Neurocognitive outcomes of infants born very preterm (less than 32 weeks gestation) remain a major concern in perinatal practice. Very preterm birth rates have increased, with enhanced survival since 1990. As focal brain lesions become less common, diffuse injury to both gray and white matter is now the primary focus for improving neurologic outcomes in survivors. Recent evidence supports preoligodendrocytes as the principal cellular target of diffuse white matter injury due to their susceptibility to hypoxic-ischemic and inflammatory insults. An understanding of their development and vulnerability can inform acute nursing care of very preterm infants. JOGNN, 36, 386-395; 2007. DOI: 10.1111/J.1552-6909.2007.00156.x

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Advances in perinatal management have significantly improved the survival of very preterm infants over the last two decades. In addition, the types of brain injuries suffered by preterm infants have changed over time. In this paper, after a review of neurodevelopmental outcomes of children born very preterm during the 1990s, the changing spectrum of neuropathology in extremely preterm infants, from acute periventricular lesions to subclinical injury of both gray and white matter and particularly diffuse white matter injury (DWMI), is discussed. The susceptibility to injury of the preoligodendrocyte, the presumed cellular target in DWMI, is explained. This synopsis should aid nurses in understanding the etiology of diffuse neuropathology in the extremely preterm infant, the complex nature of strategies that will be necessary to both prevent injury and support ongoing growth processes, and the need to help parents adopt a long view of developmental monitoring to identify problems that may not emerge until late childhood.

Outcomes of Very Preterm Birth

Incidence of Prematurity

The incidence of premature birth in the United States (all births less than 37 weeks gestation) grew from 8% in the early 1980s to 12.5% in 2004 (Martin et al., 2006). This growth has been driven primarily by increases in moderate preterm birth (32-36 weeks) associated with such factors as in vitro fertilization, multiple gestation, and older maternal age (Green et al., 2005). However, the rate of very preterm birth (defined as less than 32 weeks) also increased in 2004 to 2.01% of all births or 81,645 infants (Martin et al., 2006). Infants born at extremely low birthweight (ELBW) (less than 1,000 g, or approximately less than or equal to 28 weeks gestation) rose to 0.75% of all births, numbering 30,670 in 2004 (Martin et al., 2006).

Survival to Discharge and Perinatal Morbidity

About 85% of very preterm infants now survive until hospital discharge (Fanaroff, Hack, & Walsh, 2003; Volpe, 2003). Survival rates for infants born in 1999-2000 are reported as 55% at 501 to 750 g, 88% at 751 to 1,000 g, and 93% at 1,001 to 1,500 g. Survival for 1999-2000 births was improved in all birthweight groups when compared with 1987-1988, but recent gains have slowed; survival rates improved between 1993-1994 and 1999-2000 only for those born at less than 750 g (Fanaroff et al., 2003; Vohr,
Wright, Poole, McDonald, & for the NICHD Neonatal Research Network Follow-up Study, 2005).

For these ELBW infants, survival rates to toddler age range from 52.5% for all births in Victoria, Australia, in 1991-1992 (Anderson, Doyle, & the Victorian Infant Collaborative Study Group, 2003), to 67% from one center in Ohio between 1990 and 1998 (Wilson-Costello, Friedman, Minich, Fanaroff, & Hack, 2005). Using 1990s birth data from a number of regions, Levene (2004) found survival to toddler age was 26% for those born at 24 weeks gestation, increasing to 75% survival for infants born at 27 weeks.

These differences in reported survival rates highlight two points. First, comparison of findings across studies requires consideration of several factors, including definition by birthweight versus gestational age; years of birth; inclusion of all births, all live births or only those admitted to intensive care; regional versus multiple center versus single-center cohorts; the nature of the comparison group; and rate of follow-up (Levene, 2004). Second, within the very preterm group (less than or equal to 32 weeks gestation), infants born at more than 27 weeks have a very different risk profile for mortality than infants born at less than 27 weeks (about 800 g).

This mixed picture also applies to rates of medical and neurodevelopmental morbidities. Major perinatal morbidity in very preterm infants remained essentially unchanged from 1993-1994 to 1999-2000, except for a decline in respiratory distress syndrome and periventricular leukomalacia (PVL) (Fanaroff et al., 2003). Periventricular leukomalacia decreased from 7% to 3% or less even in infants born between 501 and 750 g, while rates of patent ductus arteriosus, proven necrotizing enterocolitis, late onset sepsis, and bronchopulmonary dysplasia increased from 1987-1988 to 1993-1994, and remained essentially unchanged to 1999-2000, probably reflecting the greater survival rate in this group (Fanaroff et al.).

Neurodevelopmental Outcomes in Toddlers

Major morbidities, defined as severe cerebral palsy (CP), cognitive performance more than 2 standard deviations below population means (mental retardation), profound deafness, and bilateral blindness, are found in approximately 15% of very preterm survivors in their second year of life (Vohr et al., 2005). Rates of these severe problems increased as the gestational age at birth decreases. In geographically based birth cohorts from the 1990s, no infants born before 23 weeks gestation survived free of major neurosensory morbidity. Intact survival was less than 25% of those born at 24 weeks, approximately 50% at 26 weeks, and approximately 63% at 27 weeks (Levene, 2004).

Vohr et al. (2005) compared outcomes at 20 months corrected age between infants born in 1997-1998 at 27 to 32 weeks versus 22 to 26 weeks. Moderate to severe CP was present in 6% of the 27 to 32 week cohort but in 10% of the 22 to 26 week group, deafness in 1.8% of both groups, bilateral blindness in 0.4% of the 27 to 32 week group versus 1.0% of the 24 to 26 week group, and shunted hydrocephalus in 1.0% of the 27 to 32 week group but 3.6% of the 24 to 26 week group. Physical development was severely impaired in 17% of the 27 to 32 week group but in 26% of the 24 to 26 week toddlers, and moderate to severe impairment in mental development was identified in 23% of the 27 to 32 week group versus 37% in the more preterm group. Increased risk of these severe neurodevelopmental outcomes in the toddler year is associated with intraventricular hemorrhage, PVL, and bronchopulmonary dysplasia. Higher risk for impaired neurodevelopment is also associated with use of postnatal steroids, male gender, and lower maternal or paternal education (Vohr et al., 2000, Vohr et al., 2005; Wood et al., 2005).

Hack et al. (2005b) found that moderate to severe impairment on standardized measures of mental and physical development identified in toddlers predicted significant cognitive delays at school age when the toddlers also had significant CP or sensory deficits. Toddlers with relatively intact sensorimotor function showed improvement in cognitive performance by early school age, but even these children remained at greater risk than full-term children for other functional problems.

Functional Outcomes at School Age

Functional deficits occur in 50% to 70% of very preterm survivors but are often not apparent until early school age when, as a group, these children show intelligence scores that average 10 points below their term-born peers (Aylward, 2005). Functional problems refer to perceptual, processing, and behavioral problems that impair the individual’s ability to achieve typical learning performance. Mild to moderate deficits in cognitive performance may be combined with sensory deficits (auditory, visual, or tactile integration problems), motor problems (e.g., mild CP, ataxia, visual-motor imprecision, and movement disorders), and learning disabilities (dyslexia, visual-spatial processing, visual, and auditory memory problems). Attention deficit, hyperactivity, emotional and behavioral dysregulation, and poor executive function may contribute to the learning problems. Alternatively, they may reflect the child’s struggle with increasingly complex educational and social performance demands as he/she matures (for more detailed discussion, see Aylward).

In a population-based study, 41% of 6-year-old children born at 22 to 25 weeks gestation scored more than 2 standard deviations below the average cognitive function scores of term-born classmates, and only 20% were free of moderate or severe disability (Marlow, Wolke, Bracewell, Samara, & for the EPICure Study Group, 2005). Hack et al. (2005a) compared 219 ELBW children without significant neurologic impairment to 176 normal-birthweight
Lesions of the Developing Brain

The profile of neurodevelopmental disability is shifting, as neonatal care and infant survival change over time. The incidence of severe focal lesions in the brain’s white matter, including germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH), periventricular hemorrhagic infarction (PVHI), and PVL, all strongly associated with significant cognitive and sensorimotor disabilities, has declined in the last decade. Now, DWMI is emerging as the current prevailing pathology in very preterm infants (Volpe, 2003).

Diffuse white matter injury is emerging as the current prevailing brain pathology in very preterm infants.

Research on the genesis of neurologic lesions and the special susceptibility of the very preterm brain to maturational insults may lead to more specific perinatal care and, hence, to better functional outcomes. The following sections review the focal and diffuse alterations in white and gray matter that are associated with very preterm birth and what is known about immature cells’ particular susceptibility to injury.

Neurogenesis

At 24 weeks gestation, the brain is about half the weight it will be at term. The surface is fairly smooth and lacks the more complex gyri and sulci of the cerebral cortex at term (see Figure IA and B). These surface features reflect the maturation of cell populations, networks, and connections to underlying structures that result from normal growth in utero. Some features of the normal structure of gray and white matter in the cerebral hemisphere that are developed by term are shown in Figure IC, including the internal capsule, the major pathway for primary motor neurons that is typically involved in CP. Sites of injury to white matter in the preterm infant are shown in Figure ID.

While most neurogenesis is completed by 22 weeks gestation, many functional networks are not yet established. These integrating networks require populations of glia cells and neurons that are still proliferating and migrating to final locations. Glia cells include astrocytes that orient and provide structure and support to neurons; oligodendrocytes (OLs) that myelinate neuronal axons to support rapid signal transmission; and microglia that remove cellular debris. Astrocytes and microglia have direct contact with the neuroepithelium and thus respond to changes in the vascular system including entry of blood cells such as macrophages and inflammatory factors into the brain. Microglia have a central role in generating inflammatory responses to injury or infection. In the preterm brain, OLs are highly susceptible to such injuries, for reasons that will be developed in the sections below.

White Matter Pathology

In the preterm infant, gross structural alterations in the brain have been identified by cranial ultrasound or magnetic resonance imaging (MRI). Four specific lesions of the myelinated tracts, or white matter, are GMH-IVH, PVHI, PVL, and DWMI. While each lesion may exist in isolation, it is more common for any single infant to present with multiple lesions (for review of these lesions, see Folkert, 2005; Volpe, 1998, 2003).

Germinal Matrix Hemorrhage-Intraventricular Hemorrhage and PVHI. Hemorrhage of the germinal matrix and PVHI usually present as asymmetric lesions, involving bleeding from the thin-walled veins within the germinal matrix. These veins may rupture into the ventricular system or cause rupture of ependymal veins in the ventricle wall. This bleeding may cause obstruction of the medullary veins, resulting in venous hemorrhage and coagulation necrosis of deep periventricular white matter, resulting in a PVHI. Germinal matrix hemorrhage-intraventricular hemorrhage and PVHI may result in a residual porencephalic cyst near the ventricular, posthemorrhagic hydrocephalus, or both.
Periventricular Leukomalacia. In contrast to the venous origins of hemorrhagic lesions, PVL is linked to loss of arterial blood supply to deep white matter, in regions where small arterioles have not yet fully penetrated the cerebrum or are not yet muscularized. The result is regional hypoxia-ischemia, with or without focal infarction. When acute necrotic foci develop, they are generally surrounded by a halo of edematous tissue that may resolve leaving residual cystic lesions.

Diffuse White Matter Injury. While PVL is a focal injury in the deep periventricular white matter, DWMI is regional and involves primarily the central cerebral white matter (Volpe, 2003; Figure 1C and D). Diffuse white matter injury is diagnosed by magnetic resonance/diffusion tensor imaging. Diffuse white matter injury is believed to reflect a primary loss of oligodendroglia, resulting in reduction of myelinated axonal projections of neurons as the brain matures (Folkerth, 2005). It is also possible that the lesion reflects a decrease in amount of myelin per axon or a combination of loss of neurons and OLs. Periventricular leukomalacia and DWMI are usually bilateral lesions, although not necessarily symmetrical, and both may be associated with later bilateral enlargement of the brain ventricles.

Gray Matter Pathology

As would be expected given their biological link, abnormalities of cortical gray matter and gyral development accompany white matter abnormalities (Counsell et al., 2006). In addition to the four types of lesions of white matter, reduced growth and atypical development of cortical gray matter (thin cortex and simplified gyri) are seen by MRI in very preterm infants at 40 weeks adjusted age (Counsell et al., 2006; Limperopoulos et al., 2005; Peterson et al., 2000). The pattern of reduced gray matter is especially pronounced in infants born at less than 26 weeks gestation (Inder, Warfield, Wang, Hüppi, & Volpe, 2005). Reductions in the cerebellum...
and the volume of deep gray matter of the cerebrum (e.g., basal ganglia: caudate, putamen, globus pallidus; thalamus; and their interconnections) have been found, in addition to changes in the cerebral cortex (Limpertopoulou et al., 2005; see Figure 1C).

Gray matter abnormalities (smaller volumes in the caudate and hippocampus) have been linked to learning disorders, attention deficits, and movement disorders in adolescents who were born extremely preterm. No such correlation is seen with focal perinatal injuries such as GMH-IVH or cystic PVL (Abernethy, Palaniappan, & Cooke, 2002). Thus, functional outcomes may be related to both gray matter abnormalities and DWMI.

**Mechanisms of White Matter Injury**

**Developmental Timing**

Maturation of any individual brain structure is critically dependent upon a series of coordinated signaling events within and between various cell populations to form functional networks. These critically timed serial processes are highly vulnerable in the premature infant, as the structural components of the network are actively evolving during the last half of gestation (see Folkther, 2005, for review).

Myelination in the human cerebrum is initiated late in gestation, peaks in infancy, and the full maturation of the myelin sheath continues well into young adulthood (see Harry, Lawler, & Brunnsen, 2006; Quarles, Macklin, & Morell, 2006). Development of the myelin sheath plays a critical role in efficient conduction of signals by neurons by allowing for saltatory conduction. The very preterm infant is susceptible to DWMI due to the timing of generation of the cells that produce myelin, the OLs.

Each OL myelinates one internode—that is, forms one myelin wrapping—on an individual axon. However, each OL forms one internode on dozens of individual axons. Axons, in turn, depend on contact with OLs for growth and functional maturation in addition to maintenance of efficient impulse conduction. The critical interactions between the axon and the myelin sheath are not fully understood by basic researchers. They include interactions that are contact related, such as ion channel clustering, as well as those involving an interchange of signals and material between the OL and the neurons. Given the number of individual axons that are myelinated by any one OL, the loss of multiple OLs would generate a cumulative effect that may present as diffuse impaired axonal function.

**Preoligodendrocytes.** By 26 weeks, the germinal matrix produces primarily multipotent glia cells that migrate outward into the periventricular tissues, where they may be induced to mature into oligodendrocyte precursor cells (pre-OLs) under the influence of growth factors supplied by other cell types (Richardson, Kesaris, & Pringle, 2006). By midgestation (17-23 weeks), pre-OLs populate the cerebral cortex and subventricular zone (Jakovcevski & Zecovic, 2005) and they predominate in deep periventricular white matter between 24 and 32 weeks gestation (Folkther, 2005).

Preoligodendrocytes are induced to become mature OLs by contact with axons, which triggers initiation of myelination. Thus, at the time of very preterm birth, pre-OLs are being generated and are migrating to sites for myelination between the ventricles and the cortex (the future cerebral white matter)—a critical phase in brain development.

The pre-OLs have been demonstrated to be highly vulnerable to injury from oxidative stress by free radical release, excitotoxicity by excessive accumulation of neurotransmitters, and inflammation by release of proinflammatory cytokines. These processes have been demonstrated in the preterm brain under conditions of hypoxia-ischemia and reperfusion and in neuroinflammation (see Back, 2006; Folkther, 2005, for reviews).

**Microglia.** Microglia are the brain’s resident macrophages, normally resting cells that are activated by infection or tissue injury to secrete inflammatory proteins. Activated microglia are responsible for the phagocytic removal of debris within the brain, an essential step in localizing and limiting the extent of tissue necrosis following an injury or in minimizing the accumulation of unwanted material in the brain. Under normal developmental conditions, microglia also are involved in the removal of the debris from programmed cell death (apoptosis) and the pruning of excess connections to generate the more refined neural network present by infancy.

Between 20 and 52 weeks after conception, activated microglia are transiently increased in normally developing periventricular white matter in association with these necessary network refinement processes (Billiards et al., 2006). However, greater numbers of activated microglia are found in white matter before 37 weeks, compared with white matter after 37 weeks or cortical gray matter at either age (Billiards et al., 2006). Thus, microglia in preterm white matter that are already developmentally primed may respond to infectious or ischemic insults by producing an excessive inflammatory reaction or may be unable to respond appropriately (Billiards et al., 2006).

**Hypoxia-Ischemia and Reperfusion Injury**

Sublethal hypoxic-ischemic insult may occur in utero or after birth, challenging the brain with repetitive reperfusion injury. Hypoxia-ischemia and reperfusion injury involve preoligodendrocyte injury and activation of microglia, helping explain the vulnerability of the preterm brain to
The mechanisms of injury may include excitotoxicity, free radical damage, and inflammation.

**Hypoxia-ischemia and reperfusion injury involve preoligodendrocyte injury and activation of microglia, helping explain the vulnerability of the preterm brain to disrupted growth and maturation.**

**Excitotoxicity.** Hypoxic-ischemic insult leads to a failure of energy- and oxygen-dependent ion pumps in cells, particularly affecting mitochondria. Mitochondrial failure causes an accumulation of calcium, sodium, and potassium ions, leading to a depolarization of cell membranes and release of excitatory neurotransmitters such as glutamate from presynaptic neurons. Under normal conditions, glutamate signals both adjacent postsynaptic neurons and glial cells that express glutamate receptors. In addition, excess glutamate is removed from the synaptic space by glutamate transporters.

During hypoxia-ischemia, glutamate accumulates at synapses because normal clearance mechanisms are also energy dependent. This accumulation causes excitotoxicity during reoxygenation by overstimulation of the adjacent cells (for review, see Volpe, 2001). Excitotoxicity may manifest clinically as transient perinatal seizures on reperfusion-reoxygenation, initiated by the response of downstream neurons to glutamate (Volpe, 2001).

Preoligodendroglia are extremely vulnerable to excitotoxic injury because they express a specific subtype of glutamate receptor that is calcium permeable and also because they express high levels of glutamate transporters between 20 and 34 weeks after conception (Talos et al., 2006). Calcium-mediated glutamate uptake leads to excitotoxic death of pre-OLs, whereas mature myelinating OLs that express mature receptor subtypes and low levels of transporters are relatively resistant to this injury (Follett et al., 2004).

**Free Radical Damage.** In addition to initiating excitotoxic injury, ischemia and reoxygenation lead to damage by free radicals. High calcium levels activate enzymes that degrade phospholipids to yield increased free fatty acids and reactive oxygen species, leading to lipid peroxidation. The resulting peroxynitrite and prostaglandins are potent free radicals, creating secondary injury to surrounding cells.

Effects of free radicals on neurons and OLs are dependent on the maturation state of the cell (Folkerth, 2005; Golan & Huleihel, 2006). The pre-OLs are vulnerable to oxidative stress and free radical injury because they are relatively deficient in the antioxidant enzymes glutathione peroxidase and catalase until 30 weeks gestation. A third enzyme, superoxide dismutase, is expressed at 27 weeks but does not reach adult levels until 40 weeks. These enzymes sequentially convert reactive oxygen and nitrogen species to water and oxygen. Nitric oxide, a free radical species produced by activated microglia, also has a direct toxic effect on pre-OL mitochondria (see Folkerth; Haynes et al., 2005, for review).

**Inflammation.** Excitotoxicity and free radical damage contribute to localized cell death or injury. The products of cellular necrosis or apoptosis stimulate microglia to the activated state. Activated microglia (and reactive astrocytes) secrete a complex array of inflammatory proteins, such as the cytokines tumor necrosis factor alpha (TNFα) and interleukin (IL)-1, IL-6, and IL-8. Cytokine release within the brain initiates a cascade of events including both pro- and antiinflammatory factors. When a concurrent breach in the blood-brain barrier occurs, TNFα can serve to recruit lymphocytes and macrophages from the systemic circulation to the site of injury, thus further enhancing innate immune responses within the brain.

A full discussion of inflammatory mechanisms of pre-OL death is beyond the scope of this paper, but it should be noted that the complex signaling involved in inflammatory responses to ischemia (see e.g., Back, 2006; Hagberg & Mallard, 2005) can also occur in systemic responses to infectious processes. This interaction of activated microglia with pre-OLs is the subject of current research in relation to the possible role of maternal infection (Boggess, 2005; Goldenberg, Culhane, & Johnson, 2005) and fetal inflammatory responses in DWMI and later neurologic function (Ellison et al., 2005; Harry et al., 2006).

**Summary**

From this discussion, it should now be apparent that at the gestational time point of very preterm birth, the preoligodendrocyte in the developing white matter is selectively vulnerable to injury from reactive oxygen and nitrogen species, energy failure, excitotoxicity, and inflammatory responses. The current theory of DWMI is that loss of pre-OLs, by one or more mechanisms, leads to a decrease in the population of mature OLs, resulting in fewer cells to produce myelin and support the normal growth and maturation of neuronal networks (Back, 2006; Volpe, 2003). This process is consistent with the developmental timing of pre-OLs in future white matter as well as the types of clinical insults that lead to or follow very preterm birth.

Alternative processes that could result in a decrease in white matter include a decrease in the production of myelin by a normal number of OLs, either from a decrease in their
biochemical efficiency or from a decrease in the number or size of axons requiring myelination, or both. Any of these scenarios could result in an alteration in the integrated signaling within the brain that is essential for the maturation of sensory, motor, behavioral, and cognitive functions.

Discussion of Clinical Issues

Advances in perinatal care since the 1980s have significantly improved the survival and outcomes of all preterm infants, adding to the numbers of children surviving very preterm birth. For this group of children, reducing the risk for significant cognitive and neurobehavioral problems requires a greater understanding of the underlying cellular processes involved in DWMI and alterations in gray matter development.

The significant immaturity of the brain at birth before 27 weeks, along with other vital organs such as the lung, intestines, and endocrine glands, enhances its vulnerability. Development of safe and effective therapeutic interventions in very preterm infants requires a thorough understanding of the underlying neurobiologic processes and the timing of vulnerability to specific insults to protect essential brain growth and maturation. In addition, understanding this more subtle pathology may contribute to developing effective ongoing interventions through adolescence.

Extremely preterm infants have a prolonged postnatal period of susceptibility to repetitive mild insults, which may offer significant clinical opportunities to improve neurodevelopmental outcomes (Volpe, 2003). Although adequate evidence is not yet available to support specific interventions to prevent DWMI, logical targets include prevention and treatment of perinatal infectious and inflammatory processes, pharmacologic therapies to reduce reactive oxygen and nitrogen species and glutamate excitotoxicity, and exquisite attention to care practices that reduce physiologic and emotional stress in the acute neonatal period. Careful clinical monitoring to avoid marked hypoxia, hyperoxia, hypocapnia or hypercapnia, and stabilization of cerebral perfusion pressure is a basic responsibility of the neonatal nurse aimed at reducing repetitive ischemic insult and resulting damage from reactive oxygen species and activation of inflammation (Volpe, 1998).

Perinatal infection is a highly salient target to reduce premature rupture of membranes and consequent very preterm birth and inflammatory responses in the fetus. Obstetric and women’s health nurses have a role in recognizing and treating infections of the reproductive and urinary tracts (see Goldenberg et al., 2005) and periodontal disease (Boggess, 2005) especially when it progresses during pregnancy (Offenbacher et al., 2006). Antenatal and postnatal antibiotics have established efficacy in reducing morbidity from diagnosed perinatal infections.

Antenatal corticosteroids and postnatal indomethacin are potent antiinflammatory agents. Initially introduced to induce lung maturation and close patent ductus arteriosus, respectively, indomethacin also reduces GMH-IVH. Although short-term outcomes such as reducing incidence or severity of GMH-IVH may be seen as indicative of “neuroprotection,” effects on other groups of maturing cells such as pre-OLs or immature neurons and on long-term functional outcomes must be considered. These compounds are known to affect free radical formation and microglial activation, but each has significant negative systemic effects in the neonate.

In recent trials, ibuprofen lysine appears as effective as indomethacin for treating patent ductus arteriosus, with fewer renal side effects. Unlike indomethacin, ibuprofen shows no effect on risk for GMH-IVH, even though it enhances cerebral blood flow autoregulation and protects neurons following oxidative stress in animal studies (Aranda & Thomas, 2006). Further data are needed to gauge long-term effects of perinatal ibuprofen.

Future therapies aimed at specific cellular pathways may hold more promise than these nonspecific antiinflammatory agents. For example, topiramate is an anticonvulsant that blocks developmentally appropriate glutamate receptors and shows some promise in preliminary animal models for reducing white matter injury by targeting the developmental susceptibility of pre-OLs to excitotoxicity (Follett et al., 2004). Drugs used for labor tocolysis also may affect neurologic outcomes in the very preterm, although mechanisms are not clear. In theory, β-adrenergic receptor agonists such as terbutaline and ritodrine should support maturation of systemic cellular functions critical to acute survival but may have deleterious effects on long-term neurologic outcomes (for review, see Slotkin, Auman, & Seidler, 2003).

Considerable controversy surrounds magnesium sulfate. Maternal doses commonly given for labor tocolysis in the United States approach toxic levels in the fetus, without evidence of efficacy in halting preterm labor (Mittendorf, Roizin, & Pryde, 2004). Protective effects on incidence of CP, GMH-IVH, or PVL were not confirmed in multiple clinical trials (Canterino et al., 1999; Crowther, Hiller, Doyle, & Haslam, 2003). Dysregulation of organization of sleep states has been identified recently in a convenience sample of very preterm infants exposed to magnesium sulfate (Black, Holditch-Davis, Schwartz, & Scher, 2006). This example highlights the potential for insult to maturing integrative networks.

Serial birth cohorts must be followed to evaluate the positive or negative effects of new therapies, such as ibuprofen, as they are introduced or removed over time. For example, the widespread use of surfactant therapy after 1990 marked a change in care associated with increased survival and decreased severity of chronic lung disease. Antenatal treatment with corticosteroids and antibiotics increased between 1993 and 2000, apparently contributing...
Development of successful clinical interventions to protect neurocognitive functions will require targeting specific mechanisms of vulnerability while concurrently supporting neurologic growth and maturation.

The future consideration of specific anti-cytokine therapeutics to control neuroinflammatory processes in very preterm infants may run into similar limitations, regardless of how promising this target may seem based on current data. Control of neuroinflammation is a complex issue because proinflammatory cytokines also act as regulators of essential growth programs in normal brain development and are potent regulators of the immature immune system. Efforts to apply an anti-cytokine approach to adult human diseases have been less than successful, but further exploration is needed.

Any application of data from the bench to the patient must be weighed with strong consideration for the complexity of the whole organism, especially the developing infant. A coordinated series of steps are needed to develop a full therapeutic strategy that integrates what we currently know (and still need to learn) about the very immature brain and its vulnerability, as well as its plasticity and capability for compensatory repair.

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