Section 1 Scientific background

Chapter 1

Neurological outcome after perinatal asphyxia at term

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Introduction

It was nearly 150 years ago that an association between perinatal events and brain injury was first reported, claiming that "the act of birth does occasionally imprint upon the nervous and muscular systems of the infantile organism very serious and peculiar evils" [1]. While a great deal is now known about this association and the pathophysiology behind it, the quantification of these "evils" is still uncertain. While the World Health Organisation estimates that 25% of neonatal and 8% of all deaths under 5 years in low-income countries are due to birth asphyxia [2], there remains no agreed definition; therefore, the reported prevalence varies. Consequently, the number of infants exposed is unknown, although approximately 7% of term infants require resuscitation after birth [3]. It is well recognized that only a small proportion of these infants will go on to develop neurological signs in the neonatal period and an estimated 2 per 1000 births in the developed world [4] will develop neonatal encephalopathy.

While encephalopathy is, therefore, relatively uncommon, the outcome can be devastating to the infant and family and it remains a major cause of death and long-term disability with a substantial burden on the community as a whole. It is estimated that each infant with complex neurological sequelae will cost the state over 1 million US dollars (800,000 Euros) in health care, social support and lost productivity throughout their lifetime [5]. In addition, unmeasured impacts on behaviour, school failure and psychiatric disease are likely all to have additive effects. As well as the direct costs, other population impacts are also likely. Increasingly literature suggests a causal link between IQ and lifespan [6] and the true cost to society of perinatal asphyxia is likely to be extensive.

Perinatal asphyxia and hypoxic–ischaemic encephalopathy

Central to any discussion on perinatal asphyxia is the distinction between perinatal asphyxia, which refers to poor condition at birth, and hypoxic–ischaemic encephalopathy, which refers to acute brain dysfunction following critical lack of oxygen. The first does not automatically lead to the second and while the International Classification of Disease (10th revision) includes a diagnosis of "birth asphyxia", there is little agreement on how the diagnosis should be made [7]. Indeed, perhaps due to the difficulty in determining the timing of an asphyxial event, the phrase "perinatal asphyxia" is often used as a more general term [8].

Measures of perinatal asphyxia

The concept of perinatal asphyxia is a critical lack of oxygen delivery during labour and/or delivery which is sufficiently severe to produce objectively measurable functional de-compensation. It is important to recognize that some degree of hypoxia–ischaemia occurs during normal labour. Every time the uterus contracts, the arteries bringing oxygen to the placental bed and so to the fetus, are constricted. The fetus can tolerate these short periods of hypoxia as they tend to be brief (e.g., less than a minute) and are followed by a longer period of uterine relaxation during which oxygen delivery is resumed. Furthermore, the fetus can tolerate brief periods of hypoxia by switching energy production to anaerobic glycolysis. This production of lactic acid and subsequent acidaemia while indicating hypoxia do not immediately indicate there is energy failure at a cellular level. Indeed, the level of physiological compromise believed to represent a pathological state remains unclear and there is no agreed "gold standard" measure for the diagnosis of perinatal asphyxia.

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Table 1.1. Individual components of the Apgar score

Component	Score		
	0	1	2
Heart rate (pulse)*	No pulse felt	Less than 100	Greater than 100
Respiratory effort	Apnoea	Irregular, shallow ventilation	Breathing/crying
Reflex irritability (grimace)*	No response to stimulation	Grimace/feeble cry when stimulated	Sneeze/cough/pulls away when stimulated
Muscle tone (activity)*	Flaccid	Good tone	Spontaneous movement
Colour (appearance)*	Blue/white	Partially pink	Entirely pink

*The Apgar mnemonic introduced as a teaching tool in 1963 by Dr Joseph Butterfield.

Despite the lack of a valid and reliable test, a pragmatic definition of perinatal asphyxia is required in the assessment of causes and outcomes and in the trial of novel therapies. To diagnose perinatal asphyxia, several indicators are used. Impaired physiology is often documented by the Apgar score and abnormal biochemistry by acid–base measures in neonatal blood while others have used the presence of antenatal risk factors, meconium stained liquor, or the need for resuscitation. These measures are sometimes used individually, but more commonly are combined into a more complex diagnostic criterion. The recent trials of therapeutic hypothermia [9–11] all used a range of criteria to define infants with encephalopathy following perinatal asphyxia.

Acidosis

Acidaemia is one of the most commonly used diagnostic measures of perinatal asphyxia: measured in blood from the scalp capillary beds, the umbilical vessels of the infant immediately after birth, or blood taken within a few minutes of birth. While acidaemia can result from CO_2 retention it is perhaps lactic acidosis, as indicated by base deficit, that represents more unambiguous evidence of hypoxia. Opinion concerning the level at which acidosis is considered pathological varies, although severe acidosis is often defined as a pH of less than 7 or a base deficit $\geq$ 16 mEq/L [12] in the umbilical cord blood. Around 2.5% of infants have a low pH (by these criteria) at delivery [12] and this finding underlines the point that brief periods of anaerobic metabolism can still support vital organs.

The Apgar score and birth condition

Despite advocates for the use of pH as the "best" measure of perinatal hypoxia, the most commonly used measure of birth condition remains the Apgar score and consequently it is often used in studies of perinatal asphyxia (Table 1.1). Proposed in 1953 by Virginia Apgar, it was suggested that a combined score to assess the status of newborn infants in the first few minutes of life would provide "clear classification or "grading" of newborn infants which can be used as a basis for discussion and comparison of the results of obstetric practices, types of maternal pain relief and the effects of resuscitation" [13]. While other scores have been suggested since [14], none have been widely accepted.

While it provides an ordinal measure of the clinical status of the infant, little agreement exists as to what a "low" or "normal" score should be. Like measures of acidosis, many studies have proposed a "cut-off" value (and specified the time at which the infant should have achieved it) to identify infants likely to have been exposed to perinatal asphyxia. There is currently little evidence in the literature on which to base these judgements and little consensus on what a "low" or "normal" score should be, or what a particular score suggests for an individual infant. The American Academy of Pediatrics suggest that a score of 7 or above should be considered a normal value, with a score of 3 or below severely low [15]. Virginia Apgar suggested 8 or above as an appropriate "normal" score [16], while others have suggested a cut-off value of 6 [7]. The number of infants with low Apgar scores, therefore, differs

Table 1.2. The Sarnat grading of encephalopathy

Measure	Sarnat grade		
	1	2	3
Conscious level	Hyperalert	Lethargic	Stupor
Muscle tone	Normal	Hypotonic	Profound hypotonia
Posture	Mild distal flexion	Strong distal flexion	Decerebrate
Stretch reflexes	Normal	Overactive	Overactive
Moro reflex	Strong	Incomplete	Absent
Suck reflex	Normal	Weak	Absent
Tonic neck reflex	Slight	Strong	Absent
Pupils	Dilated	Constricted	Poorly reactive
Gut motility	Normal	Increased	Variable
Seizures	Uncommon	Focal or multifocal	Generalized

between studies, although one large population study reported a prevalence of 0.70% [17] for a 5-minute score below 7. In view of the variability in consistently defining a low Apgar score, the need for resuscitation may be considered a "gestalt" indicator that, in the view of the clinician on the spot, the infant had not established regular breathing, circulation and activity.

Not surprisingly, these measures are closely correlated, with coefficients between pH and the Apgar score reported as 0.3–0.4 [18,19], while sensitivity (0.40 vs. 0.48) and specificity (0.88 vs. 0.96) were similar for both a low pH and Apgar score in predicting neonatal morbidity (defined as needing admission to a neonatal unit) [19]. Interestingly this has led to clinicians calling for both the Apgar score [20] and umbilical pH measurements [19] to be discontinued in favour of the other measure.

Diagnosis of hypoxic–ischaemic encephalopathy

Irrespective of the definition used, only a proportion of infants exposed to perinatal asphyxia will develop signs of neurological impairment in the newborn period and be diagnosed as having hypoxic–ischaemic encephalopathy (HIE). It is this group of infants in which most of the evidence of long-term outcomes exists. These infants are commonly described using a three-point grading system of mild, moderate and severe encephalopathy. First proposed by Sarnat and Sarnat in 1976 [21] (Table 1.2), the grading system has since been modified and while different interpretations of it are used, it remains a common classification in the literature. A particular strength of Sarnat's system is that it combines clinical examination with electroencephalogram (EEG) and in recent years the value of continuous amplitude-integrated EEG (aEEG) has been well demonstrated to document the depth of brain dysfunction and its change over hours and days [22]. However, while this ordinal grading is extensively used, the clinical picture of hypoxic–ischaemic encephalopathy seen is often complex and the underlying pattern of cerebral damage likely to be just as complex. The pioneering work of Myers in the pregnant monkey has, for example, shown that acute total asphyxia produced by cord clamping tends to injure the basal ganglia, thalamus and brain stem while prolonged partial asphyxia produced by high-dose halothane to the mother over hours tended to produce watershed injury in the frontal and occipital cortex and sub-cortex [23].

Long-term outcome after perinatal asphyxia

The neurological outcome of infants who are exposed to perinatal asphyxia has important impacts on

the population as a whole, guides discussion with parents and influences the immediate neonatal management. It is also critical to the assessment of new therapies. While the literature for perinatal asphyxia is extensive (a PubMed MeSH search for "asphyxia neonatorum" returns over 6,000 results), the data on long-term, pragmatic outcomes are surprisingly scarce and heterogeneous in nature. Studies are often small and have limited power to identify modest, but important effects. Indeed, while there is overwhelming evidence for an association between perinatal asphyxia and death, cerebral palsy (CP) or impaired cognition, the quantification and prediction of these outcomes is complex and several questions remain difficult to answer.

Many studies concentrate on the outcome of infants with moderate or severe HIE, but even here the outcomes are often restricted to short-term follow-up. While appropriate for objective and persistent measures of outcome such as mortality or CP, long-term impairments in cognition or behaviour and in particular pragmatic measures of function are less well reported. Data from work involving preterm infants suggest that the burden of neuropathological disabilities may increase as the child gets older (and is expected to perform more complex cognitive processes) and that even certain diagnoses believed to be robustly identified during infancy, such as CP, may alter in prevalence over time [24]. A further caveat of these studies remains: these studies can only show association and not causation. While less of a concern for major (and otherwise rare) outcomes such as death or CP, subtle deficits in IQ are socially patterned, as is the risk of perinatal asphyxia [25]. The possibility of residual or uncontrolled confounding is likely and may result in distorting the apparent strength of any associations found. Bias may also be a concern and even in studies where follow-up is complete (minimizing selection bias), the initial cohort may not represent the population as a whole: an increasing concern in randomized control trials.

However, infants with evidence of a substantial perinatal asphyxia insult represent a group of infants in whom substantial risks for poor outcomes exist and consequently the outcome of infants with moderate or severe HIE is considered separately to the larger population of infants likely exposed to milder levels of perinatal asphyxia.

Outcome of infants with moderate or severe HIE

Mortality

Many infants who develop moderate or severe HIE are likely to die in the neonatal period and this is well reported in the recent randomized controlled trials (RCT) of therapeutic hypothermia [9–11]. These infants (enrolled between 1999 and 2006) represent a group of term infants who received intensive care support after a perinatal asphyxial insult sufficient to produce moderate or severe encephalopathy. While entry criteria differed between the studies, all recruited infants with some evidence of perinatal asphyxia who then developed clinical and, in two trials, electroencephalopathic evidence, of encephalopathy. Mortality was, not surprisingly, substantial, with between 27% [9] and 38% [11] of the infants in the control groups dying before 18 months of age. A composite estimate from the three studies suggested the pooled mortality would be 33%. It should be noted that a major cause of mortality is likely to be active withdrawal of care in infants believed to have poor neurological outcomes: dependent on the clinicians' perception of the probable outcome and potentially reinforcing certain prognostic factors. The long-term mortality is likely to be higher than these estimates and data from Finland suggest that a further 2% of infants with encephalopathy who survive the neonatal period may die before their 14th birthday [26].

Cerebral palsy

Next to neonatal death, cerebral palsy is arguably the most recognized consequence of perinatal asphyxia and while specifically a defect of motor development, it remains a strong risk factor for the development of deficits in cognitive functioning later in life [27]. The most common pattern of CP in infants with HIE remains dyskinetic or spastic quadriplegia [4] (consistent with basal ganglia damage) and the recent RCTs have reported rates of CP in survivors (at 18 months) between 30% [11] and 41% [9]. A pooled estimate from all three control groups would suggest that 35% of survivors have identifiable CP at 2 years of age, although the proportion after moderate HIE is likely to be lower than after severe disease (e.g., 28% vs. 43% [10]).

Cognitive Impairment

Cognitive impairment has also been well established as a consequence of perinatal asphyxia but the quantification of any impact remains elusive. Again, perhaps the most rigorously followed up group of infants in recent years is the infants enrolled in trials of neuroprotective hypothermia. At 18 months of age, the recent RCTs suggested rates of poor cognition (Bayley Mental Development Index < 70) were around 36% of survivors in the control groups.

However, longer term measures of IQ are likely to be more important and only a handful of studies have successfully measured cognition beyond 2 years of age. Many of these studies were able to report only on a small number of infants, while the inclusion criteria, length of follow-up and outcomes measured and reported differ between studies. While some have reported outcomes compared to a contemporaneous group of "control" infants, others have no such group, or compare to established "normal ranges" [27,28]. Overall, there is strong evidence that infants who survive encephalopathy have lower IQ scores than their peers. In one population-based study, infants with all grades of HIE had an IQ deficit of approximately 10 points compared with a control group of infants with no evidence of perinatal compromise [3]. Which infants are at risk of developing cognitive impairment is still debated and some have suggested that only those infants in whom the perinatal event was substantial enough to cause noticeable cerebral palsy [15] are at risk, although there is a growing body of evidence suggesting otherwise [29,30]. A consequence of this debate is that many recent studies report only the cognitive outcome of infants who otherwise appear to have escaped a substantial movement disorder, leaving it difficult to apply the data to an infant in the neonatal period before it is known if they are destined to develop CP or not.

In general, the IQ of infants with severe HIE is likely to be lower than their peers, although Marlow (who recruited infants with any encephalopathy in the first 7 days and not just HIE infants) estimated the mean score to be as high as 103 in survivors without CP [30]. In contrast, the IQ score of survivors with CP after severe HIE was estimated as only 48 by Robertson at 8 years of age [31]. Infants with moderate HIE (again, without obvious CP) have been reported to have mean IQ scores either similar to their peers (Marlow *et al*: 112 vs. 114, $P = 0.57$ [30]) or slightly lower (Robertson *et al*: 102 vs. 112, $P < 0.001$ [31], Viggedal *el al*: 106 vs. 116 [32]). Van Handel reported a low mean IQ of 87 (SD 22) in infants who survived moderate HIE without developing severe motor, sensory or developmental delay [33].

Papers that have combined the outcome of all infants with mild, moderate or severe HIE have also reported evidence for lower IQ measures, but again the difference between studies makes conclusions difficult (Table 1.3). Some studies have preferred to report the risk of developing a low IQ score rather than assuming that there is a shift in the population mean. The "cut-off" points used to define a low (and perhaps importantly low) score differ, but below 70 (2 standard deviations [SD] from the mean) is commonly reported. Robertson reported the risk of a low score (≤70) at the age of 5 years as increasing from 1.8% in infants with mild encephalopathy through to 83% in infants with severe disease [27], although peer comparison data were not presented.

While childhood IQ is strongly associated with longer term cognitive measures, it also tends to be more influenced by social and environmental factors than adult-age measures of cognition which should perhaps be considered the gold-standard. Not surprisingly, these are rarely measured, although Lindstrom *et al* have reported that the majority (71%) of infants with moderate neonatal encephalopathy who do not develop CP have some degree of cognitive impairment as teenagers [29].

Differential cognitive impairment

IQ, while a reliable measure of cognition, fails to tell the whole story and if survivors of HIE do develop cognitive impairment, is it global or are specific domains, perhaps associated with high-risk areas of the brain known to be at risk of perinatal asphyxia, selectively damaged? Interpretation of the data is complicated as the localization of specific brain functions to specific anatomic areas is often difficult. Working memory in children has been shown to be more localized in the caudate nucleus and anterior insula than in the dorsolateral prefrontal cortex as in adults [34], while comprehension has not been consistently localized to one area [35,36] and any study looking at specific function would have to consider the possibilities that different profiles of ischaemic damage are likely to involve different areas of the newborn brain [23].

Table 1.3. IQ beyond 2 years of age

Paper	Category of HIE	Age at outcome (years)	Measure	HIE infants		Control infants		Evidence for difference (reported *P* values)
				n	IQ	n	IQ	
Barnett [53]	Mild, moderate or severe without CP	5–6	WPPSI	53	102 (16)	–	–	–
Marlow [30]	Moderate without motor disability Severe without motor disability	7	BAS-II	32 18	112 (11) 103 (13)	49 49	114 (14)	0.57 <0.01
Odd [3]	Mild, moderate or severe (CP included)	8	WISC-III	26	95 (20)	5461	105 (16)	0.007
Robertson [31]	Mild Moderate (all) Moderate (non-impaired) Moderate (impaired) Severe	8	WISC-R	56 84 66 18 5	106 (13) 95 (23) 102 (17) 68 (27) 48 (21)	155 155 155 155 155	112 (13)	>0.05 <0.001 <0.001 <0.001 –
Van Handel [33]	Mild (without severe motor, sensory or developmental delay) Moderate (without severe motor, sensory or developmental delay)	9–10	WISC-III	33 47	98 (12) 86 (22)	46	109 (12)	<0.001
George [28]	Mild Moderate or severe	12	MISIC	41 5	87 (14) 72 (11)	– –	– –	– –
Viggedal [32]	Mild (without known neuro-developmental disability) Moderate (without known neuro-developmental disability)	25	WAIS-R	20 11	107 (IQR 96–116) 106 (IQR 100–113)	18 18	116 (IQR 105–132)	>0.05 >0.05

WPPSI, Wechsler Preschool and Primary Scale of Intelligence; BAS, British Ability Scales; MISIC, Malin's Intelligence Scale for Indian Children; WISC, Wechsler Intelligence Scale for Children; WAIS, Wechsler Adult Intelligence Scale.

However, certain studies have reported differential effects of perinatal asphyxia on cognitive domains. There are data to suggest that watershed brain injury (likely caused by more chronic, partial hypoxic insults) may selectively affect verbal skills [37]. Steinman [37] reports the outcome of 81 term infants with HIE and suggested that evidence of damage in the watershed areas is associated with lower verbal IQ scores in infants at 4 years of age (independent of basal ganglia injury). Small studies have also suggested that the cognitive impairment from more acute asphyxial insults may result in part from selective memory deficits, with hippocampal injury a recognized consequence of HIE [38]. Consistent with this, Marlow *et al* [30] followed up 65 infants with encephalopathy to 7 years and reported increased risks of attention and memory problems [30] although the effect size seen was relatively modest for those with moderate HIE (approx. 0.5 SD) and more pronounced in those after severe HIE (around 1 SD). Lindstrom *et al* have also reported that infants suffering neonatal encephalopathy had a much higher risk of problems with short-term memory (64% vs. 13%, $P < 0.002$) at age 15–19 years. However, other studies have found little evidence of any differential effect, with data suggesting more global impairment of function [3,28,39].

Visual and hearing impairment

As well as movement and cognitive function, critical neuronal pathways involved in vision and hearing are also affected by perinatal asphyxia. Survivors of moderate or severe HIE also have reportedly higher rates of sensori-neuronal hearing loss, with rates in recent trials suggesting prevalence at 18 months is around 6% [9–11]. These same studies suggest a prevalence of visual impairments of around 13% [9–11]. The long-term visual and hearing disability impact is not clear, although increased risks of more subtle dysfunction, such as myopia and strabismus, have been reported [40].

Epilepsy and other neurological disorders

While neonatal seizures are common in infants with moderate or severe HIE (indeed for some diagnostic groups they are required), the development of epilepsy in childhood occurs less frequently. At 18 months, the prevalence of seizure disorders is likely to be around 15% [9–11], although longer term prevalence and severity of seizures are less clearly defined. At 3.5 years, 7% of moderate or severe HIE survivors had developed poorly controlled epilepsy, having daily or weekly seizures [41]. However, a Norwegian study suggested that infants who had low (0–3 at 5 minutes) Apgar scores and then developed neurological signs in the neonatal period had only a 5% chance of a diagnosis of epilepsy by the time they were 8–13 years old [40].

In addition to the risks of epilepsy, other neurological disorders may also be more common in survivors of HIE. Work has suggested that the prevalence of autistic spectrum disorder is around 4% in survivors of moderate/severe encephalopathy compared with less than 1% in the control group [42]. Others have reported that non-disabled survivors of HIE scored higher in measures of hyperactivity than controls [27,33], although this has not been found in all studies [29]. Interestingly even if measures of attention or hyperactivity are worse, it remains unclear if the rates of attention deficit hyperactivity disorder (ADHD) itself are higher. Some studies have suggested an increased risk [40], while others (who reported worse scores in several measures of social function and attention) found little evidence for increased risk of defined neuro-psychiatric disorders (including ADHD) [33].

Other less well defined psychiatric disorders may also be more common in the survivors of HIE and more general behavioural problems have also been reported. Van Handel reported poorer functioning in measures of anxiety/depression as well as social problems in survivors of moderate encephalopathy [33], while George *et al* reported that there were behavioural problems in 15% of infants who had had mild HIE and 57% of those who survived moderate or severe HIE although no peer comparison group was assessed [28].

If these associations truly exist, it seems entirely reasonable that these other neuro-psychiatric problems are directly caused by an asphyxial insult to the developing cerebrum. However, they are also all more common in infants with learning difficulties and so these associations (while real) may simply be dependent on the cognitive problems already described above.

Educational performance

Given the raft of potential neurological impairments that may develop in infants who survive encephalopathy, perhaps a better functional measure of neurophysiological outcomes is that of school performance. Likely to be dependent on cognitive, movement, and sensory functions and behaviour, it is not surprising that educational failure is common in survivors of

HIE. Robertson *et al* reported on the school performance of survivors of neonatal encephalopathy at age 8. They reported that all infants with severe HIE were receiving additional educational support (compared to 20% in their peer group) and all were functioning at least 1 grade below that which they were expected to [31]. The effect on survivors of moderate encephalopathy was less severe, but still 38% were receiving additional help and there was a substantial chance of performing worse than their peers: more noticeable in infants with motor disability. Marlow reported on several educational measures and suggests again that even non-disabled survivors of encephalopathy have worse performance at several school measures and that this increases as the degree of encephalopathy worsens [30].

In the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort based in the United Kingdom, infants who had moderate or severe HIE were 6 times more likely than controls to need support at school [43].

Composite and social outcomes

While mean differences in summary IQ values (for example) are important for objective assessment of outcome and new therapies, all too often after the birth and resuscitation of an infant who develops HIE, the question that parents ask is "Will my baby be normal"? As discussed above, it is likely that infants with moderate or severe HIE who survive will have some degree of cognitive impairment and increased risk of CP. Several other pathologies appear to be more common in these infants, many of which are poorly quantified as yet, while new burdens may develop as the infant develops into adulthood. However, these outcomes are likely to be inter-dependent; i.e., it is those infants with CP, low IQ and epilepsy that will need support at school and a proportion of infants is likely to have a "normal" life.

To this end, many studies report pragmatic outcomes such as "death or disability". Definitions vary, but in short-term follow-up (e.g., preschool) this definition often includes death, severe low IQ (<70 points), CP or severe visual or hearing impairment. Overall (and dependent on definitions), the risk of a poor outcome tends to be reported between 53% [9] and 66% [11]. These more recent values are higher than some others reported. Badawi *et al* suggested (using similar criteria) that 39% of infants had a poor outcome in early childhood (compared with 2.7% of control subjects) [39].

Longer term outcomes than these are, again, less commonly reported. Marlow *et al* [30] reported outcome on 65 infants who had encephalopathy of any type in the first week and suggested that 6% of infants with moderate encephalopathy and 42% with severe encephalopathy had evidence of major disability at 7 years of age. A large population study in Finland followed over 12,000 infants born in 1966 [26] and using a composite measure of probable perinatal asphyxia and encephalopathy, it was estimated that 20% of 14-year-old survivors had an IQ of less than 71, CP or epilepsy.

Perhaps the most pragmatic measure of outcome is that of social functioning: a complex process and dependent on multiple competencies. While it seems likely that many infants with severe encephalopathy will (if they survive) have cognitive or movement deficits that will have a functional impact on social and educational performance, the outcome of infants with moderate encephalopathy is less clear. Despite increased risks of disability and uncertainty over long-term problems (and in particular disabling neuro-psychiatric disease) many of these infants are likely to have normal range IQ and school and social performance and this proportion is likely to improve with the advent of novel therapies.

However, quantification of these measures is difficult, although the few studies that have reported measures of social performance suggest (not surprisingly) that important levels of functional deficits exist. Lindstrom *et al* have reported that following neonatal encephalopathy 36% of infants had problems interacting with peers [29] compared with none of the controls ($P < 0.01$). Kjellmer *et al* [44] reported that infants with moderate encephalopathy were more likely to be living with parents (44% vs. 17%) and be unemployed (19% vs. 7%) than their peers in adult life, although the study was based on small numbers and the results correspondingly imprecise. In a study using the Swedish birth registry, survivors of HIE appeared to be less likely to have attended university (32% vs. 43%), to be earning money (71% vs. 89%) and to be employed (62% vs. 86%) and more likely to be living with their parents in early adulthood (23% vs. 11%) [48]. However, of note, a third of infants who survived encephalopathy did attend university, while over half were in employment.

Outcome of mild or clinically silent neurological damage

The continuum of reproductive casualty

While some imprecision remains about the likely outcome of moderate or severe encephalopathy, very few data exist on the outcome of infants with mild or clinically silent perinatal asphyxia. While any long-term effects of perinatal asphyxia are likely to be less pronounced (if they exist at all), these infants represent a much larger proportion of infants than those with moderate or severe encephalopathy (and hence they may have an important population impact). The pathophysiological threshold needed to produce persistent, functional, neurological deficits is unknown. Indeed, it may be that no threshold exists at all. In 1862, Little suggested that "the greater or smaller the impairment of intellect may safely be attributed to the greater or less mischief inflicted upon the cerebrum" [1]. The concept has been referred to in the literature repeatedly and in 1956 Pasamanick *et al.* more formally postulated that a "continuum of reproductive casualty" existed [45]; such that while profound perinatal events cause death or obvious neurological deficit, milder insults may cause subtle defects in functioning only detectable as the child grows older. However, a robust test of this hypothesis has proved difficult to carry out and surprisingly few data have been produced to either refute or support the theory, although it is widely reported that clinically important brain damage leading to learning disability can only occur if the asphyxial insult around birth is significant enough to produce moderate or severe encephalopathy in the neonatal period [8,15].

Specific studies of mildly asphyxiated infants

While much of the published outcome data have reported on infants with moderate or severe HIE, some work exists on the outcome of infants believed to have developed only mild encephalopathy. In Robertson's papers, infants with mild HIE had outcomes similar to their peers [27,31]. Similar findings have been presented by others [32], although a brief report from India reported a mean IQ score of 87 at 12 years of age in infants who developed mild HIE [28], but did not recruit any comparison group. Van Handel recently reported reduced IQ scores compared with a peer group in children at 10 years who had developed mild HIE after birth (98 vs. 109) [33]. However, numbers of infants in these studies have been small and any effect of mild (or clinically silent HIE) is likely to be only modest.

Few papers have attempted to assess the outcome of infants who after an episode of perinatal asphyxia do not go on to develop any obvious signs of neurological impairment. While some have found little evidence of an association [46], there is often limited power/precision to identify a small association, which due to the much larger number of infants exposed may still be of importance.

Two recent papers have reported data from large population based studies capable of excluding infants who develop neurological signs and have specifically reported the outcomes of infants in poor condition at birth who did not develop noticeable encephalopathy. In one, infants born in the 1970s with low Apgar scores (<7 at 5 minutes) but no history of neonatal pathology were investigated using an IQ test administered during military conscription (at age 18 years) [25]. There appeared to be an increase in the risk of a low score (less than 80) when compared to those in good condition at birth (odds ratio [OR], 1.35 (1.07 to 1.69)). In another paper based on the ALSPAC cohort study, infants found to have needed resuscitation at birth (but who did not develop encephalopathy symptoms) were found to have higher risk of a low IQ score (<80) than a group of non-resuscitated peers (OR, 1.65 (1.13 to 2.43)) [3].

As with infants with encephalopathy, less information is available on the long-term educational and social outcomes of infants likely exposed to mild degrees of perinatal asphyxia. Medniek *et al* [47] reported the outcome of 24 infants who had transient (< 8 days) neonatal symptoms. When compared to matched controls, they had similar IQ measures, but had lower scores in a measure of social maturity ($P < 0.05$). Van Handel reported worse scores in measures of behaviour at age 10 compared to peers in infants who survived mild HIE, although no obvious increase in psychiatric diagnoses (including ADHD) [33]. Finally, in a study using the Swedish birth registry, infants born in poor condition without neurological symptoms appeared to be less likely to have attended university (39% vs. 43%) or be earning an income (87% vs. 89%) than a control group in early adulthood [48].

Other evidence of poor outcomes

As well as being analysed for the more commonly measured outcomes, some large linkage studies have been used to provide additional evidence for an impact

of perinatal asphyxia on other long-term morbidities. These papers tend to investigate the association between a measure of perinatal asphyxia (often the Apgar score) and a variety of outcome measures. While the lack of neonatal clinical data does restrict the interpretation of any potential causal pathway, it does provide supportive evidence for other effects. Studies using techniques such as these have reported increased risks of psychiatric symptoms [49] and schizophrenia [50] for infants born with signs of perinatal asphyxia. While the size of these studies often makes the associations unlikely to be due to chance, the possibility of important residual confounding limits interpretation. Whether these infants have increased risks of mental health issues, what that increased risk is and if this is in addition to that expected from the cognitive impacts of HIE still needs to be clarified.

Predictors of outcomes

If the data reviewed above allow broad conclusions to be drawn about the overall effects of perinatal asphyxia, the prediction of outcome for the individual infant is far more problematic. Over the years, several clinical predictors have been proposed and while many factors (including the Apgar score) are strongly associated with outcome, their predictive value is often too poor to be of clinical use. While the intensity and duration of the asphyxial insult is likely to be an important predictor of outcome, the extent of neuronal damage is also dependent on other (mostly unmeasured, or unmeasurable) factors as well: polymorphisms in certain candidate genes have been implicated, while concomitant clinical conditions such as infection, pyrexia and inflammation may also increase the risk of permanent neurological injury in the presence of similar asphyxial insults. Despite these and other limitations, prediction of outcome remains important in clinical practice to guide management, provide advice to parents and in targeting of novel therapies. In common with the studies reporting outcome discussed earlier in the chapter, many studies considered below are relatively small and so imprecision is a concern: confidence intervals around the point estimates are rarely presented for measures of sensitivity or specificity, while the development of the predictors is often performed using short-term outcomes and they are often not validated in an independent population.

There is also the possibility that measures derived early in the neonatal course (e.g., in the first 24 hours) may become self-fulfilling while recent changes in the treatment of HIE may alter the predictive value by differentially affecting the marker over the outcome. This is a particular concern when looking at the clinical grade of HIE where the clinical grade of encephalopathy is unlikely to be affected by therapeutic hypothermia or other novel treatments despite potentially improving outcomes.

Encephalopathy grade, clinical examination and biochemical measures

The development and severity of the encephalopathy is perhaps the most commonly used predictor of long-term outcome and consequently many of the outcome data listed above have been presented with this in mind. Infants with mild (or indeed no) measurable encephalopathy are likely to have similar rates of CP and death to the general population [46,51] although the potential impact on other measures is discussed above. Infants with moderate HIE have a substantial risk of death, CP and cognitive impairment. However, even infants within this clinical category have varied outcomes: the risk of a composite "poor" outcome at 18 months was reported as 66% in a recent RCT [9]. The overall outcome of infants with severe disease is often considered more certain, with earlier studies reporting death or impairment in all infants [31]. However, it appears that even in infants with severe disease outcome may be variable; one recent RCT reported a composite poor outcome of only 2% higher than the moderate group (68% [9]) and Badawi suggested only 62% of surviving infants with severe encephalopathy had a poor outcome at 2 years (compared with 25% with moderate disease (and 2.1% of controls)) [52]. In one paper assessing the variance in outcome in a cohort of infants with mild to severe HIE, grade of encephalopathy accounted for less than 20% of the variance seen in reading skills (in comparison with maternal social-demographic measures which accounted for over 30% [31]).

In addition to the encephalopathy severity, changes in neurological signs over time also have important prognostic significance. Sarnat and Sarnat in their original study found that encephalopathic infants who normalized by 5 days did not go on to develop cerebral palsy [21]. One study looked at neurological status at discharge and found good correlation ($r = 0.65$) with neuro-developmental outcome at 24 months (sensitivity 77% and specificity 83%) [53], while infants taking longer than 7 days to establish