Knowledge of the nature, prognosis, and ways to treat brain lesions in neonatal infants has increased remarkably. Neonatal hypoxic-ischaemic encephalopathy (HIE) in term infants, mirrors a progressive cascade of excito-oxidative events that unfold in the brain after an asphyxial insult. In the laboratory, this cascade can be blocked to protect brain tissue through the process of neuroprotection. However, proof of a clinical effect was lacking until the publication of three positive randomised controlled trials of moderate hypothermia for term infants with HIE. These results have greatly improved treatment prospects for babies with asphyxia and altered understanding of the theory of neuroprotection. The studies show that moderate hypothermia within 6 h of asphyxia improves survival without cerebral palsy or other disability by about 40% and reduces death or neurological disability by nearly 30%. The search is on to discover adjuvant treatments that can further enhance the effects of hypothermia.

Introduction

Disorders that damage the developing brain are a substantial cause of death or permanent disability such as cerebral palsy. Hypoxic-ischaemic encephalopathy (HIE) in term infants occurs at a rate of about three per thousand live-born infants in developed countries, but the rate is estimated to be higher in the developing world. As many as a million deaths worldwide might be caused by perinatal asphyxia. Less common but no less important causes of brain injury in neonates are ischaemic strokes, including venous sinus thrombosis, encephalopathy associated with severe congenital heart disease, intraventricular haemorrhages, and periventricular leukomalacia (PVL) in premature infants. Infants with encephalopathy secondary to rare metabolic disorders such as urea-cycle disorders should also be included in this group. Physicians who care for these children in the period after injury have traditionally provided supportive care with little expectation that their interventions would salvage brain tissue or have an effect on the final outcome. However, this situation has changed over the past 5 years with the publication of positive results from several controlled trials of therapeutic moderate hypothermia for term infants with neonatal HIE. Publication of these results has led to wider clinical application of therapeutic hypothermia for neonatal encephalopathy. This new therapy is increasingly being given to babies in special neonintensive care nursery units where they can be monitored with amplitude integrated electroencephalography (aEEG) and continuous conventional electroencephalography (EEG) by specially trained nurses. Time to recovery of a normal background pattern on aEEG seems to be a better predictor of outcome in infants treated with therapeutic hypothermia than in normothermic infants with HIE.

These advances in treatment are based on knowledge gained from clinical observation of babies with asphyxia and extensive laboratory research with experimental models. Data from these experiments led to a heuristic model in which hypoxia-ischaemia triggers a delayed series of events that lead to cell death in the brain. This period of delay, or latent interval, suggested that post-insult interventions could be protective if started in time. Discoveries of the role of glutamate-mediated excitotoxicity, oxidative stress, and cell-death signalling pathways in perinatal brain injuries have provided a foundation for these trials in humans, and continuing research on basic mechanisms of cell death is important to improve treatment and identify new treatment targets. These basic studies suggest that combination of hypothermia with adjuvant treatments, including the anaesthetic gas xenon, erythropoietin, or anticonvulsants, might improve outcome. In this Review we discuss three advances: progress in understanding the cascade of neurochemical events that mediate brain damage after a hypoxic-ischaemic insult in term infants; data from clinical trials that show benefit of therapeutic hypothermia for term infants with HIE; and early clinical results of trials of erythropoietin and other adjuvant drugs that might enhance neuroprotection.

Neonatal encephalopathy in term infants

Signs of encephalopathy in newborn babies older than 34 weeks’ gestation can include hyperalmentness, lethargy, somnolence or coma, seizures, poor feeding, hypotonia, and respiratory problems that might need mechanical ventilation. Sarnat and Sarnat were the first to define this syndrome as neonatal encephalopathy following foetal distress in 21 infants older than 36 weeks’ gestation. They distinguished three stages of encephalopathy: stage 1, or mild encephalopathy associated with hyperalmentalness, sympathetic overdrive, and a normal EEG; stage 2, or moderate encephalopathy marked by obtundation, hypotonia, multifocal seizures, and an EEG showing periodic or continuous delta activity; and stage 3, or severe encephalopathy in which infants were stuporous and flaccid with an isoelectric or periodic EEG. Infants who did not enter stage 3 and who had signs of stage 2 for fewer than 5 days were normal on follow-up, but persistence of stage 2 for a week or failure of the EEG to normalise predicted later neurological impairment or death. Levene and colleagues used a similar system to classify 122 term infants with asphyxia into mild, moderate,
or severe groups. On follow-up at 2·5 years of age, all children with mild encephalopathy were normal, whereas 25% with moderate encephalopathy and 76% with severe encephalopathy died or had a disability. The severity of encephalopathy was more predictive of neurological handicap than was the Apgar score, and none of the children with neurological disability had a low Apgar score without also having moderate or severe encephalopathy.

Definition of neonatal encephalopathy as a clinical syndrome was supported by the publication of two papers from the Western Australian case-control study by Badawi and colleagues. This was the first population-based study of neonatal encephalopathy and included all term infants in Western Australia who met the study criteria; however, it included some infants who would not have met criteria for the study by Sarnat and Sarnat or more recent trials of brain cooling. The causes of neonatal encephalopathy in this study were heterogeneous, and more than 70% of infants had no evidence of intrapartum hypoxia. Antepartum factors that were strongly associated with neonatal encephalopathy included maternal thyroid disease, severe pre-eclampsia, intrauterine growth retardation, and intrapartum factors such as maternal fever and acute obstetrical events. At follow-up, 28% of children with encephalopathy were reported to have genetic disorders, dysmorphic features, or malformations compared with 4% of controls. This study showed that differential diagnosis of encephalopathy in neonates is broad and includes infection, endocrine, genetic, and metabolic disorders.

Pathogenesis of perinatal brain injury

The excito-oxidative cascade

Implicit in the early descriptions of the syndrome of neonatal HIE was the notion that its clinical signs progress after a latent period of hours to days and then resolve within several weeks. Recognition of this concept led to clinical and basic research aimed at understanding the cascade of neurochemical processes responsible for brain injury to improve intervention and salvage brain tissue. An important early discovery made by Reynolds and colleagues was termed “secondary energy failure”. They reported that high-energy-containing phosphate compounds in the brains of term infants fell during the initial period of asphyxia, defined by low Apgar score and severe metabolic acidosis, and rebounded quickly during resuscitation, only to fall again permanently after about 24 h. Reynolds’ group also reported this effect in piglets—a noteworthy example of clinical observations promoting laboratory research, the results of which were then translated back to the clinic. The interval between the initial hypoxic-ischaemic insult and delayed energy failure includes the latent period after resuscitation when the infant appears more active for 8–24 h, but then develops seizures and other signs of encephalopathy. The mechanism of brain injury is thought to involve a series of events that we refer to as the “excito-oxidative cascade” (figure 1). We prefer this term because experimental evidence suggests that activation of excitatory glutamate receptors, especially NMDA receptors, occurs very early during the initial hypoxic-ischaemic insult. Then oxidative stress associated with worsening mitochondrial dysfunction and mitochondrial failure becomes an important factor that determines whether neurons and glia survive or die by apoptosis or necrosis. This cascade probably accounts for the process of secondary energy failure in mitochondria, in which the brain’s energy supplies fall over a period of about 24 h in babies and sheep models.
Glutamate-receptor-mediated injury

The first events to occur during a severe hypoxic-ischaemic episode associated with metabolic acidosis are depolarisation of neuronal membranes and power failure of glutamate transporters on perisynaptic glia that ordinarily remove the neurotransmitter from the synaptic cleft (figure 1). The ischaemia reduces ionic gradients across neuronal membranes leading to membrane depolarisation and neurotransmitter release. Glutamate reuptake transporters can operate anaerobically in hypoxic conditions, but become impaired when ischaemia secondary to falling cardiac output restricts the delivery of glucose. Transporter failure then causes glutamate to accumulate within synapses and spill over into the brain’s extracellular space. This accumulation is consistent with notable increases in concentrations of the excitatory amino acids glutamate and aspartate in the CSF of babies with moderate or severe encephalopathy. Studies in fetal lambs have also shown that hypoxia-ischaemia causes extracellular overflow of glutamate and other amino acids in the cortex and basal ganglia. Loss of membrane potential, combined with high concentrations of glutamate, opens calcium-permeable NMDA glutamate channels and voltage-gated calcium channels allowing calcium to move into neurons (figure 2). Strong evidence suggests that many types of calcium conductance channels are open during sustained hypoxic-ischaemic-induced depolarisation; substantial non-specific transmembrane leakage also occurs. Calcium flooding into cells activates a cascade of events that can cause cell death. Endogenous activation of adenosine A1 receptors during severe asphyxia mediates the initial suppression of neural activity and is an important protective mechanism. Pretreatment of 7-day-old rats with the NMDA channel blocker MK-801 before hypoxia-ischaemia is strongly protective, but the temporal window for protection by this drug after hypoxic-ischaemia is less than 3 h, suggesting that the cascade downstream of NMDA receptors quickly becomes irreversible, self perpetuating, and unresponsive to channel blockade. Magnesium is neuroprotective against damage caused by HIE in neonatal rodent models, probably due to its ability to block NMDA-receptor channels. AMPA-type glutamate receptors are also activated by excess glutamate and probably contribute to seizures during hypoxic-ischaemic encephalopathy.

The prominence of NMDA-mediated injury in the immature brain is related to the fact that NMDA receptors are functionally upregulated in the perinatal period because of their role in activity-dependent neuronal plasticity. Immature NMDA channels open more easily and stay open longer than do adult channels, and the voltage-dependent magnesium block that is normally present in adult channels at resting membrane potentials is more easily relieved in the perinatal period. Increased expression of NR2B subunits on NMDA receptors is thought to be responsible for their greater excitability and longer open time during the neonatal period. Normally
this increased opening time serves the developing brain well by enhancing physiological forms of activity-dependent plasticity such as long-term potentiation, which is associated with coding of memories.\(^45\) However, when energy shortages occur, this arrangement becomes a liability, and the increased excitability can lead to neuronal damage. In addition to the enhanced excitability of immature glutamate synapses, the neonatal brain is more excitable than the adult brain because the inhibitory neurotransmitter GABA produces excitation rather than inhibition in the neonatal period.\(^6\) This excitation occurs because neuronal chloride transporters expressed during the neonatal period raise the intracellular concentration higher than the extracellular concentration.\(^7\) When GABA binds to its receptor, chloride channels open, which allows chloride to move outward causing depolarisation, rather than moving inward causing hyperpolarisation and inhibition, as it does in the mature brain.\(^8\)

**Mitochondrial impairment and oxidative stress**

Open NMDA channels allow calcium to enter the intracellular compartment and activate neuronal nitric oxide synthase, leading to production of the oxygen free radical nitric oxide (figure 2). Nitric oxide can form a complex with superoxide to form toxic peroxynitrite molecules that can add nitrate to tyrosine groups on proteins and contribute to the production of hydroxyl radicals, causing lipid peroxidation of proteins and DNA (figure 2). Nitric oxide can also disrupt mitochondrial respiration by impairing the function of cytochrome oxidase (complex 4) and complex 1, which increases production of superoxide and peroxynitrite ions in mitochondria, especially during hypoxia.\(^9,10\) Accumulation of lactic acid in part reflects progressive loss of mitochondrial membrane potential and mitochondrial failure, and can be measured with proton magnetic resonance spectroscopy during the progression of HIE.\(^11\) These ions can enhance the movement of the proapoptotic proteins cytochrome C and apoptosis-inducing factor (AIF) across the outer mitochondrial membrane into the cytoplasm where they trigger apoptosis through the so-called intrinsic pathway. Hagberg and colleagues\(^12\) reported that outer mitochondrial membrane permeabilisation in neonates was initiated by the proapoptotic protein Bax and regulated by the anti-apoptotic Bcl proteins (figure 2). They also noted that a Bax-inhibiting peptide reduces neonatal brain injury and functional impairment in a mouse model of HIE,\(^13\) an effect that was confirmed by Han and colleagues.\(^14\) On the one hand, in the cytoplasm, cytochrome C binds with caspases in the apoptosome to trigger activation of caspase 3 by proteolysis, and activated caspase 3 in turn can trigger apoptotic DNA fragmentation (figure 2).\(^15,16\) AIF, on the other hand, moves into the nucleus and triggers DNA fragmentation via a non-caspase-mediated mechanism that is stimulated by heightened activity of the DNA repair enzyme PARP1 (poly-ADP-ribose polymerase; figure 2).\(^17\) Calcium entering through NMDA receptors can also activate caspase 3 directly without activating neuronal nitric oxide synthase through activation of calpain.\(^18\) Caspase 3 is expressed to a much greater degree in the immature brain than in the adult brain. Similar to the developmental differences in NMDA and GABA receptors, enhanced activity of caspase 3 is another feature of the neonatal brain that makes it more vulnerable to injury. Apoptosis can also be triggered by the
Fas cell-death protein cell-surface receptor through activation of caspase 8 and then caspase 3 in the so-called extrinsic cell-death pathway (figure 2). Transgenic mice that lack Fas receptors are resistant to hypoxic-ischaemic brain injury.\(^7\)

An imbalance between increased reactive oxygen and nitrogen species (superoxide anions, singlet oxygen ions, hydroxyl radicals, and hydrogen peroxide) and marginal or low supplies of antioxidant defenses such as superoxide dismutase, glutathione peroxidase, catalase, glutathione, and vitamin C in the neonatal period make an important contribution to brain injury (figure 2).\(^8\) X-linked inhibitor of apoptosis protein has strong antioxidant capacity through its roles in upregulating superoxide dismutase 2 and thioredoxin 2 and reducing release of cytochrome C from mitochondria.\(^9,10\) Studies of genetic manipulation of antioxidant compounds in the brains of mice have shown the importance of this system in modulation of perinatal brain injury.\(^11\) Several drugs can impede oxidative stress and reduce brain injury, including NMDA receptor antagonists and neuronal nitric oxide synthase inhibitors.\(^12,13,14\) West and colleagues\(^15\) reported that antioxidant pomegranate polyphenols and resveratrol protected rat pups from hypoxia-ischaemia on postnatal day 7 when given to the dam before birth. Necrostatin 1, which inhibits receptor interacting protein (RIP-1) kinase and programmed necrosis through a caspase-independent mechanism, also inhibits non-specific oxidative damage to proteins of many molecular weights in the immature brain and provides neuroprotection in the immature mouse model of hypoxia-ischaemia.\(^16\) Melatonin has also been shown to have antioxidant and protective effects in excitotoxic models of neonatal brain injury.\(^17\)

Inflammation

Inflammation plays an important part in the excitotoxic cascade of injury in the perinatal period.\(^18\) Lipopolysaccharide has been shown to sensitise the perinatal brain to hypoxia-ischaemia and worsen injury;\(^19\) injury can be reduced by administration of the antioxidant N-acetylcysteine.\(^20\) This effect seems to depend on activation of microglia and upregulation of inflammatory mediators that are under the control of nuclear factor kappa B (NF-κB). Treatment with an inhibitor of NF-κB, after the onset of neonatal hypoxia-ischaemia, has been shown to provide substantial protection against neonatal hypoxia-ischaemia by inhibiting apoptosis.\(^21\) The mast-cell inhibitor sodium cromoglicate has also been shown to provide neuroprotection against hypoxia-ischaemia in a rodent model,\(^22\) an effect that was first discovered in an excitotoxic model of injury.\(^23\) Russell and colleagues\(^24\) showed that pentraxin 1, a member of the large pentraxin family of molecules that have complement activating and opsonic activity, mediates damage in a model of hypoxic-ischaemic perinatal brain injury; this is an example of the molecular links between damage caused by hypoxia-ischaemia and inflammation.

Delayed cell death after hypoxia-ischaemia

Histological studies and MRI show that cell death in the brain exposed to hypoxia-ischaemia is delayed over several days and continues over days to weeks after an injury because groups of cells seem to commit to die.\(^25,26\) In experimental mouse and rat models, neuropathological studies show a mixture of apoptosis and necrosis and hybrid or continuum phenotypes, depending on the region and severity of injury.\(^7,27\) Advances in cell biology and biochemistry suggest that apoptosis or autophagy mediated by programmed cell death mechanisms predominate.\(^28\) Various forms of programmed cell death make a prominent contribution to degeneration from HIE in animal models and in newborns.\(^7\) Programmed cell necrosis also contributes to the neurodegeneration seen in animal models of HIE and perhaps in newborns.\(^7\) Since the process of apoptosis requires energy, a determinant of when cells die is likely to be the ability of mitochondria to provide adequate energy. Another determinant of classic apoptosis is the loss of neuronal connections, which can continue over days to weeks after an injury because groups of cells seem to commit to die.\(^27,28\)

Sex differences in pathways to brain injury

Evidence suggests that sex is an important determinant of which cell-death pathways are activated during HIE, and it can also influence effects of neuroprotective drugs. Hagberg and colleagues\(^8\) reported that knock-out of PARP1 preferentially protected male but not female transgenic mice from hypoxic-ischaemic damage. McCullough and colleagues\(^9\) reported that in adult mice PARP1 knockout or pharmacological inhibition of PARP1 protected males from stroke damage, but worsened injury in females. Du and colleagues\(^10\) also showed that male and female rodent neurons, grown in separate cultures, differ in their activation of cell-death pathways. They reported that male neurons in culture are more sensitive to death from exposure to NMDA and nitric oxide, whereas female neurons were preferentially sensitive to caspase 3 inhibition. When exposed to stress caused by oxygen-glucose deprivation, male neurons preferentially release AIF from mitochondria into the nucleus, whereas female neurons preferentially release cytochrome C from mitochondria to activate caspase 3. In agreement with these results, experiments with AIF-deficient Harlequin mice showed that males but not females are protected from ischaemic brain injury.\(^6\) Male neurons are also more vulnerable to autophagy or autophagy/cytoskeleton trigger by starvation than are female neurons.\(^11\) The nitric oxide synthesis inhibitor 7-nitroindazole has been reported to be more protective for male than for female neurons,\(^12\) whereas the selective pan-caspase inhibitor QVD-OPh (MP Biochemicals, Illkirch,
France) protects female but not male rat pups from stroke damage.16 The neuroprotective drug 2-iminobiotin, which inhibits release of cytochrome C and activation of caspase 3, has been reported to protect female but not male 7-day-old rat pups from HIE.16 We reported that the competitive glutamate antagonist dextromethorphan is more protective against ischaemia in male than in female immature mice,18 whereas erythropoietin has been reported to be more protective in female rat pups.67,68 These differences need to be accounted for when designing trials of neuroprotective treatments. Long-term reduction in caspase 3 activity during development leads to upregulation of AIF-dependent pathways, suggesting that there is interplay between these two pathways.69 These sexually dimorphic differences in cell-death pathways might contribute to the higher incidence of cerebral palsy and stroke in boys than in girls.66,67

Selective network degeneration after HIE
MRI of the brains of babies with HIE often shows damage to selected neuronal systems rather than global injury. For example, Cowan and colleagues92 reported that babies with multiple signs of encephalopathy usually had evidence of bilateral deep basal ganglia injury, cortical injury, or both, whereas babies with seizures alone usually had focal ischaemia or haemorrhage. Term infants exposed to brief (10–30 min) but very intense hypoxia-ischaemia due to umbilical-cord compression in association with cord pH less than 7 and severe lactic acidosis often develop focal brain lesions on MRI in the peri-Rolandic cortex, ventrolateral thalamus, and posterior putamen.93–95 (figure 4). Infants with these lesions exhibit abnormalities in generalised movements at 1 month and 3 months of age.96 Children with this pattern of injury after asphyxia have also been shown to develop the clinical syndrome of extrapyramidal cerebral palsy including athetosis and dystonia with impaired motor speech and impaired use of their hands compared with their legs.97 This selective pattern of injury suggests that some specific neuronal circuits are more vulnerable to injury98,99 and has been suggested to mirror damage in areas that are relatively rich in excitatory synapses in term infants;100 this is supported by evidence that striatal injury in a newborn piglet model of near total asphyxia is mediated by NMDA-receptor activation.101 A similar systems-selective pattern of network degeneration in the hippocampus has been seen with diffusion tensor MRI in mice with hypoxic-ischaemic injury.102

Neuroprotection mediated by hypothermia
Hypothermia has been used successfully since the 1950s as a protective measure to allow babies with complex congenital heart disease to undergo circulatory arrest for corrective surgery,103 but its use in neonatological settings was impeded by data showing that it increased the death rate in premature infants.104 However, interest in this technique was renewed with the publication of data on the pathogenesis of HIE reviewed above, especially that which showed the importance of delayed secondary energy failure and the excito-oxidative cascade in neurological damage. Experiments that showed efficacy and safety in clinically relevant large animal models were especially important in bringing this technique to the clinic.

Mechanisms for hypothermic neuroprotection
Although our understanding of the mechanisms for the neuroprotective effect of hypothermia remains incomplete, experimental studies have shown that it inhibits many steps in the excito-oxidative cascade including secondary energy failure,105 increases in brain lactic acid, glutamate, and nitric oxide concentrations,106,107 and epileptic activity.108 Protective effects have also been associated with inhibition of protease and calpain activation, loss of mitochondrial membrane potential and mitochondrial failure, free radical damage, lipid peroxidation, and inflammation.109 Experiments in which the glutamate agonist NMDA was injected directly into the brains of 7-day-old rat pups to produce excitotoxic lesions showed that injury was directly proportional to temperature over a range of 25–40°C.110 This suggests that hypothermia can reduce injury triggered by NMDA-receptor activation alone without hypoxia-ischaemia. Ikonomidou and colleagues111 also showed that hypothermia enhances the protective effect of the non-competitive NMDA channel antagonist MK-801 in a model of hypoxic-ischaemic brain injury in rat pups. Brief periods of moderate hypothermia to 32°C after injury have been shown to delay cell death in 7-day-old rat pups by as much as a week, after which brain atrophy occurs.112 This result suggests that moderate hypothermia can delay programmed cell death, independent of its role in other aspects of metabolism, and might be able to extend the therapeutic window for other interventions.

Clinical trials
The publication of three randomised controlled trials of moderate hypothermia or conventional treatment for HIE in term infants, published from 2005 to 2009, is

Figure 4: T1-weighted MRI of a baby at 2 weeks of age who had undergone severe, near-total asphyxia around the time of birth.
Asphyxia was associated with a cord blood pH of 7·6 and base deficit of 25 mmol/L (calculated base deficit in standard arterial blood gases). Injured T1-enhancing areas are very focal and localised to regions of the thalamus, putamen, and peri-Rolandic cerebral cortex that contain synapses that connect the developing motor circuits.
Panel: Drugs that might augment neuroprotection by mild hypothermia

Anticonvulsant or antieexcitatory
- Phenobarbital,
- Topiramate,
- Levetiracetam,
- Memantine,
- Xenon,
- Magnesium sulphate,
- Bumetanide

Anti-inflammatory or antioxidant
- Sodium cromoglicate,
- Minocycline,
- Indometacin,
- Melatonin,
- N-acetylcysteine,
- Allopurinol,
- Pomegranate polyphenols,
- 7-nitroindazole,
- Bumetanide

Multiple mechanisms
- 2-iminobiotin,
- Necrostatin 1
- N-acetylcysteine,
- Allopurinol,
- Pomegranate polyphenols,
- 7-nitroindazole,
- Sulphate,
- Bumetanide

Growth factors
- Nerve growth factor,
- Insulin-like growth factor 1,
- Brain derived neurotrophic factor

Therapies to augment neuroprotection

In view of the definite but incomplete success of hypothermia after asphyxia for reducing disability from HIE, the hunt is on for treatments that might augment neuroprotection (panel). Phenobarbital and the AMPA-receptor antagonist topiramate are used commonly for seizures in neonates and have good safety profiles. Experimental evidence suggests that xenon might exert a protective effect against HIE brain injury in neonatal rodent models, acting through anti-inflammatory, antioxidative, antiapoptotic, and neurotrophic mechanisms, and stimulation of neurogenesis. This is consistent with the probable role of erythropoietin in protection by hypoxic preconditioning, which upregulates genes in the PI3K/AKT pathway in 7-day-old rat pups; two studies of term infants with HIE have shown promising results. These drugs and growth factors could enhance neuroprotection when combined with hypothermia, and warrant further investigation (panel).
In addition to small molecule drugs and growth factors, cell-based treatment has been discussed as a potential therapy for HIE and could also be used with hypothermia.10,11 Animal studies support the idea that cord blood and mesenchymal stem cells, cell types that are available in a clinical setting, have a neuroprotective effect in neonatal HIE.20 These effects have been attributed to immunomodulation, activation of endogenous stem cells, release of growth factors, and antiapoptosis mechanisms.20 Only one registered clinical study in the USA is investigating the role of autologous cord-blood transplantation in HIE.15 This trial administers moderate cooling plus cord-blood cells to term infants with HIE at less than 6 h of age, and cord blood alone to infants with HIE between 6 h and 24 h of age.

Conclusions
Over the past decade, substantial progress has been made in neuroprotection and neurointensive care for neonates. Decades of clinical and basic science research into the pathogenesis of HIE in term infants have been translated into the use of moderate hypothermia for infants with mild or moderate HIE, and much evidence shows that this therapy substantially, although incompletely, reduces neurological disability. This therapy is increasingly being given to babies in special neurointensive care nursery units where they can be monitored with continuous electrophysiological monitoring such as aEEG. More research will be needed to follow-up children treated in this way to determine whether benefits identified at 18 months are maintained into childhood, and whether any harmful effects emerge. Follow-up electrophysiological data also need to be collected to improve understanding of associations between seizures, treatment, and outcome.

Other issues that deserve attention are the optimum timing of initiation and duration of hypothermia and rewarming and whether this technique is useful for other disorders such as perinatal stroke or status epilepticus. Effects of hypothermia on the metabolism and action of other drugs being given in combination with hypothermia also need further investigation. Because the neuroprotective effects of hypothermia for HIE are not fully understood, further research is needed to find adjuvant treatments that are compatible with hypothermia; this will require more basic science research focusing on the mechanisms of injury, especially those associated with mitochondrial failure, inflammation, and genetic mechanisms. Mitochondrial failure seems to be the key to survival for many cells in the brain, and treatments that target the mitochondria might be especially useful. Inflammation enhances the effects of HIE, and anti-inflammatory drugs might turn out to be neuroprotective in human infants. Cell-based treatments are also being explored in preclinical models, and they might act in part by modulating inflammation. Genetic differences are likely to play a part in the variable effects of HIE on infants, and clear differences in cell-death pathways have been established between male and female rodents. Sex should be accounted for when designing and testing new treatments, because preclinical testing shows that treatments might be protective in one sex but ineffective in the other.

Contributors
MVJ did the search of published works, prepared figures, and revised the Review. AF wrote, reviewed, edited, and revised the Review. MAW did research, contributed data, prepared figures, and reviewed the manuscript. FN contributed to the search of published works, writing, revisions, and preparation of the figures.

Conflicts of interest
AF has received consultancy fees from Acorda Therapeutics, Inc. MVJ, MAW, and FN declare that they have no conflicts of interest.

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