The age of viability has continually been challenged in neonatal medicine over the past 20 years, and as a consequence, greater numbers of extremely premature infants survive at 23 to 26 weeks' gestation. An increasing number of centers are actively resuscitating the very youngest fetuses who were not resuscitated just 5 years ago.

The survival rate is surprisingly high in infants with birth weight greater than 500 grams due to advances in neonatal cardiorespiratory intensive care, including better alternative modes of ventilation, routine surfactant use, referral of mothers for advanced obstetric monitoring, and antenatal steroid administration. Unfortunately, neurologic problems in the preterm population have not necessarily decreased with mortality. Extremely premature newborns are vulnerable to the hazards of extrauterine life, with fragile cerebral vasculature and ongoing neurogenesis and synaptogenesis. They are susceptible to even mild hypoxic-ischemic events, and yet the infants are frequently tough and tenacious with life.

To help us improve neurologic morbidity in these infants, clinical practice is building upon excellent research focused on premature brain injury. We are learning more and more about antenatal and postnatal antecedents of premature brain lesions and the mechanisms and mediators of disease. Sophisticated imaging technologies permit the detection of more diffuse white matter pathology, which was previously only suspected, and these lesions are being correlated with outcomes. Noninvasive bedside techniques are being applied to preterm infants and allow timely identification of central nervous system injury and recovery. Neonatal neurointensive care is on the horizon.

Survival and Neurologic Outcome in Preterm Infants

From 1981 to 2002, the percentage of preterm births in the United States has increased 28% (from 9.4 to 12.0%), and the percentage of very low birth weight births (< 1,500 g) increased 21% (from 1.15 to 1.4% of all live births). Hoekstra reports that the survival for the extremely preterm infants from 23 to 26 weeks' gestation has increased steadily from 53% in 1986 to 89% in 2000 in their tertiary-care center. For 23 weeks' gestation premature infants alone, survival rate from 1986 to 2000 increased from 40 to 66%. Follow-up data for the 23 to 26 weeks' gestation cohorts born in 1990 indicate that 62% were free from handicap at 4 years of age and were performing at grade level for all but one subject at 8 years of age. Only 17% and 20%, respectively, were mild or moderately or severely handicapped at the 4- and 8-year assessments.

In spite of these encouraging statistics, practitioners consistently underestimate survival rates and neurologic outcomes. When pediatricians and obstetricians were asked to state expected survival rates and handicap-free rates for the youngest gestational age premature infants, those who were characterized as the most optimistic about survival were actually closer to the true survival rate than those who were more neutral or pessimistic. Many practitioners directly responsible for delivering and resuscitating infants are not aware of the increasing survival rate.

As this knowledge is disseminated into communities, more infants at the youngest gestational ages will be given a chance. Although expectations for morbidity and good
quality of life influence resuscitation decisions, except for a few extreme clinical situations, we cannot adequately predict in the delivery room which infants will have the worst outcomes. As a result, we fully expect that the incidence of premature births and resuscitation of extremely premature infants will increase. Neurologic manifestations of premature birth will continue to be important well into the future.

Lesions of Premature Brain Injury

Neurologic lesions of the preterm brain comprise primarily intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and posthemorrhagic hydrocephalus (PHH). A nonprogressive form of ventriculomegaly, under low pressure, may also be detected late in the hospital course or as an outpatient, representing volume loss from atrophy of gray and white matter. Newer imaging technologies are also allowing detection of noncystic white matter injury (WMI), cerebellar hemorrhage, and lenticulostrate vasculopathy, lesions whose prognostic significance is still being determined.

Intraventricular Hemorrhage

The vast majority of IVHs occur in premature infants less than 32 weeks’ gestation and within the first 3 days of life. Surveillance for hemorrhage is performed by bedside head ultrasound examination performed on days of life 1 to 3 if the baby has physiologic instability or coagulopathy, or more routinely on day of life 7, when greater than 95% of all bleeds will be detected.

A modification of Papile’s standardized classification system is universally used to grade IVH. IVH grades I, II, and III occur in the fragile capillary-venules of the germinal matrix, damaging this vascular-rich area, which serves as a nursery for precursors to oligodendroglial cells and astrocytes. Grades I–III IVH are largely precipitated by volume expansion, hypotension and cardiovascular instability, or infection.

A grade IV IVH is thought to evolve from a preceding germinal matrix hemorrhage. A more localized IVH induces ischemia and edema, occluding terminal veins coursing through the germinal matrix of the lateral ventricle. The obstruction results in impairevous drainage from the cortex through medullary veins, and a venous hemorrhagic infarction into the lateral ventricles and parenchyma results.

These grade IV IVH are historically quite extensive, leaving a large deposit of hemoglobin and iron in the midst of an ischemia-reperfusion event in white matter and possibly gray matter. Premature infants’ glutathione and other antioxidant systems are overwhelmed, as iron is a ready electron transfer agent. Iron and oxygen free radicals can cause fatty acid peroxidation in lipid membranes, threatening cellular integrity and propagating the already widespread injury.

Neurologic Outcome after Intraventricular Hemorrhage

The uniform classification of IVH allows collection of good data across many centers on incidence and outcome. Vermont Oxford network is one such system, with data from national and international neonatal intensive care units. Their reported incidence of different grades of IVH for 2002 are reported in Table 82-1.

Severity of outcome increases with severity of hemorrhage. Grade II hemorrhages can result in major neurologic deficits in 15% of infants, while grade III hemorrhages have a 35% incidence of neurologic sequelae. All grades of IVH have a worse prognosis for neurologic outcome if parenchymal echodensities are present on a head sonogram.

Grade IV IVH with large intraparenchymal echodensities historically have resulted in a 90% chance of major motor deficits and more than 50% incidence of cognitive impairment. Extensive white matter involvement and subsequent connectivity derangements in gray matter account for much of the increased morbidity of grade IV hemorrhages. Connectivity is lost with necrosis or apoptosis of subplate neurons, which lie just above the white matter and guide ascending axons from thalamic or other cortical sites to their cortical targets.

Previously, the ability to detect grade IV IVH was limited by ultrasound transducers of lower Hertz, which are much less sensitive than those in use today. Currently, we are detecting smaller parenchymal hemorrhages by ultrasound that are technically grade IV IVH, but may not have the same extensive white and gray matter injury associated with previous outcome studies of grade IV IVH. Future studies will help determine whether the expected outcomes of parenchymal bleeds will change on the basis of increased ability to detect smaller lesions.

Prevention of IVH

Several large studies have shown that antenatal glucocorticoid treatment lowers the incidence of IVH. A complete

| TABLE 82-1. Percentage Incidence of Ultrasound-Detected Intraventricular Hemorrhage by Gestational Age in 2002: Data from the Vermont Oxford Network (58 Centers Reporting) |
|---------------------------------|---------|---------|---------|---------|
| Intraventricular Hemorrhage     | Gestational Age (completed weeks) |
|                                 | < 27   | 27–29  | 30–32  | 33–36  |
| No IVH                          | 52%    | 73%    | 86%    | 90%    |
| IVH grade I                     | 13%    | 12%    | 11%    | 7%     |
| IVH grade II                    | 12%    | 7%     | 2%     | 1%     |
| IVH grade III                   | 11%    | 5%     | 1%     | 1%     |
| IVH grade IV                    | 12%    | 3%     | 0%     | 1%     |
| Cystic PVL                      | 7%     | 3%     | 2%     | 1%     |

All data are used with permission of the Vermont Oxford Neonatal Network. IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia.
steroid course comprises 24 hours of betamethasone (or dexamethasone) administered to the mother, with delivery at least 24 hours after the first dose. A complete steroid course results in 40% reduction in severe IVH in infants < 1,500 grams birth weight, while an incomplete course is partially protective. Although one 24-hour course of antenatal steroids has no known long-term effect on brain development, repeated courses of antenatal steroids result in decreased total brain volume and surface area with a lower convolution index.

Postnatal indomethacin has also been shown to decrease the incidence of severe IVH (grades III and IV), particularly in centers with a high incidence of severe IVH (> 10%) and in infants >1,000 grams birth weight. Per Ment's protocol, three doses of prophylactic indomethacin treatment may be given over 30 minutes, starting at 6 hours after birth, in clinically stable babies < 1,250 grams. Indomethacin inhibits prostaglandin synthesis via the cyclooxygenase pathway and enhances microvascular integrity and maturation. Important side effects of indomethacin infusions are decreased cerebral and renal blood flow, possibly resulting in ischemic injury. Renal complications of indomethacin infusions are frequent and clinically evident with rising serum creatinine levels. Although grades III and IV IVH are less frequent with this regimen, and would be expected to lead to improved outcomes, incidence of cerebral palsy was not significantly different between groups at 4.5 and 8 years of age (9.7% in the indomethacin group, 7.6% in control subjects). Failure to demonstrate long-term neurologic improvement may have many etiologies. However, concerns persist over possible ischemia increasing injury in those infants who have any IVH, and we now know that diffuse cerebral ischemic lesions are rarely demonstrated by ultrasonography. This has led to some reservations about using indomethacin in all premature infants and limited its worldwide acceptance.

Posthemorrhagic Hydrocephalus

Identification of IVH on screening ultrasound requires weekly follow-up to evaluate ventricular size and to detect possible PHH. PHH results from obliterator arachnoiditis (communicating) or obstruction of foramina or the aqueduct (noncommunicating). Progressive ventricular dilatation may be rapid and require cerebrospinal fluid drainage by shunt, either ventriculogaleal or ventriculoperitoneal, to avoid adverse consequences of increased pressure on cerebral blood flow and cortical development. Ventricular dilation that progresses somewhat slower may still be under increased pressure, but may be managed with serial lumbar punctures, and dilation may ultimately arrest. Diuretic and acetazolamide therapy is ineffective in decreasing the rate of shunt placement and may actually worsen outcome at 1 year. Of the patients in whom ventricular dilation arrests, approximately 5% will have late PHH, with rapid head circumference increases around 3 to 6 months of age, and will require shunting. Current recommendations are that all patients with PHH be followed carefully for at least the first year for signs of increased intracranial pressure. Outcome data indicate behavioral and cognitive deficits in addition to 60% incidence of motor disability with ventricular width greater than 4 mm, and an early deterioration in memory function in adults after arrested hydrocephalus.

Cerebellar Hemorrhage

In the extremely preterm infant, cerebellar hemispheres are newly recognized sites of hemorrhage using posterior fossa transcranial ultrasonography. This area has not previously been evaluated by conventional ultrasonography and requires scanning from the posterior lateral fontanel. The so-called “mastoid” view allows excellent visualization of the posterior fossa and permits evaluation of the cerebellum that is difficult from the anterior fontanel approach. This view is now standard at many institutions, and its use has resulted in a new appreciation of the vulnerability of the cerebellum to injury.

Hemorrhage occurs in the lateral regions of the cerebellar hemispheres in preterm infants less than 28 weeks’ gestational age and may be unilateral or bilateral. Cerebellar hemorrhage may be associated with IVH, but an increasing number are being described as isolated bleeds. Although the full ramifications of such hemorrhages are currently unknown, new information indicates a role of the cerebellum in learning new information as well as coordination of motor activity.

Lenticulostriate Vasculopathy

Echogenic vasculature has been previously described in the basal ganglia of neonates noted on routine head ultrasound examinations. These findings were formerly attributed to calcification of the vessels in this area secondary to a variety of conditions, including neonatal infection and trisomies. Histologic examination of several of these patients showed that the echogenicity of the vessels is secondary to intramural and perivascular mineralization with iron and deposition of basophilic material. The new evidence supports the theory that lenticulostriate “calcifications” on sonograms are non-specific indicators of vasculopathy, possibly due to hypoxic ischemic injury to a sensitive area of the developing brain. Echogenic lenticulostriate vasculature can be present on ultrasound studies obtained immediately after birth or develop and progress in the face of new or continuing insult. Limited follow-up data on these patients indicate possible increased risk for developmental delay and neurologic deficits.
Periventricular Leukoalacia

PVL, literally “softening of the white matter,” results from a focal or global ischemia in the periventricular white matter. The immature brain is particularly vulnerable to hypoxic-ischemic injury in this arterial watershed area due to incomplete vascularization. In addition, the ability to regulate cerebral blood flow over a range of arterial pressures and metabolic demands is very limited in preterm infants. Respiratory and cardiovascular instability and systemic hypotension can result in ischemia when cerebral autoregulation is not able to accommodate systemic instability. Preterm infants who have a loss of autoregulation and pressure passive cerebral circulation frequently exhibit ischemic injury to white matter.

Inflammatory mediators can aggravate these dysfunctional cerebral hemodynamics, contributing to injury even with milder ischemic stresses. Directly, inducible nitric oxide, and indirectly, oxygen free radicals and cytokines, are common mediators of cerebral loss of autoregulation. Vascular endothelium is activated by focal or global hypoxia-ischemia and endotoxin, resulting in expression and secretion of cytokines and intercellular adhesion molecules. Platelets and neutrophils are recruited to the site of injury. Microglial activation and excitatory amino acid secondary mediators, such as glutamate, amplify the reperfusion injury and extend the insult.

PVL results from neuronal necrosis and apoptosis after such a hypoxic-ischemic insult. Larger cystic lesions of the periventricular white matter take several weeks to develop, and may be foreshadowed by echogenicity in these triangular areas just lateral to the ventricles on head sonogram. Ultrasound screening with an 8-MHz transducer near discharge or at 36 weeks’ gestation is currently recommended.

Outcome in PVL

PVL may have been underappreciated in the past, as focal cysts may reabsorb in a few weeks’ time, leaving only slightly enlarged ventricles, and more diffuse WMI may only be demonstrated by magnetic resonance imaging (MRI). Many times there is no appreciable volume loss by head ultrasound with PVL. However, developmental potential has been lost, resulting in a decrease in myelination and afferent connections that would have been made with subplate neurons. Loss of precursor oligodendroglial cells and subplate neurons may be particularly important for determining outcome, because the injury in PVL is larger than what appears by ultrasonography or even MRI. Contagious apoptosis propagated by secondary mediators may negatively influence survival of subplate neurons, important chaperones for connectivity. Far-reaching developmental deficits may therefore, result from regions undersupplied by connecting white matter that are important in coordination of different cortical functions. Both decreased cortical gray matter volume and abnormal white matter maturation have been shown to be related to WMI in the preterm infant.

Bilaterality of echogenic foci and smaller cyst size of ≤ 2 mm are associated with a 32% incidence of cerebral palsy, whereas PVL with large cysts ≥ 3 mm carries a risk for cerebral palsy of 90%. More posteriorly located cysts confer a worse prognosis for multiple impairments, including visual, cognitive, and motor deficits.

Other Complications of Preterm Brain Injury

Porencephalic cysts may result from large grade IV IVH or a cerebral arterial infarction and consist of necrotic cavitation and cyst formation extending through the cortex. Low-pressure ventriculomegaly is a slowly evolving lesion due to white and gray matter atrophy. The ventriculomegaly will stabilize and will not show rapid head circumference growth as in posthemorrhagic hydrocephalus but is clearly associated with increased risk of cognitive and motor deficits.

Treatments Known to Injure the Preterm Brain

Postnatal steroids in premature infants were routinely used in the past to decrease pulmonary inflammation and enhance surfactant production. Large randomized trials showed that 14-day (and 42-day) courses of dexamethasone facilitate weaning sick preterm infants from ventilators. Only later did evidence of disruption of somatic and brain growth become evident with postnatal steroids. Good follow-up studies in randomized trials of postnatal steroid treatments for bronchopulmonary dysplasia have shown worse neurologic outcomes compared with control subjects, including more abnormalities on head sonograms. Steroid-treated premature infants also had a 35% decrease in cortical gray matter volume at term compared with premature infants not treated with steroids, similar to findings in growth-retarded infants. Atrophy of dendrites in the hippocampus, decreased neurogenesis, and inhibition of long-term potentiation have been shown with high-dose glucocorticoids. To try to reach a happy medium between the harm of prolonged ventilator support and adverse growth effects of steroids, shorter 3-day courses of steroids have been tested, but follow-up data on development for this group is currently lacking. Until proof of safety is established, the American Academy of Pediatrics is not recommending routine use of postnatal steroids in the preterm population.

Hypocarbia is well known for its associated decrease in cerebral blood flow in preterm infants, and PaCO₂ levels below 30 mm Hg are to be avoided, as even a 7-hour duration of such hypocarbia has been shown to cause WMI. Hyperoxia has been shown to induce apoptosis and neu-
rodegeneration in the immature rat brain but not in more mature brains.

**Noncystic WMI: Diagnosis by Advanced Imaging Techniques**

The vast majority of lesions in the extremely premature infant, whether hemorrhage or infarct, involve noncystic WMI. This is a region in the preterm brain most vulnerable to hypoxic-ischemic injury, oxidative stress, and glutamate toxicity. These lesions have been underdiagnosed in the past, because routine head ultrasonography rarely detects them, as they are characterized by diffuse and subtle high-signal intensity. At the present time, noncystic white matter lesions on sonograms remain a subjective judgment. Higher-resolution transducers and 3-dimensional imaging should result in improved routine bedside screening for diffuse white matter disease.

Recent research studies have used MRI to diagnose WMI with greater accuracy, combining MRI and diffusion-weighted imaging. Magnetic resonance diffusion-weighted imaging shows the restriction in water diffusion throughout the brain in response to insult. This technique is sensitive to early injury and is readily available on most MRI scanners.

Diffusion tensor imaging (DTI) is a newer tool that can measure relative anisotropy, defined as the directionality of water diffusion in cerebral white matter. DTI results in a more sophisticated and less subjective interpretation of restriction of water diffusion seen after injury. The greater the degree of anisotropy by DTI, the more directionally restricted water movement is by fiber tracts and columnar organization. Preterm infants typically have less organized bundles in their immature white matter than older infants and reduced relative anisotropy on DTI. With maturation of white matter bundles, anisotropy increases in normal preterm infants.

After acute hypoxic ischemic injury, there is reduced diffusion of water in extracellular and intracellular spaces, possibly due to cellular and axonal edema. Diffusion-weighted imaging may be helpful in identifying early white matter injury in preterm infants and in tracking recovery. In preterm infants with WMI, anisotropy does not increase with increasing gestational age, as it does in normal premature infants. Later neuroimaging by DTI may, therefore, be a particularly effective way to follow WMI in premature infants.

**Other Methods for Monitoring Brain Physiology**

MR spectroscopy using peak values for lactate and N-acetylaspartate is being investigated for use in preterm chronic hypoxic-ischemic injury. Research studies are being done when preterm infants are closer to term, but correlations with outcome are needed, because lactate is normally more elevated in preterm infants. Transportation of unstable preterm infants to the MRI scanner is frequently prohibitive, but bedside monitoring of neonates is evolving with Doppler blood flow, near infrared spectroscopy (NIRS), and amplitude-integrated electroencephalogram (EEG).

**Cerebral Blood Flow Velocity**

In many centers, obstetricians have been routinely measuring and using fetal pulse oximetry and Doppler middle cerebral artery blood flow velocities to help make delivery decisions, particularly in the setting of fetal anemia. However, use of Doppler cerebral blood flow measurements in premature infants is underused in the intensive care nursery. Normal values are well established, and alterations in flow have been described in hypoxia-ischemia, and in the presence of a large patent ductus arteriosus or hydrocephalus. The transcranial Doppler technique can detect disturbances in cerebral autoregulation with injury and alterations in cerebral blood flow velocities caused by ventilatory strategies, such as permissive hypercapnea, repetitive symptomatic bradycardia, PDA, and persistent pulmonary hypertension. This noninvasive, readily available bedside technique will likely have an important part to play in the monitoring of the response of cerebral blood flow to injury, recovery, and changes in therapy.

**Near Infrared Spectroscopy**

NIRS is a noninvasive bedside monitor able to continuously display changes in cerebral oxygenation. With this technology, light from a laser diode passes through cerebral tissue from a probe placed on the skin. Reflected light is measured by an adjacent probe. The absorption of light in the tissue varies depending on the oxygen saturation of the hemoglobin, and permits calculation of the concentration change in oxygenated hemoglobin, deoxygenated hemoglobin, and blood volume in the cerebral tissue over time. NIRS can augment cerebral blood flow velocity data by providing a measure of cerebral blood volume and the amount of oxygen extraction. Increased flow and total blood volume, combined with decreased oxygen extraction, is a well-described response to hypoxic-ischemic injury in term and preterm infants. In research studies in term infants, these cerebral blood flow alterations are being used to track injury and are being correlated to outcome. Application to the preterm infant in the near future may also allow bedside detection of hypoxic-ischemic injury.

**Amplitude-Integrated EEG**

Diagnosis of seizures in preterm infants may be extraordinarily difficult owing to the subtle features of such seizures. However, it is important to diagnose and treat repeated seizures because of their detrimental effects on brain growth and development.
Although not a true EEG, amplitude-integrated EEG by a cerebral function monitor may be of use in certain situations to identify patterns consistent with seizure activity. The bedside cerebral function monitor (Olympic Medical, Seattle) uses two parietal leads to give a one-channel recording and a channel for impedance, using a compressed recording of 6 cm/h. The ability to detect seizures is particularly helpful, because full-montage EEGs are rarely available on short notice or in off hours, and subclinical seizures have been correlated with poor outcome in neonates. Amplitude-integrated EEG is a very useful bedside tool to help identify abnormal activity and seizures, but it does not obviate the need for a standard EEG.

Amplitude-integrated EEG has also been used to determine burst suppression and low-voltage patterns in term infants with hypoxic-ischemic injury and, thereby, give an indication of severity of asphyxia. Studies have correlated frequency-amplitude EEG with standard EEG in its basic indication of severity of asphyxia. Amplitude-integrated EEG is particularly helpful, because full-montage EEGs are rarely available on short notice or in off hours, and subclinical seizures have been correlated with poor outcome in neonates. Amplitude-integrated EEG is a very useful bedside tool to help identify abnormal activity and seizures, but it does not obviate the need for a standard EEG.

Plasticity of Preterm Brain

Neuronal organization is a prominent feature of brain development after 24 weeks’ gestation. Cortical afferents in gray matter and waiting neuronal efferents from the white matter use subplate neurons as physical intermediaries to establish appropriate connections. Subplate neurons then undergo apoptosis when their job of making connections is accomplished. Efficient columnar organization of cortical neurons with other cortical and thalamic afferents may be disrupted by either large hemorrhages or white matter injury. The ability of the potential connections that are lost to be rerouted may allow for some restoration of pathways, and is now being revealed by functional MRI of former premature infants. Further studies of this population will provide specific insights into regional adaptation to injury during the cortical organization period.

Continuous, endogenous reparative mechanisms certainly help counteract all injury types discussed in this chapter. Neurogenesis and corticogenesis are now known to occur even in adult brain after ischemic injury, and although many of the cells produced will ultimately die, they may have important functions of guiding and re-establishing connections. Connectivity continues to be modified in the postinjury period and for many years in the premature infant. Neurotrophic factors are essential to this process, but some other less-likely mediators, such as interleukin-6, may also contribute acutely and more chronically. Such pleiotropism of action makes neuroprotection difficult, because blocking specific cytokines or even enhancing specific growth factors may have unwanted side effects. Use of such agents will require precise knowledge of their roles in reconstruction at different time points after injury so that we inhibit secondary extension of injury and augment the native physiology of recovery.

Suggested Readings


Practitioner and Patient Resources

United Cerebral Palsy
http://www.ucp.org/
UCP is the leading source of information on cerebral palsy and is a pivotal advocate for the rights of persons with any disability. This page also contains research and information on preterm brain injury.

March of Dimes
http://www.marchofdimes.com/
The March of Dimes is the leading charity supporting research, community service, and education to prevent birth defects and infant mortality. The page provides resources for those seeking information about research and treatment for preterm brain injury.

National Association of Neonatal Nurses
http://www.nann.org/
The NANN envisions that the lives of all newborns, infants, and their families will be improved through excellence in neonatal nursing practice, education, research and professional development. This resource provides practitioners with the standards of practice and caring for neonates.