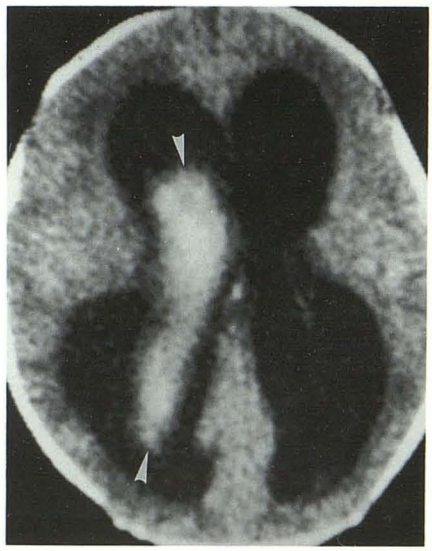
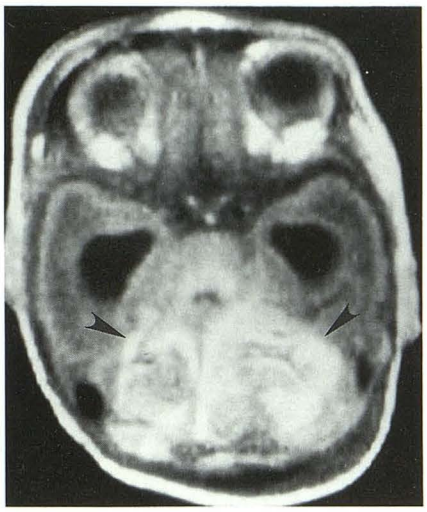
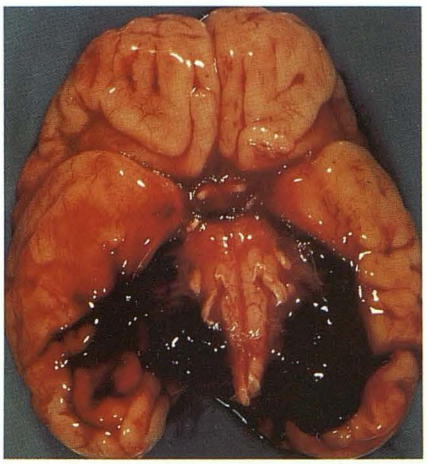


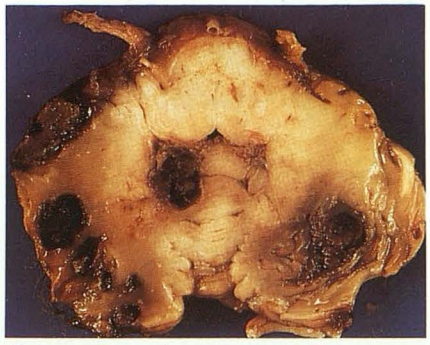
Fig. 19. Choroid plexus hemorrhage in full-term infant. Noncontrast axial CT shows a hyperdense bleed (*arrowheads*) in the right choroid plexus and bilateral hydrocephalus.



A



B



C

Fig. 20. Cerebellar hemorrhage.

*A*, Axial T1-weighted MR shows high signal intensity hemorrhage (*arrowheads*) involving both cerebellar hemispheres. There is compression of the fourth ventricle and dilatation of the temporal horns, consistent with hydrocephalus.

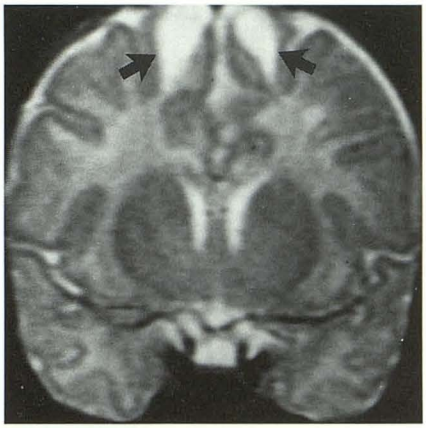
*B*, Basal view of brain from infant with massive hemorrhage filling the subarachnoid space and obscuring underlying cerebellum.

*C*, Transverse section of brain stem and cerebellum demonstrating bilateral intracerebellar hemorrhages.

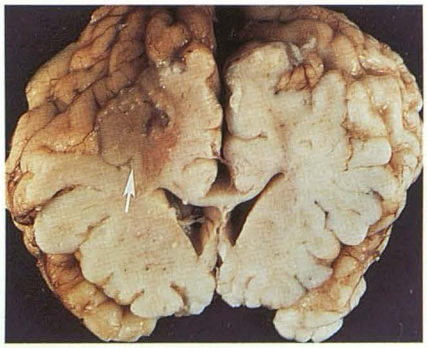
and the medial surface posteriorly between the anterior and posterior cerebral arteries. Border zones between the arterial distributions are also located on the ventral surface of the brain, but lesions here are relatively infrequent.

The deep cerebral border zone-terminal field of supply is located in the dorsal portions of thalamus-basal ganglia and periventricular white matter.

As already noted, the physical principles governing flow through the cerebral vasculature are summarized in Poiseuille's law. Flow is normally maintained by the intrinsic mechanism of autoregulation. Cerebral flow becomes pressure passive when autoregulation is lost (as in the distressed premature infant). If then only the physical factors determine flow, it is clear that tissues served by the most distal portions of the vascular system will be most subject to damage.



A

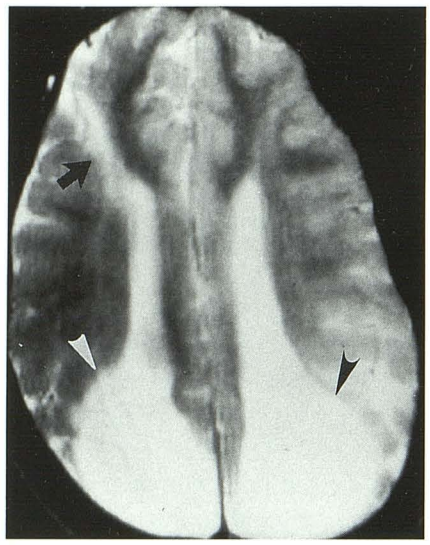


B

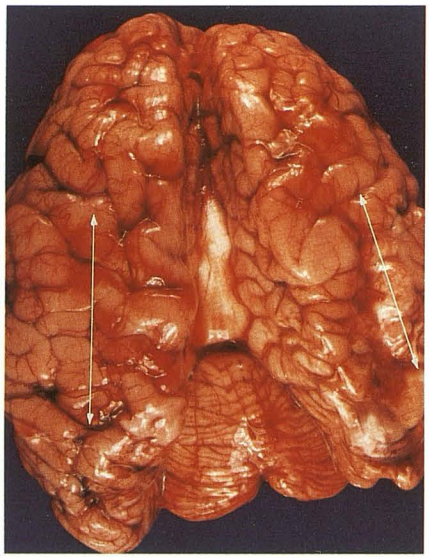
Fig. 21. Parasagittal water-shed infarcts.

*A*, Coronal T2-weighted MR shows bilateral parasagittal areas of high signal intensity infarction (*arrows*) in a watershed distribution.

*B*, Coronal section of 33-day-old infant with hypoplastic left heart syndrome displays bilateral chronic parasagittal watershed infarcts and superimposed recent infarction on the left side (*arrow*).



A



B

Fig. 22. Watershed infarcts.

*A*, Axial T2-weighted MR shows bilateral parieto-occipital watershed infarcts (*arrowheads*), and a right anterior watershed infarct (*arrow*). These infarcts are old.

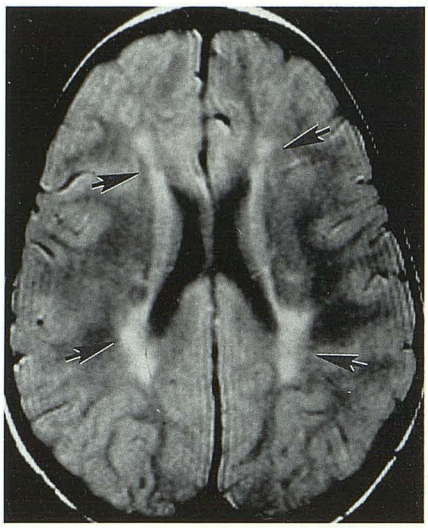
*B*, Dorsal view of the brain from a 6-month-old infant who sustained severe perinatal H-I showing bilateral areas of sclerosis in a parasagittal distribution.

In combination with these factors is the fact that the cortex has a much richer vascular supply than does the white matter. Hence it enjoys a protective advantage in some circumstances not shared by the white matter.

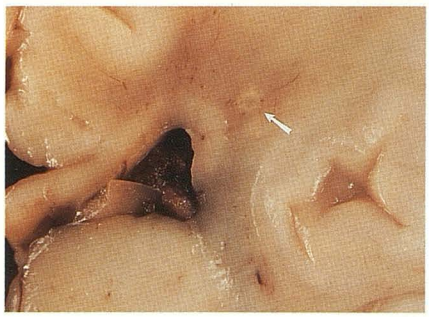
1. Lesions of white matter—White matter of the developing brain is especially vulnerable to injury. The range of lesions includes necrosis, gliosis and disturbances in myelination. The term most commonly used for these lesions is periventricular leukomalacia (55), even though it inaccurately covers the spectrum of lesions. Other terms include perinatal telencephalic leukoencephalopathy (56), subcortical leukomalacia (57), and simply gliosis. Detailed review of the lesions and terminology associated therewith may be found elsewhere (49, 58).

Salient features may be summarized as follows:

- White matter in any portion of the nervous system may be damaged but the white matter of the cerebrum is most commonly affected (Fig. 23);
- Whereas necrosis may be restricted to periventricular sites, it often extends into the centrum ovale and even into the subcortical white matter;
- Lesions may be ischemic or contain hemorrhage (Fig. 24), but thromboses within intrinsic vasculature are exceptional;



A



B

Fig. 23. Periventricular leukomalacia.

*A*, Axial proton density MR shows hyperintense periventricular leukomalacia (*arrows*) surrounding the lateral margins of the lateral ventricles.

*B*, Typical "white spot" (*arrow*) representing partially mineralized focal necrosis highlighted by surrounding dusky field.

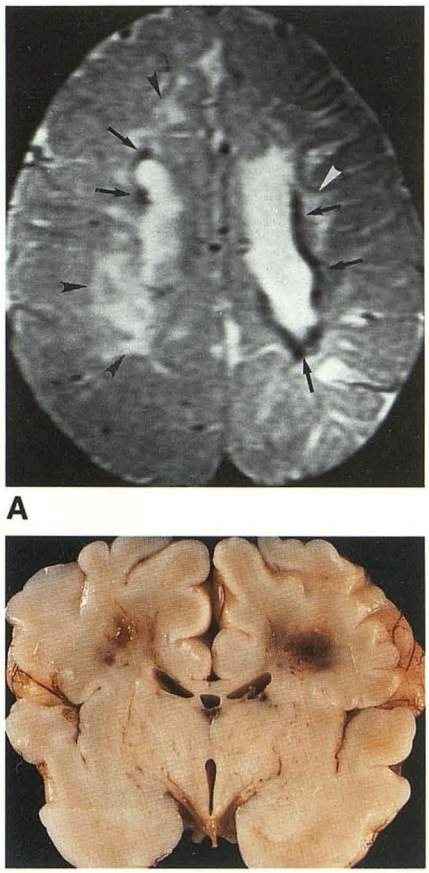


Fig. 24. Hemorrhagic periventricular leukomalacia.

*A*, Axial T2-weighted MR shows hypointense blood products (*arrows*) outlining the periventricular margin of the left and right lateral ventricles. Note the adjacent periventricular high signal intensity (*arrowheads*).

*B*, Coronal section of the brain of a low birth weight infant containing bilateral foci of periventricular necrosis with associated hemorrhage.

- Small foci of necrosis tend to calcify whereas larger areas of damage evolve into cysts (Fig. 25);
- White matter necrosis is not restricted to distressed low birth weight infants but occurs in term infants as well;
- The pathogenesis of these lesions has been disputed for years. The present consensus favors circulatory disturbances, but the role of infectious agents remains unsettled (59);
- Insults to developing white matter—short of frank necrosis—are recognized by astroglial proliferation and disturbances of myelination (Fig. 26). Pathogenesis of these may include H-I, but it is likely that other causes are operative in their genesis. For example, there is an established association between intrauterine rubella infection and retardation in myelination (59).

2. Lesions of gray matter—Gray matter in any or all portions of the CNS may suffer damage at any age if the circulatory insult is sufficiently severe. Several patterns of injury are characteristically found in the immature brain. Uncommonly, infants may show the lesions typically found in the mature nervous system, such as infarction in a vascular distribution or laminary necrosis.

Widespread necrosis in utero weeks before birth, generally produces microcephaly (Fig. 4). Restricted damage at any stage may not be visible by ultrasonography, CT, or MR scans, whereas acute global necrosis incompatible with life is

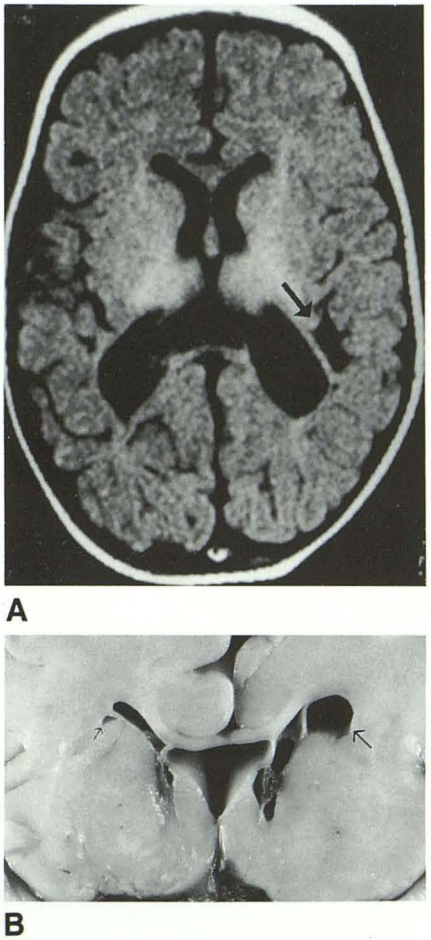


Fig. 25. Cystic periventricular leukomalacia.

*A*, Axial T1-weighted MR shows a decrease in the periventricular white matter in the periatrial region, enlargement of both lateral ventricles, and a hypointense area of cystic periventricular necrosis (*arrow*) on the left.

*B*, Coronal section of the brain of a 5-week-old infant showing sharply-demarcated periventricular cysts bilaterally (*arrows*), larger on the left than on the right side. Note the adhesions of the choroid plexus and ventricular wall.

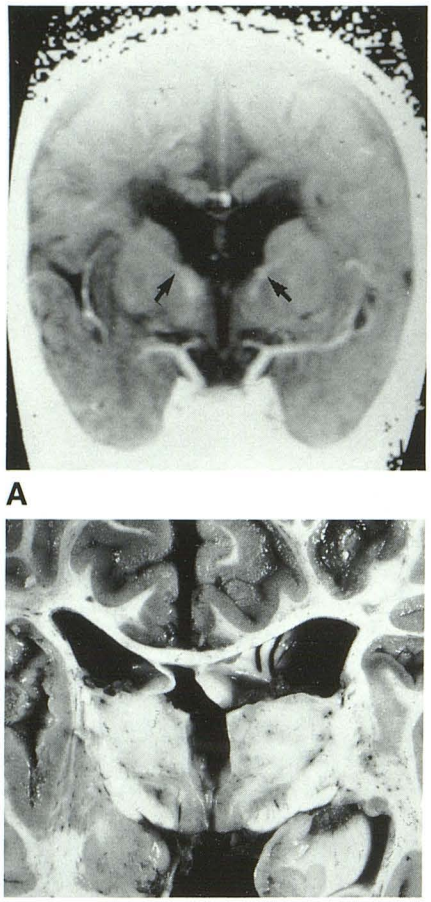


Fig. 26. White matter loss secondary to H-I injury in a premature infant.

*A*, One-year-old infant examined by short inversion recovery imaging. Note the absence of the expected high signal intensity white matter myelination throughout the brain, including the corpus callosum which appears markedly thin. High signal intensity myelination (*arrows*) is present in the internal capsules.

*B*, Coronal section of the brain of a 2-year-old infant who sustained severe perinatal H-I. There is striking reduction in the volume of the centrum ovale, a thin corpus callosum, and passive dilatation of the lateral ventricles.

easily diagnosed. A brain that has suffered an acute, general, nonlethal insult usually becomes edematous, which may mask more specific lesions that emerge after days or weeks.

Infarcted regions can usually be seen on imaging studies, and without difficulty at the postmortem table. The patterns of damage include:

(i) Global necrosis—Global necrosis, may cause obvious micrencephaly, replacement of brain tissue by multiple cysts with sclerosis of the intervening tissue (designated cystic sclerosis or "bubble-brain") (Figs. 27 and 28), or small size and sclerosis of the entire brain, as in twin-twin transfusion syndrome (Fig. 2). Indeed, one or more fetus in twin or multiple pregnancy is at increased risk for brain damage. Residue of selective damage may be cystic or sclerotic and may be in a vascular or laminary distribution. The chronic lesions in a vascular distribution are often large and cystic, producing porencephaly that may or may not communicate with a ventricle. Damage most commonly occurs in the cerebrum but brain stem and cerebellum may also be affected separately or as a component of a global insult. Cerebral lesions are common in infants whose treatment has included extracorporeal membrane oxygenation.

(ii) Border zone infarction—Infarction limited to border zone regions between arterial distributions of major vessels is not frequent in infants who come to necropsy, but is easily diagnosed when present (Figs. 21 and 22).

(iii) Hippocampal sclerosis—Damage to the subiculum and $CA_1$ of the hippocampal formation is a relatively common finding in infants who come to necropsy and is said to account for epilepsy in those who do not. Whereas pathogenesis is most likely related to selective vulnerability (54, 60), there has been a widespread belief that hippocampal sclerosis originates during the birth process from deformation of the skull, with resultant medial temporal herniation and local ischemia (61).

(iv) Basal ganglia and thalamus—Selective damage to these structures occurs in both the prematurely born and term infant, but destruction of these regions may also be seen in conjunction with lesions elsewhere (Fig. 29). Lesions probably result from a combination of diminished flow and selective neuronal vulnerability.

Occasionally, there is striking proliferation of small capillary-type vessels in the reparative phase that likely provides the morphologic basis for the finding of "the bright thalamus" observed on ultrasonography by Shen et al (62, 63). In the chronic phase the tissues are usually densely gliotic, or, less commonly, display abnormalities in the myelin pattern, the so-called "status marmoratus" (Fig. 30).

## Brain Stem

A variety of lesions may affect the brain stem selectively or in concert with damage at other CNS sites. Unless the destructive process involves the neuropil, the lesion is difficult to visualize by radiographic techniques. The relative rarity of brain stem lesions is most likely consequent to maintenance of high CBF to these regions in H-I

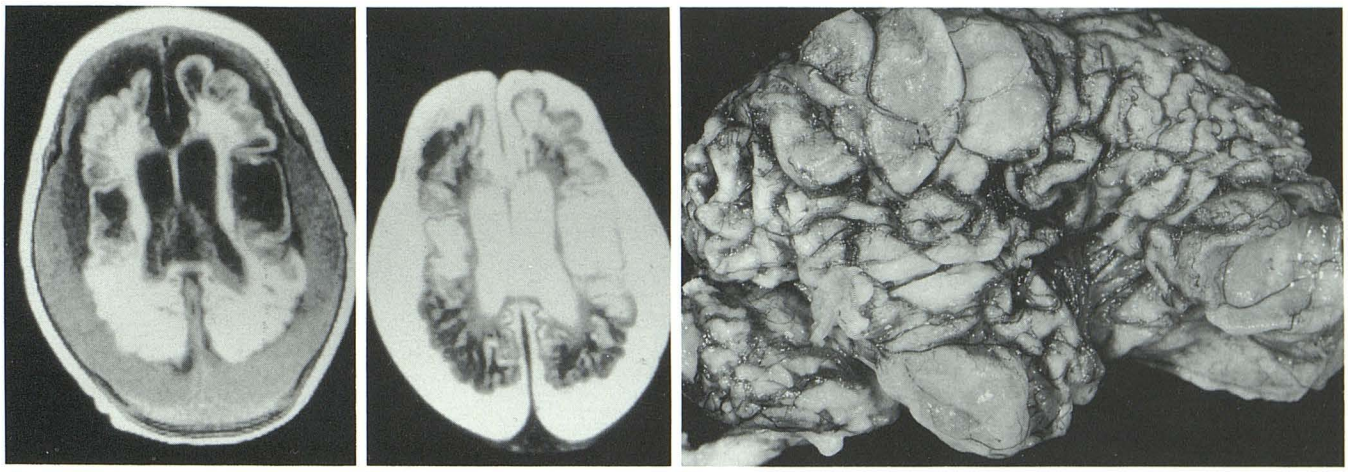



Fig. 27. Four-month-old infant, postplacenta previa with resultant H-I injury.

*A*, Axial T1-weighed MR shows marked decrease in the brain mass, with evidence of partially cystic cortical and subcortical encephalomalacia. The ventricles are dilated due to atrophy. Bilateral subdural collections surround the brain.

*B*, Axial T2-weighted MR shows diminished, damaged brain tissue with cystic encephalomalacia, surrounded by high signal intensity subdural collections.

*C*, Seven-month-old infant of drug-addicted mother who sustained severe intrapartum asphyxia secondary to cocaine-induced vaso-occlusion resulting in global brain necrosis. The brain is severely micrencephalic and manifests a combination of sclerosis and bubble-like cystic protrusions in lateral frontal, temporal, and parietal lobes.

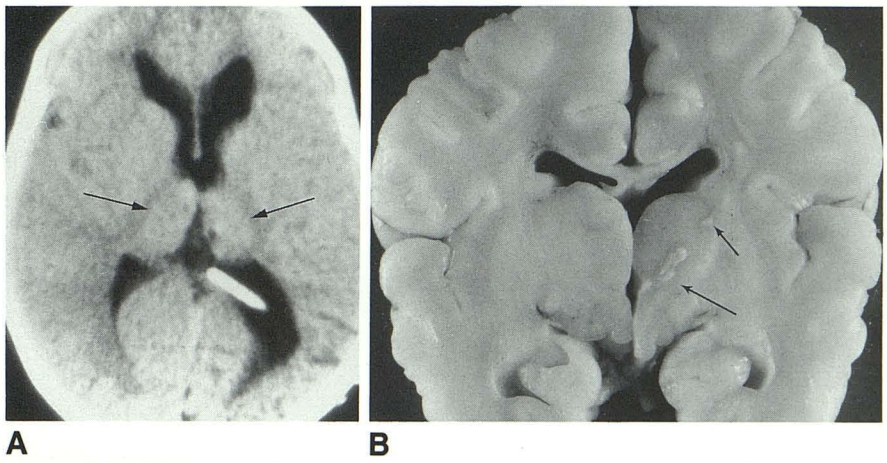



Fig. 28. Post H-I, multicystic encephalomalacia.

*A*, Axial T1-weighted MR shows hypointense, multicystic cortical and subcortical encephalomalacia. The frontal horns and lateral ventricles are somewhat dilated. There is a cavum septum pellucidum. The basal ganglia appear preserved.

*B*, Coronal section of the cerebrum and the upper brain stem of 4-month-old infant of a mother who sustained an abruptio placenta during use of "crack" (cocaine). The basic configuration of the brain is preserved but there has been multicystic replacement of most of the tissue.

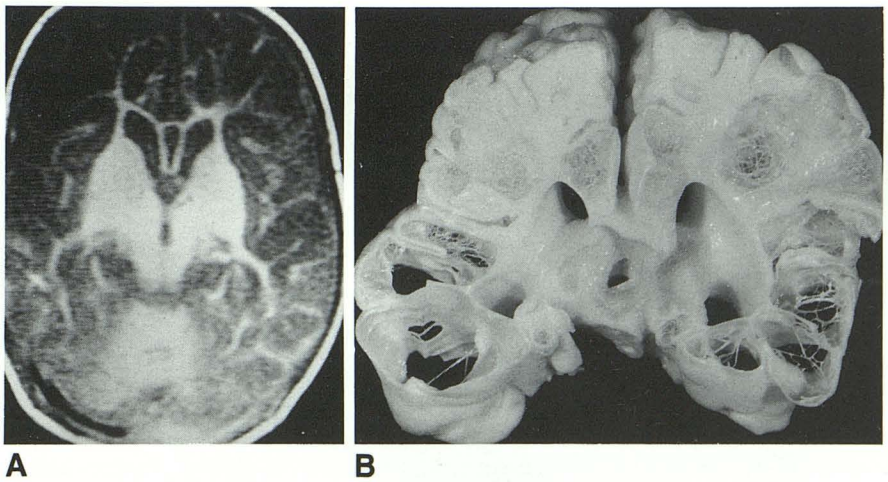



Fig. 29. H-I injury through the thalami.

*A*, Axial noncontrast CT shows slightly increased density within both thalami (*arrows*) due to calcification. A shunt is present in the atrium of the left lateral ventricle. Both frontal horns and the left atrium are dilated.

*B*, Coronal section of the brain of 2-month-old infant shows multifocal calcification of the thalamus, most obvious on the right side (*arrows*).

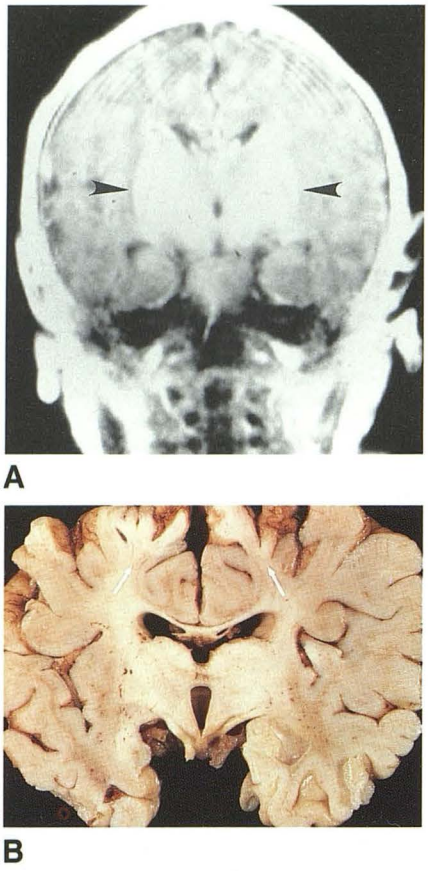


Fig. 30. Status marmoratus.

*A*, Coronal T1-weighted MR shows bilateral hyperintensity (*arrowheads*) involving the thalami and the basal ganglia in an infant in the first month of life. Postmortem examination confirmed the presence of status marmoratus.

*B*, Coronal section of the brain of a 5-month-old infant who sustained intrapartum hypoxia-ischemia secondary to prolapse of the umbilical cord. There is diffuse white transformation of the thalamic nuclei (which were dense on palpation), passive dilatation of the lateral and third ventricles, and severe sclerosis of frontal gyri in a parasagittal distribution (*arrows*).

states. A detailed discussion of brain stem lesions may be found elsewhere (54, 58). Pathogenesis is most likely multifactorial but circulatory factors and especially hypotension undoubtedly play a major role (Fig. 31). A small fraction of brain stem lesions results from damage to the vertebral arteries during difficult delivery (64–66).

## Cerebellum

Damage to the cerebellum is not common in H-I, even though Purkinje cells are among the most sensitive to hypoxemia. Nevertheless, lesions do occur and may exhibit one of the following patterns: 1) necrosis of selected regions or all grey matter; 2) borderzone infarction between major cerebellar arteries; 3) damage in the distribution of a single vessel; or 4) white matter necrosis or gliosis (54, 66). In the chronic stage the affected tissue is either sclerotic or cystic, as is also characteristic of such damage in other portions of the CNS.

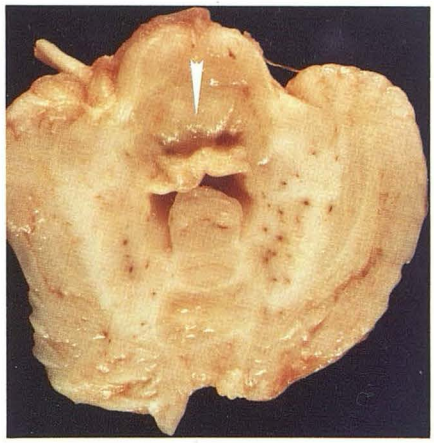


Fig. 31. Transverse section of the brain stem and cerebellum from a neonate who sustained a catastrophic episode of hypotension, following which he survived for about 24 hours. Note the necrosis of the tegmentum pontis characteristic of so-called "hypotensive brain stem necrosis" (*arrow*).

## Spinal Cord

H-I damage to this often forgotten portion of the CNS is rare (67, 68). Unless lesions are large they are difficult to visualize by ultrasonography or CT, although MR is a more sensitive detector of cord abnormalities. Post-traumatic damage of sufficient severity to produce clinical symptoms is more easily diagnosed by radiographic techniques (Fig. 10).

## Acknowledgments

The authors are indebted to Joanne Thomas and Valerie Tsafos, secretaries, and Joanne Taylor, photographer, for their expert assistance.

## References

1. Goodlin RC. Fetal distress. In: Iffy L, Kaminetzky HA, eds. *Principles and practice of obstetrics and perinatology*. Vol 2. New York: Wiley, 1981:825–931
2. Babcock DS, Bove KE, Han BK. Intracranial hemorrhage in premature infants: sonographic-pathologic correlation. *AJNR* 1982;3:309–317
3. Chow PP, Horgan JG, Taylor KJW. Neonatal periventricular leukomalacia: realtime sonographic diagnosis with CT correlation. *AJR* 1985;145:155–160
4. Grant EG, Kerner M, Schellinger D, et al. Evolution of porencephalic cysts from intraparenchymal hemorrhage in neonates: sonographic evidence. *AJNR* 1982;3:467–470

5. Rumack CM, McDonal MM, O'Meara OP, et al. CT detection and course of intracranial hemorrhage in premature infants. *AJR* 1978; 131:493–497
6. Ludwig B, Becker K, Rutter G, Bohl J, Brand M. Postmortem CT and autopsy in perinatal intracranial hemorrhage. *AJNR* 1983;4:27–36
7. Flodmark O, Becker LE, Harwood-Nash DC, Fitzhardinge PM, Fitz CR, Chuang SH. Correlation between computed tomography and autopsy in premature and full term neonate that have suffered perinatal asphyxia. *Radiology* 1980;137:93–103
8. Adsett DB, Fitz CR, Hill A. Hypoxic-ischemic cerebral injury in the term newborn: correlation of CT findings with neurological outcome. *Dev Med Child Neurol* 1985;27:155–160
9. Johnson MA, Pennock JM, Bydder GM, Dubowitz LMS, Thomas DJ, Young IR. Serial MR imaging in neonatal cerebral injury. *AJNR* 1987; 8:83–92
10. McArdle CB, Richardson CJ, Hayden CK, et al. Abnormalities of the neonatal brain: MR imaging. I. Intracranial hemorrhage. *Radiology* 1987;163:387–394
11. McArdle CB, Richardson CJ, Hayden CK, Nicholas DA, Amparo EG. Abnormalities of the neonatal brain: MR imaging. II. Hypoxic-ischemic brain injury. *Radiology* 1987;163:395–403
12. Baker LL, Stevenson DK, Enzmann DR. End-stage periventricular leukomalacia: MR evaluation. *Radiology* 1988;168:809–815
13. Wilson DA, Steiner RE. Periventricular leukomalacia: evaluation with MR imaging. *Radiology* 1986;160:507–511
14. Flodmark O, Roland EH, Hill A, Whitfield MR. Periventricular leukomalacia: radiologic diagnosis. *Radiology* 1987;162:119–124
15. Barkovich AJ, Truwit CL. Brain damage from perinatal asphyxia: correlation of MR findings with gestational age. *AJNR* 1990;11: 1087–1096
16. Walsh SZ, Meyer WW, Lind J. *The human fetal and neonatal circulation.* Springfield, IL: Thomas, 1974:65
17. Jäykka S. The problem of dormant fetal organs: the kidneys, lungs and gut. *Biol Neonate* 1990;57:261–278
18. Larroche JCL, Droullé P, Delezoide AL, Narcy F, Nessman C. Brain damage in monozygous twins. *Biol Neonate* 1990;57:261–278
19. Cocker J, George SW, Yates PO. Perinatal occlusion of middle cerebral artery. *Dev Med Child Neurol* 1965;7:235–243
20. Clark RM, Linell EA. Case report: prenatal occlusion of the internal carotid artery. *J Neurol Neurosurg Psychiatry* 1954;17:295–297
21. Gross RE. Arterial embolism and thrombosis in infancy. *Am J Dis Child* 1945;70:61–73
22. Gunn TR, Mok PM, Becroft DM. Subdural hemorrhage in utero. *Pediatrics* 1985;76:605–609
23. Stafford PA, Biddinger PW, Zumwalt RE. Lethal intrauterine fetal trauma. *Am J Obstet Gynecol* 1988;159:485–489
24. Greisen G. Cerebral blood flow in preterm infants during the first week of life. *Acta Paediatr Scand* 1986;75:43–51
25. Low HC, Lassen NA, Friis-Hansen B. Impaired autoregulation of cerebral blood flow in the distressed newborn. *J Pediatr* 1979;94: 118–121
26. Low HC. The "lost autoregulation hypothesis" and brain lesions in the newborn: an update. *Brain Dev* 1988;10:143–146
27. Tweed WA. Cerebral blood flow regulation and fetal hypoxia. In: Plum F, Pulsinelli W, eds. *Cerebrovascular diseases.* New York: Raven, 1985:143–148
28. Pryds O, Greisen G, Friis-Hansen B. Compensatory increase of CBF in preterm infants during hypogylcemia. *Acta Paediatr Scand* 1988; 77:632–637
29. Cavazutti M, Duffy TE. Regulation of local cerebral blood flow in normal and hypoxic neuwborn dogs. *Ann Neurol* 1982;11:247–257
30. Volpe JJ, Herscovitch P, Perlman JM, Kreusser KL, Raichle ME. Parasagittal impairment of cerebral blood flow in the asphyxiated term infant. In: Plum F, Pulsinelli W, eds. *Cerebrovascular diseases.* New York: Raven, 1985:123–132
31. Auer RN. Hypoglycemic brain damage: an experimental neuropathologic study in the rat. Doctoral thesis, University of Lund, Lund, Sweden, 1985
32. Myers RE. Anoxic brain pathology and blood glucose. *Neurology* 1976;26:345
33. deCourten-Myers G, Myers RE, Schoolfield L. Hyperglycemia enlarges infant size in cerebrovascular occlusion in cats. *Stroke* 1988;19: 623–630
34. Voorhies JM, Lipper G, Lue BCP, Vannucci RC, Auld PAM. Occlusive vascular disease in asphyxiated newborn infants. *J Pediatr* 1984; 105:92–96
35. Rosenberg AA, Murdaugh E. The effect of blood glucose concentration on postasphyxia cerebral hemodynamics in newborn lambs. *Pediatr Res* 1990;27:454–459
36. Versmold HT, Linderkamp O. Oxygen transport to tissues in RDS. In: Raivio KO, Hallman N, Kowalakinen K, Valimaki I, eds. *Respiratory distress syndrome.* London: Academic Press 1984:187–199
37. Versmold HT, Lister G, Dallman PR, Rudolph AM. Limits of $O_2$ delivery during propanolol-induced reduction of cardiac output in lambs after birth. *Pediatr Res* 1980;14:176
38. Miller JR, Myers RE. Neuropathology of systemic circulatory arrest in adult monkeys. *Neurology* 1972;22:888–904
39. Vaagenes PR, Cantadore P, Safar P, et al. Amelioration of brain damage by lidoflazine after prolonged ventricular fibrillation cardiac arrest in dogs. *Crit Care Med* 1984;12:846–855
40. Gisvold SE, Safar P, Rao G, Moossy J, Bron K, Alexander H. Prolonged immobilization and controlled ventilation do not improve outcome after global brain ischemia in monkeys. *Crit Care Med* 1984; 12:171–179
41. Kirino T. Delayed neuronal death in the gerbil hippicampus following ischemia. *Brain Res* 1982;239:57–69
42. Kato H, Kogure K. Neuronal damage following non-lethal but repeated cerebral ischaemia in the gerbil. *Acta Neuropathol* 1990;79:494–500
43. Hirsch H, Euler KH, Schneider M. Ueber die Erholung und Wiederbelehung des Gehirns nach Ischaemie bei Normothermie. Pflügers Arch 1957;265:281–313
44. White BC, Wiegenstein JG, Winegar CD. Brain ischemic anoxia. *JAMA* 1984;251:1586–1590
45. Hossmann KA. Post-ischemic resuscitation of the brain: selective vulnerability vs global resistance. *Prog Brain Res* 1985;63:3–17
46. Jackson JC, Blumhagen JD. Congenital hydrocephalus due to prenatal intracranial hemorrhage. *Pediatrics* 1983;72:344–346
47. Darrow VC, Alvord EC, Jr, Mack LA, Hodsin WA. Histologic evolution of the reaction to hemorrhage in the premature human infant's brain. *Am J Pathol* 1988;130:44–58
48. Rakic P. Embryonic development of the pulvinar-LP complex in man. In: Cooper IS, Ricklin M, Rakic P, eds. *The pulvinar-/LP complex.* Springfield, IL: Thomas, 1974:3–35
49. Larroche JCL. Perinatal brain damage. In: Adams JH, Corsellis JAN, Duchen LW, eds. *Greenfield's neuropathology.* 4th ed. London: Arnold, 1984:451–489
50. Strauss A, Kitz D, Modanlow HD, Freeman RK. Perinatal events and intraventricular/subependymal hemorrhage in the very low birth weight infant. Am J Obstet Gynecol 1985;151:1022–1027
51. Low JA, Galbraith RS, Sauerbrei EE, et al. Maternal, fetal and newborn complications associated with newborn intracranial hemorrhage. *Am J Obstet Gynecol* 1986;154:345–351
52. Beverley DW, Chance GW, Coates CF. Intraventricular hemorrhage: timing of occurrence and relationship to perinatal events. *Br J Obstet Gynaecol* 1984;91:1007–1013
53. Alonso A, Taboada D, Alvarez JA, Vida-Sampedro J, Vieito X. Spontaneous hematomas caused by microangiomatosis of the basal ganglia. *Child's Brain* 1984;11:202–211
54. Rorke LB. *Pathology of perinatal brain injury.* New York: Raven, 1982

55. Banker BQ, Larroche JCL. Periventricuklar leukomalacia of infancy: a form of neonatal anoxic encephalopathy. *Arch Neuronl* 1962;7: 386–410
56. Gilles FH, Murphy SF. Perinatal telencephalic leucoencephalopathy. *J Neurol Neurosurg Psychiatry* 1969;32:404–413
57. Takashima S, Armstrong D, Becker L. Subcortical leukomalacia: relationship to development of the cerebral sulcus and its vascular supply. *Arch Neurol* 1978;35:470–472
58. Rorke LB. Perinatal brain damage. In: Adams JH, Duchen LW, eds. *Greenfield's neuropathology*. 5th ed. London: Arnold, 1992
59. Gilles FH. Perinatal neuropathology. In: Davis RL, Robertson DM. *Textbook of neuropathology*. Baltimore: Williams & Wilkins, 1985: 243–283
60. Corsellis JAN, Meldrum BS. Epilepsy. In: Blackwood W, Corsellis JAN, eds. *Greenfield's neuropathology*. 3rd ed. London: Arnold 1976; 771–795
61. Earle KM, Baldwin M, Penfield W. Incisional sclerosis and temporal lobe seizures produced by hippocampal herniation at birth. *Arch Neurol Psychiatry* 1953;69:27–42
62. Shewman DA, Fine M, Masdeu JC, Palacios E. Postischemic hypervascularity of infancy: a stage in the evolution of ischemic brain damage with characteristic CT scan. *Ann Neurol* 1981;9:358–365
63. Shen EY, Huang CC, Chyou SC, Hung HY, Hsu CH, Huang FY. Sonographic finding of the bright thalamus. *Arch Dis Child* 1986;61: 1096–1099
64. Yates PO. Birth trauma to the vertebral arteries. *Arch Dis Child* 1959; 34:436–441
65. Adams JH, Cameron HM. Obstetrical paralysis due to ischaemia of the spinal cord. *Arch Dis Child* 1965;40:93–96
66. Friede RL. *Developmental neuropathology*. 2nd ed. Berlin: Springer-Verlag, 1989
67. Sladky JT, Rorke LB. Perinatal hypoxic/ischemic spinal cord injury. *Paediatr Pathol* 1986;6:87–101
68. Clancy RR, Sladky JT, Rorke LB. Hypoxic-ischemic spinal cord injury following perinatal asphyxia. *Ann Neurol* 1989;25:185–189