CONSEQUENCES OF BIRTH ASPHYXIA

Submitted for the degree of Doctor of Philosophy,

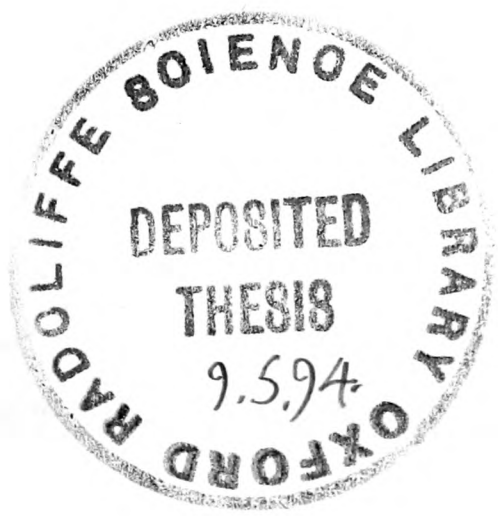
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ABSTRACT

To investigate the relationship between birth asphyxia and neurological impairment a cohort of 184 infants with a low (≤ 3) one-minute Apgar score was studied. All were singletons, apparently normally formed, and born at term (≥ 37 weeks' gestation) in the John Radcliffe Hospital, between January 1984 and September 1985.

The 181 cohort survivors were traced at the age of five years; 159 were assessed by a paediatrician on a battery of neurodevelopmental tests, and information about a further eight was obtained from other sources.

Three infants in the cohort died neonatally with a diagnosis of birth asphyxia, and three had spastic quadriplegia, profound developmental delay and visual impairment. Examination of the perinatal histories of these six children, including their fetal heart rate patterns in labour and acid-base status at delivery, found convincing evidence of birth asphyxia. Only one other child in the cohort exhibited similar signs of birth asphyxia; he was unimpaired at the age of five.

To assess the impact of birth asphyxia on the overall rate of cerebral palsy, all cases of cerebral palsy born to Oxford residents in the study period were identified. Of 30 cases of cerebral palsy, the three identified in the follow-up study were the only ones whose impairment could be attributed to birth asphyxia in a full-term birth. Birth asphyxia therefore accounted for 10% of all cases of cerebral palsy, a fraction that agrees with previous estimates. The frequency of cerebral palsy due to birth asphyxia was estimated as 1 in 3800 full-term livebirths.

A detailed analysis of the test scores of the 159 children assessed by the paediatrician failed to show any association between their acid-base values at delivery and test scores, or between their fetal heart rate patterns in labour and test scores. These results conform with the view that birth asphyxia has an " all or nothing" effect, and that it presents as a cluster of abnormal neonatal signs, including persistent cerebral depression, severe acidaemia, neonatal encephalopathy, and multiorgan dysfunction.

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CHAPTER I

CLINICAL MARKERS OF BIRTH ASPHYXIA AND THEIR ASSOCIATION WITH LONG-TERM OUTCOME

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CHAPTER I

CLINICAL MARKERS OF BIRTH ASPHYXIA AND THEIR ASSOCIATION WITH LONG-TERM OUTCOME

1. BACKGROUND

1.1. Experimental birth asphyxia

Birth asphyxia can cause death and serious neurological damage; a result first shown experimentally in primates by Ranck and Windle (1959). At this time, there was a strong presumption that brain damage was caused by a failure to breathe at delivery - a complication termed "apnea neonatorum", or equivalently "asphyxia neonatorum" (Bloxsom, 1943). Ranck and Windle simulated this complication by delivering rhesus monkeys with the amniotic sac intact, waiting 11 to 16 minutes, then rupturing the membranes and resuscitating the infant. All five infant monkeys in their series showed abnormal neurological signs and were lacking in responsiveness and spontaneous activity. Two showed poorly co-ordinated random movements, and one convulsive seizures. The monkeys were sacrificed to perform brain histology, but three of the five were not expected to survive beyond a few days.

These observations were later confirmed and extended by Myers (Myers, 1968; Myers, 1972). Working with rhesus monkeys at term, he induced a period of anoxia at delivery by clamping the umbilical cord and preventing the onset of lung breathing by placing a rubber sac over the fetal head for a measured length of time. After removal of the sac the infant monkey was resuscitated by intubation and cardiac massage. Neurological abnormalities resulted only after a prolonged period of total asphyxia: more than 8-10 minutes if the mother was awake or 12-13 minutes if deeply anaesthetised. All affected animals showed difficulty in feeding, and sensory loss in the extremities, shown by malpositioning of the hands and feet when sitting, standing

or walking. Only the worst affected showed motor deficits, with increased tone and an inability to initiate voluntary movement. Seizures were rare, and did not constitute a prominent part of the clinical picture. Myers noted that these clinical abnormalities were different from those seen in "brain damaged" children, in whom sensory loss rarely presented on its own, but was nearly always accompanied by motor deficits.

In both sets of experiments, it was observed at autopsy that the first (and sometimes the only) part of the brain to be damaged was the inferior colliculus - one of the nuclear structures in the brain stem. As the period of total asphyxia increased, other brain stem nuclear structures were also likely to be involved, but cerebral oedema was never seen (Myers, 1972). This pattern of brain pathology was quite different from that observed in human infants in whom brain damage following assumed birth asphyxia was usually located in the hemispheres rather than the brain stem (Towbin, 1969; Pryse-Davies & Beard, 1973; Grunnet *et al.* 1974). These observations suggested that brain damage in the human resulted from circumstances other than total asphyxia at delivery, and led Myers and his colleagues to investigate the effects of intrauterine partial asphyxia on the newborn infant.

Partial asphyxia - that is, a reduction rather than a suspension of the oxygen supply to the fetus - can occur during pregnancy and labour for reasons such as cord occlusion, poor placental perfusion, placental abruption and uterine hyperactivity. It was induced experimentally by various methods, including depressing the oxygen-carrying capacity of maternal blood by respiring the mother with carbon monoxide (Ginsberg & Myers, 1976), stimulating the uterus by oxytocic drugs (Myers *et al.* 1969) and inducing maternal hypotension by administration of halothane (Brann & Myers, 1975). The fetuses were exposed to varying degrees of partial asphyxia for an hour, and then delivered. At delivery, they were immediately ventilated with 100 per cent oxygen.

Some animals required only a short period of resuscitation at delivery and were later neurologically intact. Others were flaccid at delivery, required prolonged mechanical ventilation, and showed severe neurological impairment, including seizures, spastic quadriparesis, and visual and auditory defects. Some of the severely damaged infants survived only an hour or two (Brann & Myers, 1975; Ginsberg & Myers, 1976). Myers noted that for a fetus to sustain brain injury, marked asphyxia had to be sustained for 25-30 minutes. He argued that "the probability that an asphyxia of this magnitude will develop and be maintained steadily for this length of time without further progressing to kill the fetus is small" (Myers, 1977). For this reason, he postulated that survival with brain damage would be a relatively uncommon result of birth asphyxia, with sudden death or apparently intact survival much the most likely outcomes.

At autopsy, the infant monkeys who had been exposed to prolonged partial asphyxia showed brain damage at similar sites to those observed in human infants (Towbin, 1969; Pryse-Davies & Beard, 1973; Grunnet *et al.* 1974). Cerebral oedema was present in varying degrees, often resulting in impaired cerebral blood flow and cerebral necrosis. In some animals the cerebellum and brain stem were also affected (Myers *et al.* 1969; Brann & Myers, 1975).

In these experiments, the severity of any resulting neurological abnormality in the infant was related to the degree of asphyxia experienced, but the correspondence was not exact. One possible explanation for this came from a separate series of experiments on young adult monkeys (aged two to four years). The animals were subjected to 10-14 minutes of anoxia, some after 10-24 hours of food deprivation, others immediately after an infusion of glucose. Those starved before the episode of anoxia survived neurologically intact, while glucose loading led to severe hypotonia, seizures and death (Myers, 1976; Myers & Yamaguchi, 1977). At autopsy, the brains of the glucose-fed animals showed widespread necrosis and some oedema, and in compari-

son with the brains of the survivors, showed high concentrations of lactate in the cerebral cortex (Myers & Yamaguchi, 1976). It was hypothesised that this accumulation of lactate was responsible for the damaging effect of a high serum glucose at the time of anoxia.

This finding has been pursued in experiments on immature, rather than adult, animals. Working with 7-day old rats, Voorhies *et al.* (1986) compared the neuropathology after two hours of hypoxia in animals previously injected with glucose and those injected with saline. The amount of glucose was sufficient to produce a roughly threefold increase in blood glucose for up to 90 minutes. Ten of the twelve experimental pairs survived the hypoxia, and were sacrificed at 30 days. At postmortem, no differences in brain pathology were observed between the treated and control animals, showing that, unlike in adults, glucose supplementation in the immature rat does not increase the extent of hypoxic-ischaemic brain damage. On the contrary, in an experiment on 7-day old rats injected with even higher concentrations of glucose before exposure to two hours of hypoxia, a dramatic protective effect of extreme hyperglycaemia was observed. After sacrifice at 28 days, the brains of the hyperglycaemic animals were essentially normal, while in over half of the saline-treated controls, atrophy of the hemispheres and cystic infarction were apparent (Reeves *et al.* 1992). These results have led Vannucci and Mujsce to suggest that physicians probably should not restrict glucose administration to an acutely asphyxiated fetus or newborn infant, but rather that maternal glucose supplementation in labour should be considered (Vannucci & Mujsce, 1992).

At the same time, recent experiments (Yager *et al.* 1992) have shown a protective effect of fasting before a hypoxic perinatal episode - a result consistent with the original finding of Myers & Yamaguchi (1977). The protective effect was not seen when hypoglycaemia was induced by insulin administration. Various explanations

have been suggested for this complex relationship between glucose levels and brain damage following subsequent hypoxia (Yager *et al.* 1992), but the mechanism of brain damage following hypoxia is far from completely understood (Gluckman *et al.* 1991).

1.2. **Current issues in human reproduction**

The observed link between birth asphyxia and neurological outcome is clearly relevant to human reproduction, but the human situation is more complex. Asphyxia is not experimentally induced, and there is no obvious way of identifying its occurrence or of measuring its duration and severity. A further problem is that the range and shades of neurological impairment that can be observed in a human child are far more extensive and subtle than those discernible in a monkey. For these and other reasons, the relationship between birth asphyxia and neurological outcome in the human infant is not yet well understood.

An understanding of this relationship is important for several reasons. It would help to clarify the extent to which neurological damage is preventable by obstetric or paediatric intervention; an issue that is not yet resolved (Grant, 1988; Hall, 1989; Hill, 1991; Nelson & Leviton, 1991). Further, if neurological deficit is preventable in some cases, it would help to identify those children most likely to benefit from any intervention. Finally, it would elucidate the ethical and legal confusion surrounding responsibility in this area of medicine (Bax, 1992; Freeman & Freeman, 1992).

In order to understand the link between birth asphyxia and neurological outcome, the following questions need to be addressed:

(i) In human infants, what types of neurological deficit are observed to be associated with birth asphyxia? (ii) Where neurological deficit is observed to be associated with birth asphyxia, has asphyxia caused the deficit? (iii) If asphyxia does cause neurological deficit, could this deficit be prevented by obstetric or paediatric management? (iv) What contribution is made by birth asphyxia to the sum of neurological

deficit in the population?

In this chapter, I shall consider only the first of these questions; some of the subsequent questions will be addressed later in the thesis.

I have so far used the term "birth asphyxia" to mean asphyxia occurring around the time of birth, including (in animal experiments) after delivery. In what follows, I shall use the term to mean (in humans) an asphyxial process occurring intrapartum. Because the process may have been initiated and sustained by factors operating earlier in pregnancy, I prefer the term to the alternative "intrapartum asphyxia".

Neurological impairment is strongly associated both with prematurity and multiple birth (Dowding & Barry, 1988; Grether *et al.* 1992). To avoid these confounding factors, I shall therefore concentrate on singleton children born at term.

2. IDENTIFICATION OF ASPHYXIA IN THE HUMAN FETUS

2.1. What is asphyxia?

Since birth asphyxia involves a severe disturbance in fetal respiration, it is helpful to consider first how fetal respiration is normally regulated. The umbilical vein carries oxygenated blood from the placenta to the fetus; the brain and upper extremities receive the richest supply of oxygen, while slightly less well oxygenated blood is carried to the fetal trunk and lower limbs. Deoxygenated blood returns from the fetus to the placenta in the umbilical arteries.

The transfer of oxygen from mother to fetus, and of carbon dioxide back from fetus to mother normally occurs by simple diffusion across the placenta. Decreased maternal-fetal transfer can be due to problems on the maternal or fetal side. Decreased uterine blood flow can result simply from changes in maternal posture, from strong uterine contractions, or, more seriously, from partial separation of the placenta. There may be placental dysfunction due to prolonged pregnancy, or to maternal

complications such as pre-eclampsia or diabetes. On the fetal side, blood flow in the umbilical cord may be impeded by cord compression, or, rarely, fetal oxygen transport may be reduced by a complication such as fetal anaemia. If there is a failure of respiratory gas exchange for any reason, the level of oxygen carried to the fetal tissues falls, while fetal carbon dioxide levels rise. This simultaneous occurrence of hypoxia and hypercarbia, which leads to fetal respiratory and metabolic acidosis, is termed asphyxia. The acidosis results from the retention of carbon dioxide and the accumulation of lactic acid from anaerobic metabolism of glucose when oxygen is not available (Towell, 1966). Since asphyxia is a disturbance from the normal, measured on a continuous scale, it can in principle occur in any degree.

Although this definition of asphyxia is generally accepted, there is wide disagreement about the best way of identifying and measuring it in clinical practice (Hull & Dodd, 1991). Since there is no direct measure of the asphyxial insult which initiates and maintains the subsequent biochemical process, markers of asphyxia must be secondary: a reflection of the fetal response to its disturbed conditions, rather than the disturbed conditions themselves. Some suggested markers, such as fetal pH and base deficit, are close to the asphyxial event; others, such as depression at birth, are conceptually more distant.

To examine the link between birth asphyxia and neurological damage, any suggested marker of asphyxia should fulfil certain criteria. First and foremost, the marker should identify birth asphyxia, and not some other fetal problem. Secondly, it should identify not only the most severe asphyxia (which is known to cause neurological damage), but also the less severe, whose effect on long-term outcome is not known. Thirdly, it should be reliable and objective. Finally, it should be practical; that is, reasonably easy to obtain for large numbers of infants. Several different clinical markers of asphyxia have been proposed, and their strengths and weaknesses will be examined.

2.2. **Acid-base values in the umbilical artery**

Blood in the umbilical artery at delivery best represents the oxygenation and acid-base status of the fetus in the preceding moments. The three markers of acid-base status generally measured in the umbilical artery are carbon dioxide, pH, and base deficit. As carbon dioxide accumulates during an asphyxial episode, there is a direct increase in hydrogen ion concentration by dissociation of carbonic acid into hydrogen ion and bicarbonate. pH therefore falls, indicating respiratory acidosis. With a prolonged or severe depletion in the oxygen supply, the fetus initiates anaerobic metabolism of glucose, resulting in an accumulation of lactic acid. The buffering of this lactic acid reduces the availability of bicarbonate, haemoglobin and plasma proteins, which normally act as buffers, and base deficit (the shortfall in total body buffer base from its normal level) increases. The level of base deficit thus reflects the degree of metabolic acidosis exhibited by the fetus. It is usual to separate respiratory from metabolic acidosis, depending on the level of base deficit; some workers however, distinguish three types of acidosis: respiratory (low pH, normal base deficit, high CO_2); metabolic (low pH, high base deficit, normal CO_2) and mixed respiratory-metabolic (low pH, high base deficit, high CO_2) (Wible *et al.* 1982).

The interpretation of the pH and base deficit in umbilical arterial blood as indicating fetal acidosis assumes that these blood values accurately represent the values of pH and base deficit in fetal tissue.

Acid-base measurements made on umbilical arterial blood at delivery relate to a single moment, and can only roughly illuminate the preceding sequence of events. It is not possible, for instance, to separate out the duration from the intensity of any preceding insult. Nor is it possible to assess why a particular fetus has responded to a given insult in a particular way. Further, if there had been an asphyxial episode in the past which was corrected before delivery, this would remain undetected.

Fetal acid-base status (usually expressed by pH and/or base deficit) is widely

Table 1.1

Components of the Apgar score

Heart Rate (beats per minute)	**Score**
More than 100	2
Less than 100	1
Absent	0
Respiratory Effort	
Regular	2
Irregular	1
Absent	0
Muscle tone	
Normal, with movement	2
Normal, no movement	1
Limp	0
Colour of trunk	
Pink	2
Blue	1
White	0
Reflex irritability (response to catheter)	
Cough or sneeze	2
Grimace	1
None	0

advocated as an essential marker both for identifying, and for excluding, birth asphyxia (Low, 1988; Thorp *et al.*1989; Martin & McColgin, 1990; Johnson *et al.*1990). Such discrimination calls for cut-off values to separate "acidotic" from "normal". It is striking that the mean (and S.D.) values of pH in consecutive births reported from various centres range widely, from 7.20 (0.08) in Oxford (Sykes *et al.*1982) to 7.23 (0.08) in Copenhagen (Nickelsen & Weber, 1987) and 7.27 (0.01, sic) in Chicago (Fee *et al.*1990). These differences, as well as different opinions about how much of the tail of a distribution should be labelled as "abnormal", result in a variety of suggested cut-off levels for acidosis. It is not clear why different centres report such different mean blood gas values, but since these values are affected by certain aspects of labour management, including the use of oxytocin and pethidine (Yudkin *et al.*1987; Ruth & Raivio, 1988) the variation may arise partly from different styles of care.

There are some practical problems associated with routine recording of acid-base measurements in the umbilical artery, notably the difficulty of withdrawing blood from this small vessel. But in general, the procedure is thought to be "easy, uncomplicated and inexpensive" (Wible *et al.*1982). Nevertheless, some studies which set out to make routine measurements managed to cover only 65%to 78% of their target (Huisjes *et al.*1980; Sykes *et al.*1982; Josten *et al.*1987; Steer *et al.*1989).

2.3. **Apgar score**

General description

The Apgar score (Apgar, 1953) is based on five clinical signs in the newborn baby: heart rate, respiratory effort, reflex irritability (response to catheter), muscle tone, and colour. Each sign is rated 0,1 or 2, and the ratings are added to form the Apgar score, which can thus range from 0 (the infant with no sign of life) to 10 (the vigorous infant with no sign of depression) (Table 1.1). It was originally recom-

mended that the score should be assigned 60 seconds after the complete birth of the baby since this was judged to be the time of maximal depression. Subsequently, Apgar scores have been recorded at later times as well.

The declared purpose of the score was to provide "a basis for discussion and comparison of the results of obstetric practices, types of maternal pain relief and the effects of resuscitation" (Apgar, 1953). The score was noted to be lower after operative delivery, compared with spontaneous, and after general anaesthesia, compared with spinal. Apgar and her colleagues also reported later that the more acidotic the infant at birth the lower the score tended to be (Apgar *et al.* 1958), and they suggested that a score of 3 or less usually indicated asphyxia (Apgar & James, 1962). Later studies made it clear that while asphyxia was one reason for a low Apgar score, there were others such as congenital malformation, intrauterine infection, trauma and maternal anaesthesia (Ikonen, 1973; Naeye, 1979; American Academy of Pediatrics Committee on Fetus and Newborn, 1986).

Few studies on the reliability of the scoring system have been reported, but there are several reasons for doubting its complete objectivity. Although the rating of the signs constituting the score were chosen to be as clear as possible, it was recognised by Apgar that some items would produce disagreement between observers, and this has been confirmed (Auld *et al.* 1961). Since the score has come to be regarded as indicating the quality of care, one might expect a tendency for obstetric staff to overestimate it; this bias was observed in a small study in which scores assigned by labour ward staff were compared with those assigned by independent observers (Rothberg *et al.* 1986). Finally, although it was intended that the Apgar score should be assignable without interfering with the care of the infant, modern neonatologists would be unlikely to wait the allotted 60 seconds before beginning cardiopulmonary resuscitation of a distressed neonate, so that the score would have to be assigned

retrospectively in some cases (Fields *et al.* 1983; Editorial, 1989).

From her original experience with the score, Apgar observed that infants with a one-minute score of 0-2 had a 14% risk of neonatal death; those with a score of 3-7 had a 1% risk, and those with a higher score had a risk of 1.3 per 1000 (Apgar, 1953). Apgar and James (1962) later suggested that the score might be used to predict not only mortality but also long-term mental development. Since its origin 40 years ago, the Apgar score has become widely accepted and internationally applied. Because it is perceived to be clinically useful and is easy and cheap to record, it is available for all infants in many maternity hospitals. It thus provides a practical base for research into associations between birth events and long-term outcome.

Relation between Apgar score and acid-base status at delivery

To understand the extent to which a low Apgar score could be due to a deranged acid-base state, many investigators have examined the relationship between Apgar score and acid-base values in umbilical arterial blood. The infants studied have included unselected series of consecutive births (Sykes *et al.* 1982; Lauener *et al.* 1983; Josten *et al.* 1987), a randomly selected group of singletons (Fields *et al.* 1983), a randomly selected group of singletons, delivered vaginally at term (Page *et al.* 1986), a consecutive series of term singletons, born after a complication of labour (Gilstrap *et al.* 1989) and two groups of unspecified source (Silverman *et al.* 1985; Dijxhoorn *et al.* 1986), the latter full-term, vaginally born infants with birthweight appropriate for dates. All these studies reported some association between Apgar score and acid-base status, but not a very close one; a result that is not surprising in view of the unspecific nature of the Apgar score. Their findings are summarised in Table 1.2. Numbers in the study of Gilstrap *et al.* were estimated from a Figure in that paper.

The wide range in the reported incidence of a low (<7) one-minute Apgar score - from 7.1% to 30.2% - is striking. This is likely to reflect subjective scoring rather

Table 1.2
Relationship between low one-minute Apgar score and acidaemia in umbilical arterial blood

	Definition		Total	Low Apgar score		Acidaemia		Proportion of low Apgar group with acidaemia		Proportion of acid-aemic group with low Apgar score	
	Low Apgar score	Acidaemia	Number	N	%	N	%	N	%	N	%
Sykes *et al.* 1982	< 7	pH ≤ 7.10 and base deficit >12mmol/l	895	97	10.8	76	8.5	20/97	20.6	20/76	26.3
Fields *et al.* 1983	< 7	pH < 7.20	172	52	30.2	31	18.0	24/52	46.2	24/31	77.4
Lauener *et al.* 1983	< 5	pH < 7.15	1904	35	1.8	121	6.4	13/35	37.1	13/121	10.7
Silverman *et al.* 1985	< 7	pH < 7.15	1032	184	17.8	126	12.2	54/184	29.3	54/126	42.9
Dijxhoorn *et al.* 1986	< 7	pH ≤ 7.10	803	57	7.1	86	10.7	17/57	29.8	17/86	19.8
Page *et al.* 1986	< 7	pH < 7.20	75	16	21.3	13	17.3	6/16	37.5	6/13	46.2
Josten *et al.* 1987	< 7	pH < 7.14	257	21	8.2	39	15.2	11/21	52.4	11/39	28.2
Gilstrap *et al.* 1989	< 7	pH < 7.15	2738	*265	9.7	168	6.1	*43/265	16.2	*43/168	25.6

* Numbers estimated

than real differences in the condition of newborn infants in the study centres. The small study sizes, and their large sampling errors, may also account for some of the variation in reported rates. On the other hand, the incidence of a low umbilical arterial pH appears to be more stable; a pH of less than 7.20 occurred in 17% or 18% of births, and a pH of less than 7.15 in 6% to 15% of births. However, close inspection of these results shows that two studies were out of line with the others in reporting as many as 10% of births with a pH $\leq$ 7.10 (Sykes *et al.* 1982; Dijxhoorn *et al.* 1986).

Not surprisingly, the overlap between a low Apgar score and acidaemia varied considerably between the different centres. However, apart from one outlying study (Fields *et al.* 1983), less than half of all acidaemic infants had a one-minute Apgar score <7, and less than half of all infants with a one-minute Apgar score <7 were acidaemic.

The lower value of ≤ 3 for the one-minute score, suggested by Apgar and James as indicating asphyxia (Apgar & James, 1962), has been used by other investigators. They have reported rates of 4.5% in term singletons (Nelson & Ellenberg, 1981), 3.8% in a cohort of consecutive births (Sykes *et al.* 1982) and 1.9% in term, singleton deliveries following a complication of labour (Gilstrap *et al.* 1989). Among very acidaemic infants (those with umbilical arterial pH <7.00), a one-minute Apgar score ≤ 3 is much more common, with an incidence of 28% to 30% (Gilstrap *et al.* 1989; Goldaber *et al.* 1991; Winkler *et al.* 1991).

2.4. **Fetal Heart Rate (FHR) patterns**

General description

By the turn of this century evaluation of the fetal heart rate (FHR) by auscultation had become widely accepted as a technique for detecting "fetal distress", and marked alterations in the FHR were assumed to denote fetal asphyxia (Hon, 1977). With the development of electronic methods for continuous recording of the fetal heart

rate, it became possible to describe and classify FHR patterns and their abnormalities in more detail.

Early work with continuous fetal monitoring in labour showed that uterine contractions could provoke a slowing of the FHR, and that three patterns of deceleration could be distinguished. The first - the early deceleration - coincided with the onset of the contraction, and resolved before the contraction finished. It was assumed to be due to compression of the fetal head, since the same response could be produced if the fetal head was compressed experimentally (Hon, 1958). The second - the variable deceleration - started sometimes early and sometimes late in the uterine contraction, and was variable also in its length and severity. The third - the late deceleration - started late in the contraction (roughly when it had reached its peak), and continued after the contraction was over. The late deceleration that involved a very marked slowing of the FHR over a prolonged period was observed to be associated with serious fetal compromise, including impending intrauterine death (Hon, 1958; Hon, 1959). Hon suggested that late decelerations arose from uteroplacental insufficiency, triggered (perhaps in an already compromised fetus) by the decreased intervillous space blood flow consequent on uterine contraction. Variable decelerations, on the other hand, were thought to be due to cord compression (Hon, 1977). This latter association was later confirmed by several experimental and human studies in which variable decelerations were reproduced by either cord compression or fetal head compression (Ball & Parer, 1992).

Hon, Kubli and colleagues provided the basic and enduring terms to describe FHR patterns, and the normal ranges of each of them (Hon, 1963; Hon & Quilligan, 1967; Kubli *et al.*1969). They specified three aspects of the FHR: (i) basal heart rate: the baseline FHR during the major portion of a 10-minute interval between contractions; (ii) periodic FHR changes: accelerations or decelerations, superimposed on the baseline FHR and usually associated with contractions (iii) baseline variability: varia-

Table 1.3

Fetal Heart Rate (FHR) classification

Baseline FHR (beats per minute): *evaluated over a 10-minute interval between contractions*

Normal	120-160
Tachycardia, moderate	161-180
Tachycardia, marked	>180
Bradycardia, moderate	100-119
Bradycardia, marked	<100

Periodic changes: *a transitory change in the FHR from a given baseline level, followed by a return to the base. Can be further classified in terms of duration and amplitude*

Acceleration	Increase in rate coincident with contraction
Deceleration, early	Fall in rate starting early in contraction; uniform shape
Deceleration, late	Fall in rate starting late in contraction; uniform shape
Deceleration, variable	Variable time of onset; variable shape

Variability: *classified on the basis of the amplitude of the FHR fluctuations, which have a frequency of 3-5 cycles per minute. Amplitude is measured as a percentage of the baseline level*

Average	4-9 percent
Moderate	10-15 percent
Marked	>15 percent
Minimal	<3 percent
Absent	No visible fluctuations

(Based on Hon & Quilligan, 1967)

tion of the FHR around the baseline rate. A summary of the early classifications is presented in Table 1.3.

The relationship between FHR patterns and birth asphyxia has been studied by two approaches. In animals, continuous FHR monitoring and intermittent fetal blood analysis has been carried out during experimentally-induced asphyxia. In humans, FHR patterns in labour have been compared with concurrent acid-base measurements in fetal blood, and with Apgar score at delivery. Both approaches have led to similar conclusions. Firstly, there is in general only a weak relationship between FHR patterns and coincident fetal acid-base status (Myers, 1972; Kubli *et al.* 1969); abnormality of the FHR generally precedes a significant fall in fetal pH (Wood *et al.* 1967). Secondly, late decelerations are associated with a disturbed acid-base status. In fetal monkeys, late decelerations were observed during severe partial asphyxia, and became more pronounced as the asphyxia progressed (Myers, 1972). In humans, late decelerations were accompanied by an acidaemic shift, which was more marked as the deceleration became deeper and its onset more delayed (Kubli *et al.* 1969; Wood *et al.* 1969; Beard *et al.* 1971). Thirdly, multiple FHR changes, for instance decelerations with loss of variability or with tachycardia, are more likely to be associated with acidaemia than are the same patterns in isolation (Beard *et al.* 1971; Paul *et al.* 1975).

While these studies made it clear that FHR abnormalities could follow an asphyxial insult, other studies have shown that marked changes in fetal heart rate can occur for quite different reasons. These include maternal sedation, fetal congenital anomalies and congenital infection (Garite *et al.* 1979; Paul *et al.* 1986; Boylan, 1987; Martin, 1978).

There are two methods of recording fetal heart rate in clinical use: external, using ultrasound through the mother's abdomen; and internal, via an electrode attached to the fetal presenting part. This latter method can cause fetal trauma or (very

Table 1.4
Relationship between abnormal FHR patterns and acidaemia in umbilical arterial blood

	Definition		Total Number	Abnormal FHR		Acidaemia		Proportion of abnormal FHR group with acidaemia		Proportion of acidaemic group with abnormal FHR	
	Abnormal FHR	Acidaemia		N	%	N	%	N	%	N	%
Gilstrap *et al.* 1982	2nd stage only	pH < 7.20 in artery or vein	833	403	48.4	99	11.9	80/403	19.9	80/99	80.8
Page *et al.* 1986	Either stage	pH < 7.20	75	18	24.0	13	17.3	8/18	44.4	8/13	61.5
van den Berg *et al.* 1987	Operative delivery for fetal distress	pH < 7.20	2669	236	8.8	129	4.8	68/236	28.8	68/129	52.7
Steer *et al.* 1989	Either stage	pH < 7.17	698	289	41.4	88	12.6	66/289	22.8	66/88	75.0

FHR: Fetal Heart Rate

rarely) infection, but it is likely to produce a better quality trace. However, although it is possible to obtain traces that are clear and legible, they are complicated to interpret by eye, and studies have frequently shown a high degree of inter- and intra-observer disagreement (Lotgering *et al.* 1982; Nielsen *et al.* 1987). For this reason, computerised analysis of cardiotocographic traces is being developed (Pello *et al.* 1991).

Electronic fetal monitoring has not been adopted for all infants in the U.K., mainly because of doubt about its effectiveness. In the eight randomised controlled trials comparing intrapartum electronic fetal monitoring with intermittent auscultation, none has shown any long-term benefit of electronic monitoring (Freeman, 1990). Although the large Dublin trial (MacDonald *et al.* 1985) showed a reduction in early neonatal seizures, there was no reduction in subsequent neurological impairment.

Relation between FHR patterns and acid-base status at delivery

Information on the association between abnormal FHR patterns in labour and acid-base status at delivery is presented in Table 1.4. Two of these studies were based on series of consecutive births (van den Berg *et al.* 1987; Steer *et al.* 1989) and one on a randomly selected group of singletons, delivered vaginally at term (Page *et al.* 1986). The other, which considered FHR abnormalities only in the second stage of labour, was restricted to infants delivered by forceps, and excluded all those with any FHR abnormality in the first stage (Gilstrap *et al.* 1984).

The various definitions of FHR abnormality used reflect the complicated nature of this marker. In their study of the second stage, Gilstrap *et al.* defined abnormalities only in terms of bradycardia, tachycardia or reduced variability, and excluded from consideration all infants with accelerations or decelerations. Page *et al.* used criteria based on fetal heart rate, variability and periodic movements; Steer *et al.* used this approach with a slightly different set of criteria. van den Berg *et al.* counted as abnormal only those cases in which, after considering the results of fetal blood analy-

Table 1.5

Stages of Neonatal Encephalopathy

Stage 1

The main sign is jitteriness - a hyperalert state with prolonged periods of wakefulness, irritability and excessive responsiveness to stimulation. Muscle tone is normal or slightly increased, and there may be slight feeding difficulties. The electroencephalogram (EEG) is normal, and symptoms usually start to fade within 24 hours of birth.

Stage 2

The infant is lethargic for at least the first 12 hours after birth, and is hypotonic, with impaired primitive reflexes (stretch, suck, swallow, Moro). The EEG is always abnormal and seizures are common. This stage can last approximately 2 to 14 days, and may resolve, or tend to worsen, with increasingly frequent seizures and progressive hypotonia.

Stage 3

The infant is comatose and needs mechanical ventilation. There is extreme hypotonia and basic reflexes are either weak or absent. The EEG is severely abnormal, and prolonged or repetitive seizures may occur. Survivors may remain in this stuporous state for a few hours to some weeks.

(Based on Sarnat & Sarnat, 1976; Fenichel, 1983; Low *et al.* 1985; Levene *et al.* 1985; Amiel-Tison & Ellison, 1986).

sis, the FHR changes led to an operative delivery for fetal distress.

The four studies showed markedly different results. There was a wide disparity in rates of FHR abnormality across the different centres, no doubt reflecting, at least in part, the different definitions used. In each centre, the rate of FHR abnormality was higher than the rate of acidaemia, sometimes much higher. Thus among those with FHR abnormalities, a relatively low proportion (20% to 44%) were acidaemic, while among those with acidaemia, a high proportion (53% to 81%) showed FHR abnormalities. The small sizes (and large sampling errors) of some of these studies may also have contributed to their divergent results. The studies make clear the slipperiness of the concept of an abnormal FHR pattern, and the difficulties, both conceptual and practical, in using it as a marker of asphyxia.

2.5. **Neonatal encephalopathy**

Neonatal encephalopathy was defined and classified by Sarnat and Sarnat in an observational study of 21 neonates who were presumed to have suffered birth asphyxia (Sarnat & Sarnat, 1976). This presumption was based on the occurrence of "a well-defined episode of fetal distress or an Apgar score of 5 or less at 1 or 5 minutes after delivery"; there was no requirement for evidence of acidosis. Three stages of neonatal encephalopathy were distinguished by Sarnat and Sarnat; slightly different descriptions of these stages have been offered by a number of other authors (Fenichel, 1983; Low *et al.* 1985; Levene *et al.* 1985; Amiel-Tison & Ellison, 1986). A summary of these descriptions is shown in Table 1.5.

Neonatal encephalopathy has a direct link with low Apgar score, in that the respiratory depression and hypotonia of a prolonged low Apgar score are features of Stage 2 (moderate) and Stage 3 (severe) encephalopathy. However, these stages of encephalopathy may develop without low Apgar scores. In one series, only 61% of infants with moderate or severe encephalopathy had a one-minute Apgar score ≤ 3,

and 49% had a five-minute score ≤5 (Hull & Dodd, 1992). Moreover, while the Apgar score has a time frame of a few minutes, neonatal encephalopathy is a state that may continue and evolve over several weeks. In this respect, it differs from all the other suggested markers of asphyxia. The relationship between the three stages of encephalopathy - that is, the likelihood of moving from one stage to another, and the timing and probable direction of any such movements - has not been clarified (Leviton & Nelson, 1992).

Although the original connection between neonatal encephalopathy and birth asphyxia was rather tenuous, many authors have replaced the term "neonatal encephalopathy" by "hypoxic-ischaemic encephalopathy", as though it were certain that the condition were caused by asphyxia around the time of birth (Finer *et al.* 1981; Siegel *et al.* 1984; Vannucci, 1990). In fact, there is much evidence to suggest that a proportion of neonatal encephalopathy is not the result of birth asphyxia. A number of studies have reported that most infants with encephalopathy are not acidaemic at birth (Huisjes *et al.* 1980; Low *et al.* 1985; Dijxhoorn *et al.* 1986; Gilstrap *et al.* 1989), and the condition shows a poor association with "asphyxial" obstetric events (Nelson & Ellenberg, 1987). Further, many conditions other than asphyxia are known to cause the signs of neonatal encephalopathy, including congenital anomalies, cerebral infarction, metabolic disorders, trauma, and intrauterine infection (Nelson & Leviton, 1991).

Neonatal seizures, which are one of the signs of Stage 2 or Stage 3 encephalopathy, have been considered on their own as an indicator of asphyxia. In a careful study of the likely antecedents of such seizures, Dennis and Chalmers (Dennis & Chalmers, 1982) suggested four possible causes: congenital anomaly, simple hypocalcaemic tetany, postnatal insult, or a perinatal complication. They observed that, in term infants, it was the seizures starting within 48 hours of birth that were most likely to have been caused by a perinatal complication. Indirect evidence of an association

between early neonatal seizures and perinatal events has come from the Dublin randomised controlled trial of electronic fetal monitoring (MacDonald *et al.* 1985). In this trial, early seizures were more than twice as common in the auscultated group as in the continuously monitored group, in whom there was a higher rate of assisted delivery and shorter labours.

However, other studies are less supportive of this idea. In a case control study of 54 term infants with early seizures, and 41,000 controls, an association was found between seizures and peripartum factors capable of producing asphyxia (such as oxytocin augmentation and a prolonged second stage) but complications were certainly not present in all seizure cases and only 35% of infants who developed seizures needed resuscitation at birth (Minchom *et al.* 1987). In the large Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke (NCPP), at least half the newborn infants who suffered early seizures were vigorous at birth (Ellenberg & Nelson, 1988).

Reliable and consistent reporting of both neonatal encephalopathy and seizures cannot be assumed. Both diagnoses rely to some extent on the use and interpretation of vague clinical terms such as "jerky movement", "jitteriness", "abnormal movement" and "irritability". Dennis and Chalmers (1982) have pointed out that in view of the subtle and fragmentary nature of some seizures, it would be surprising if all such events were reliably reported as such.

This reservation should be borne in mind in assessing the incidence rates of seizures and neonatal encephalopathy. Some reported rates for the latter, in term livebirths, are 3.6 per 1000 (Finer *et al.* 1981), 4.6 per 1000 (Hull & Dodd, 1992), and 6.0 per 1000 (Levene *et al.* 1985). Of all cases of neonatal encephalopathy, about a third are classified as moderate or severe (Leviton & Nelson, 1992).

Rates of early neonatal seizures have been estimated as 1.6 per 1000 term

deliveries (Derham *et al.* 1985), 1.3 per 1000 term deliveries (Minchom *et al.* 1987) and 3.2 per 1000 deliveries of all gestational ages (Holden *et al.* 1982).

2.6 **Imaging techniques**

During the last decade, the development of various imaging techniques has enabled direct identification and assessment of brain injury. Computed tomography (CT) and cranial ultrasonography are widely available; newer techniques, including magnetic resonance imaging (MRI), magnetic resonance spectroscopy, positron emission tomography (PET) and xenon perfusion techniques, have limited application as yet (Hill, 1991).

These methods have great potential in diagnosing and assessing the extent of birth asphyxia, and future progress in treating asphyxia may well depend on their use. However, their expense and limited availability up till now preclude their consideration here.

2.7. **Summary**

The most important feature of a marker of birth asphyxia is that it should actually identify asphyxia and not some other fetal problem. Of the markers we have considered, low Apgar score, aberrant FHR patterns, and neonatal encephalopathy are not specific to birth asphyxia. Some of the infants identified using these markers will be affected by birth asphyxia; others will not. Because there is no "gold standard" for birth asphyxia, it is impossible to make a precise statement about this.

The most direct marker available - acidaemia in umbilical arterial blood - is more specific in that it must reflect a disturbance in respiratory gas exchange around the time of birth. But two problems arise. Firstly, how do we judge whether this disturbance is severe enough to qualify as asphyxia? And secondly, does this disturbance have a perinatal cause? Might it instead have arisen from a longstanding fetal problem? This issue of cause must be secondary, and will be considered in a

later chapter.

Many authors make the point that asphyxia is a vague term, often left undefined. They then go on to use the term to mean an event that is associated with neurological damage; sometimes with the implicit assumption that this association should be close. For example, in an Editorial entitled "What is Birth Asphyxia?" Hull and Dodd stated: "In conclusion there is still no reliable clinical indicator of birth asphyxia; CTG, acidosis, low Apgar score and delay in establishing breathing correlate poorly with outcome." (Hull & Dodd, 1991). In examining the possible link between birth asphyxia and cerebral palsy, Hall wrote "The issue" (the recognition of asphyxia) "may be reduced to the question: What are the sensitivity, specificity, and positive predictive values of any given abnormality observed during labour in relation to neonatal fits, hypoxic-ischaemic encephalopathy, or cerebral palsy?" (Hall, 1989). Addressing a similar question, Grant stated ".... the attraction of the Apgar score" (as a marker of asphyxia) "is that its (albeit weak) relationship with long-term disability has been well described" (Grant, 1988).

This use of the term asphyxia to denote an insult severe enough to cause neurological injury is soundly based in the undisputed knowledge, from animal experiments, that birth asphyxia can cause such injury. However, there is a conceptual loop here. We seek a marker of asphyxia in order to investigate associations between asphyxia and neurological outcome, but a marker is judged to be valid only if it shows just such an association. There seems no way out of this loop. A recommendation to abandon the use of the term "birth asphyxia" and refer instead to specific indications of possible hypoxic damage (such as profound acidaemia and a persistent low Apgar score) (American College of Obstetricians and Gynecologists, 1991) is not helpful here, since it would merely replace one term by others.

Suppose for the moment that a perfect marker of asphyxia were available. The

observed link between this marker and a particular neurological impairment (say cerebral palsy) would depend on the nature of the relationship between them. The sensitivity of the marker would be 100% if all those with cerebral palsy had asphyxia. The specificity would be 100% if none of those without cerebral palsy had asphyxia. The positive predictive value of the marker would be 100% if all those with asphyxia had later cerebral palsy. Its negative predictive value would be 100% if all those without asphyxia were free of cerebral palsy. Which of these situations best accords with our understanding of the relationship between birth asphyxia and cerebral palsy?

Only if birth asphyxia were a necessary cause of cerebral palsy would the sensitivity of asphyxia, and its negative predictive value, be 100%. If birth asphyxia were only one of many possible causes of this impairment, and if these other causes were more common than birth asphyxia, the sensitivity of the marker, and its negative predictive value, would be low. This surely accords with our present understanding of the aetiology of cerebral palsy. As far as specificity and positive predictive value are concerned, they would be 100% only if asphyxia led inevitably to cerebral palsy. Specificity and positive predictive value will be lowered as the likelihood increases of surviving asphyxia without cerebral palsy. In this context, Myers has written: "When the marked severity of the asphyxia that is required to produce brain injury is considered along with the necessity of its enduring for the required length of time, it is apparent why survival with brain damage due to asphyxia is relatively uncommon and why sudden death or an apparently intact survival are much the more likely outcomes of intrauterine asphyxia." (Myers, 1977). If we accept this view, then we should not expect the specificity or the positive predictive value of a marker of asphyxia to be very high.

These arguments would hold not only for cerebral palsy, but also for other types of neurological impairment thought to result from birth asphyxia. Moreover, since they relate to a hypothetical, perfect marker of asphyxia, they would hold with addi-

tional force for the imperfect markers that are in practice available. It seems then, that a marker of asphyxia should be acceptable even without high sensitivity, specificity or predictive value. Any marker that is associated with neurological impairment (in the sense of increasing the observed risk of impairment) is worth consideration.

The most direct marker of asphyxia available - acidaemia in umbilical arterial blood - is more specific than other suggested markers because it must reflect a disturbance in respiratory gas exchange around the time of birth. In general, the more disturbed the acid-base state, the more likely it is that neurological damage will ensue. However, because of biological variation, a given asphyxial insult will affect different fetuses in different ways. Not only will cord blood gases vary, but so too will the infant's neurological response. A potentially damaged subgroup could not therefore be identified on the basis of acid-base status alone. Rather, it would be expected that a combination of asphyxial markers, both biochemical and clinical, would be needed.

To understand which markers might be useful for this purpose, the relation between various suggested indicators of asphyxia and neurological impairment (including death) will be examined. Both severe impairment (especially cerebral palsy) and less severe impairment will be considered.

3. ASSOCIATIONS OF ASPHYXIAL MARKERS WITH DEATH AND NEUROLOGICAL IMPAIRMENT

Note: The terms used to describe impairment have changed over the past 25 years or so, and even now they are by no means standardised. Also, some authors have given details of the deaths and impairments found in their studies, while others have not. In this section, therefore, I have usually referred to death or impairment in general, and have not attempted to be more precise. Where an author has reported neurological outcome using the term "handicap", I have also used this term.

3.1. **Acidaemia**

Death and neonatal neurological morbidity

A number of studies have observed the relation between acidaemia at birth and neonatal neurological morbidity in infants born at term ($\geq$37 weeks gestation).

In the study of Dijxhoorn *et al.* (1985), 619 infants classified as neurologically "normal" showed no difference in umbilical arterial pH values from 30 infants classified as "abnormal", but the 156 infants in the "suspect" group (with isolated signs of neurological abnormality, but no defined syndromes) were slightly more acidaemic than the other two groups. A score reflecting neurological condition showed a weak but statistically significant association with both umbilical arterial pH and maternal-fetal pH difference, but these two variables accounted for less than 1% of the variance in the score. Low *et al.* (1990), compared 51 infants with metabolic acidosis and a matched control group. They reported no difference in any aspect of newborn behaviour either at 3 days or at 2 weeks. However, the four infants in the study with encephalopathy were all found in the acidotic group. (In all their studies Low *et al.* define acidosis as umbilical arterial buffer base $<$34mmol/l. Because the value of buffer base is a function of pH and CO_2, this definition is not directly comparable with the more usual definitions based on pH or base deficit (Davenport, 1974)).

Winkler *et al.* (1991) sought signs of severe neurological abnormality in a comparison between 358 acidotic infants (with umbilical arterial pH$<$7.20) and a control group, taken from a cohort of 2764 term livebirths. Two infants had serious complications ascribed to asphyxia; both were in the acidotic group, and had pH$<$7.00. One died at age 2 days, following delivery precipitated by a maternal eclamptic fit. A second, born after a pregnancy complicated by severe oligohydramnios, suffered acute renal failure and major motor seizures in the neonatal period.

The poor prognosis of an umbilical arterial pH$<$7.00 has been reported in two further studies (Goldaber *et al.*1991; Goodwin *et al.*1992). In 109 term singleton

infants with pH < 7.00, 30% developed moderate or severe neonatal encephalopathy, its likelihood increasing with the degree of acidaemia. There were 5 neonatal deaths, and at ages 6 to 48 months 10 (9%) were judged to have a major neurologic deficit (Goodwin *et al.* 1992). The 109 infants (representing about 1.6 per 1000 term singleton births) had all been delivered operatively for fetal distress or were depressed at birth, and so may not represent all infants with pH < 7.00. A cohort of more than 30,000 term singleton births was investigated by Goldaber *et al.* (1991). 3506 infants (12%) had pH < 7.20 and 87 (2.9 per 1000) had pH < 7.00. This extreme level of acidaemia carried an 8% risk of neonatal death and a 13% risk of neonatal seizures; a relative risk of about 40 for each outcome, compared with a pH between 7.00 and 7.19.

This last study gives the best evidence available of the increased risk of neonatal death and seizures associated with severe acidaemia. Evidence for an association between lesser degrees of acidaemia and milder neonatal abnormalities is tenuous.

Long-term neurological impairment

Studies examining the association between acid-base status and neurological outcome at age one year or later have obtained conflicting results. Most have reported no association, or a very weak one (Low *et al.* 1983; Ruth & Raivio, 1988; Dennis *et al.* 1989; Fee *et al.* 1990), but two studies have reported a clear association with both major and minor neurological abnormalities (Low *et al.* 1988; Low *et al.* 1984).

Low *et al.* (1983) compared 37 term infants with metabolic acidosis and 59 controls. Acidosis was again defined as umbilical arterial buffer base < 34mmol/l. They found no differences between the groups in any aspect of development between the ages of 1 and 6 years, and no cases of cerebral palsy. In another study by Low *et al.* (1988), 37 term infants with metabolic acidosis were compared with 76 controls. Among the 37 index children, there were five with major motor deficits at the age of

1 year (including three with cerebral palsy) and 10 with minor motor deficits. Both these rates were significantly higher than in the control group. Moreover, within the acidotic group, an association was observed between the degree of acidosis at birth and the severity of the deficit at age 1 year. The authors concluded that their findings "support the concept that, beyond a critical threshold of fetal asphyxia, a continuum of casualty in the surviving newborn infants exists". It is unclear how the 37 acidotic infants were selected for each of these studies, and why they produced such different results.

A third study by Low *et al.* (1984) followed up to age one year a group of 60 acidotic infants, of whom 32% were preterm. A gradient in neurological deficit with the degree of acidosis present at delivery was again reported, and the conclusion reached that "an episode of hypoxia less than one hour may occur without subsequent deficits. However, an episode of hypoxia in excess of 1 hour resulting in a metabolic acidosis of the order of 25mEq/l will be followed by motor and cognitive deficits in approximately 50% of children".

Ruth and Raivio (1988) carried out the first large follow-up study based on acid-base measurements, in which 964 infants of all gestational ages were assessed at the age of one year and classified as developmentally normal, questionable, or abnormal. Acidosis was defined as umbilical arterial $pH < 7.16$ for vaginal deliveries and < 7.25 for caesarean deliveries. The authors concluded that acidosis was a poor predictor of perinatal brain damage, although in comparison with a normal acid-base status it carried a relative risk of 2.0 of neonatal death or an abnormal or questionable outcome. There was one case of spastic quadriplegia in the study sample, in a child born at term with moderate acidaemia and neonatal encephalopathy.

In a study of different design, but based on a cohort of similar size, Dennis *et al.* (1989) compared developmental outcome at the age of 4½ years in acidaemic and

control children, all of whom were singletons born at term. Acidaemia was defined as umbilical arterial pH $\leq$ 7.10 and base deficit $>$ 12 mmol/l. There were no "asphyxial" deaths or severe neurological abnormalities in the study sample, and no associations between acidosis and developmental outcome were found. Unexpectedly, the subgroup of 27 children with very low pH ($<$ 7.05) scored particularly well.

The study of Fee *et al.* (1990), like that of Winkler described above (Winkler *et al.* 1991), investigated an acidaemic subgroup (with umbilical arterial pH $\leq$ 7.05 and base deficit $\geq$ 10 mmol/l) in a large cohort of births. There were 142 infants in this subgroup, representing 0.9% of the cohort of 15528 births; 110 of the selected infants were full-term. In the neonatal period, nine of these 110 infants were neurologically abnormal; two were lost to follow up, but none of the seven followed to between 12 and 24 months of age showed a major motor or cognitive abnormality. There were no deaths among the term infants in this study and only one death among the 32 preterm infants - an unexpected finding in such a large cohort.

Thus, at least in term infants, there appears to be no association between acidaemia at delivery and neurological development at age one year or later. Two small studies of Low et al. (1984 and 1988) gave results which are out of line with those of other investigators. As the source of their data is incompletely described, these results must be considered uncertain.

3.2. **Low Apgar score**

The association of a low Apgar score with neonatal death was first noted by Apgar and James (1962) and confirmed in the NCPP cohort of about 40,000 infants born some thirty years ago (Drage *et al.* 1964). Observations on this cohort also showed an association between a low Apgar score and later impairment. Among survivors of all gestational ages, the risk of cerebral palsy associated with a one-minute Apgar score $\leq$ 3 was about 6 times that associated with a higher one-minute

score (Nelson & Ellenberg, 1981). This association became stronger the longer the low Apgar score persisted, so that children whose low score persisted for 10 minutes or later had a risk of 12% of cerebral palsy, a relative risk of 11.3 compared with those whose low score resolved before 10 minutes.

Two small studies of infants with very depressed Apgar scores also reported a high death rate and a risk of cerebral palsy in survivors. Scott (1976) investigated 48 babies (both term and preterm) with either a one-minute Apgar score of 0, or failure to establish spontaneous respiration within 20 minutes of birth; 25 (52%) infants died neonatally. At the ages of 3-7 years, six of the 23 survivors (26%) had cerebral palsy, including two cases of spastic quadriplegia. Thomson *et al.* (1977) identified 86 infants with a one-minute Apgar score of 0 or a five-minute score of ≤ 3; 43 (50%) died neonatally. Of the survivors, 31 were followed for 5-10 years, and compared with matched controls. All infants in the study had normal outcomes, except for two (6%) of the severely depressed children, both of whom had spastic quadriplegia.

Evidence for less severe impairment after low Apgar scores is sparse. Among the 87 children in the NCPP study who survived an Apgar score ≤ 3 at 10 minutes or later, without cerebral palsy, eight had other handicaps, including developmental delay, and hearing and speech defects. A third of these children were preterm and it is impossible to know whether this was a decisive factor in their developmental outcome.

No association has been found between mildly depressed Apgar scores and intelligence or motor ability at age 17 years (Seidman *et al.* 1991).

Evidence about the quality of survival after low Apgar scores is based on births that took place some 20 or 30 years ago. Since that time there have been great advances in methods of life support, including mechanical ventilation, and some infants who would have succumbed in the 1960s or early 1970s will now survive. Whether

their long-term prognosis is the same as that found in earlier studies is uncertain.

3.3 **Abnormal FHR patterns**

In contrast to the situation with Apgar score or acid-base status, no defined population exists for which FHR abnormalities in labour and long-term outcome have been systematically recorded (Lumley, 1988). Indeed, most studies investigating possible associations between abnormal FHR patterns and neurological outcome have focused on neonatal problems.

There is no doubt that ominous FHR patterns, particularly profound and prolonged bradycardia, may precede intrapartum death (Hon, 1959; Hon & Lee, 1963). However, the evidence relating abnormal FHR patterns to neonatal neurological function (apart from seizures) is inconclusive. Murphy *et al.* (1981), in a study of term infants, failed to show a significant association between abnormal FHR patterns and scores on the Brazelton assessment scale (Als *et al.*1977) at 48-72 hours. Ellison *et al.* (1991), whose study included infants of all gestational ages, showed not only that abnormal FHR patterns were related to scores on a battery of neonatal tests (including the Brazelton scale), but also that the association was specifically with late decelerations, both in the first and second stages of labour.

This group also reported an association between late decelerations and neonatal seizures. A more general association between any abnormal FHR pattern and neonatal seizures in term babies has been found in three further studies (Keegan *et al.*1985; Derham *et al.*1985; Minchom *et al.*1987). Derham *et al.* showed that an abnormal CTG carried a relative risk of 4.4 of neonatal seizures; Minchom *et al.* estimated the relative risk as 6.2. Keegan *et al.* reported a particular association between abnormal FHR patterns and seizures starting within 48 hours of birth.

Information about abnormal FHR and later neurological development has largely been derived from a follow up study of 50 high-risk infants who were monitored in

labour (Painter *et al.* 1978; Painter *et al.* 1988). Of the 50 in the cohort, 22 had serious FHR abnormalities, 16 moderately serious abnormalities, and 12 had normal FHR patterns. Infants with abnormal FHR patterns were more often assessed as neurologically abnormal at age 48-72 hours than were infants with normal FHR patterns. Detailed neurological tests were subsequently performed at 2,4,6,9 and 12 months, and a statistically significant deficit in the performance of children with abnormal FHR patterns was reported (Painter *et al.* 1978). Examination of the published data shows however that the statistical test supporting this claim was incorrectly carried out. Each FHR group included a small number of children, on whom repeated tests were performed. The chi-squared table comparing the normal and abnormal FHR groups treated each test result as though it were an independent observation, instead of, correctly, treating each child as the unit of observation. Correct analysis of the data does not produce statistical significance, although the results are certainly in the stated direction. A second report of these children at ages 6-9 years found no differences between the FHR groups in scores on detailed developmental tests. Only one child without congenital anomalies was neurologically abnormal at the age of 6-9 years; this child had a seriously abnormal FHR pattern, and a significant neurosensory hearing loss (Painter *et al.* 1988).

3.4 Neonatal encephalopathy and seizures

A study of term singleton survivors in the large NCPP cohort considered whether infants suffering possibly asphyxial complications in late pregnancy or labour, such as placental abruption or nuchal cord, were at increased risk of later cerebral palsy, even in the absence of abnormal neonatal behaviour. The results made it clear that to be at increased risk, the infant had to show abnormal signs in the neonatal period, such as a late low Apgar score, decreased activity after the first day of life, feeding difficulties or seizures. As the number and duration of abnormal signs increased, the

prognosis worsened, and infants with sustained neonatal neurological abnormality had a relative risk for cerebral palsy (at age 7 years) of 10.2 compared to other infants. Those infants with pregnancy or birth complications, but without abnormal neonatal signs, had no increase in risk (Nelson & Ellenberg, 1987).

Other studies have repeatedly shown a close association between neonatal encephalopathy and later neurological abnormality, infants with the most severe grade of encephalopathy having the worst outcomes. An early study by Brown *et al.* (1974) predated the classification of the term "neonatal encephalopathy" (Sarnat & Sarnat, 1976). It investigated 93 infants of all gestational ages with abnormal neonatal behaviour following possibly hypoxic events in pregnancy or labour. At follow up (mean age 21 months), 22% of the infants had died and 26% were handicapped, the majority with cerebral palsy. The severity of the handicap was related to muscle tone in the neonatal period. None of the infants with normal tone died or suffered a significant handicap, in comparison with 65% of those with persistent hypotonia (who would have been classified as Stage 2 or Stage 3 encephalopathy).

Three further studies of full-term infants found a direct relation between the grade of encephalopathy and the proportion of children experiencing each grade who died or were impaired. Finer *et al.* (1981) followed 89 singletons for between 3 months and 4 years; overall, 7% died and 28% had a moderate or severe handicap. Robertson and Finer (1985) investigated 226 infants; 11% died and of the 174 survivors followed to age 3½ years, 17% were handicapped. In both these studies, all the infants with mild (Stage 1) encephalopathy emerged intact, all the infants with severe (Stage 3) encephalopathy died or were handicapped, and those with Stage 2 encephalopathy had an intermediate outcome. In the study of Levene *et al.* (1986) 122 children were observed for 1 to 5 years; 11% died, and 7% were severely handicapped, most with cerebral palsy. Again, all those with mild encephalopathy were

unscathed, while 76% of those with severe encephalopathy died or had a significant handicap, as against 25% of those with moderate encephalopathy. These workers compared the predictive values of encephalopathy and a late low Apgar score. They made the important observation that handicap was associated with a low Apgar score only if signs of encephalopathy were also present.

Robertson and Finer followed up their cohort to the age of eight years (Robertson *et al.* 1989). As expected, the proportion of children with a definite impairment (such as cerebral palsy or deafness) increased with the grade of encephalopathy suffered. But it was also observed that children who had survived moderate encephalopathy with no definite impairment were nevertheless more likely to be delayed in reading, spelling and arithmetic than were children in a control group of the same age. The group with mild encephalopathy (none of whom was impaired) included the same proportion of delayed children as the control group. Thus moderate encephalopathy appeared to be related both to severe impairment and to milder developmental delay.

Neonatal seizures starting on the first or second day of life are one of the signs of Stage 2 or 3 encephalopathy. Some investigators have framed their enquiries in terms of early seizures rather than encephalopathy, although many infants with seizures will have other abnormal signs too. They have found that such seizures portend a high rate of death or handicap: 48% in the study of Finer *et al.* (1981); 30% in the study of Minchom *et al.* (1987) and 59% in the study of Derham *et al.* (1985), representing a 40-fold risk relative to a control group.

An analysis by Ellenberg and Nelson (1988) made it clear that seizures without other abnormal neonatal signs are far less ominous than the combination of signs constituting encephalopathy. They showed that infants with neonatal seizures, but no other abnormal neonatal signs, had a 10% risk of death in the first year, but that survivors in this group had no greater a risk of later cerebral palsy than infants with-

out seizures; that is, a risk of 1.3 per 1000. In contrast, the most potent predictor of death or cerebral palsy was the combination of three perinatal events: a 5-minute Apgar score ≤ 5, clinically recognised neonatal seizures, and at least one sign of neonatal encephalopathy. A tiny subgroup of the population (0.8 per 1000) had all three characteristics, which carried a 33% risk of death and, among survivors, a 55% risk of later cerebral palsy.

3.5 **Low Apgar score and acidaemia**

As mentioned above (section 2.3), low Apgar score and acidaemia are related, in that severe depression at birth is most likely to occur among the most acidaemic babies. For example, among term infants with umbilical arterial pH < 7.00, between 28% and 30% have been observed to have a one-minute Apgar score ≤ 3, compared with 2-3% of less acidaemic babies (Gilstrap *et al.* 1989; Winkler *et al.* 1991; Goldaber *et al.* 1991). Because acidaemia of this degree is associated with neonatal death and seizures (Goldaber *et al.* 1991), and given the prognostic importance of seizures and abnormal neonatal signs, it might be expected that the combination of a low Apgar score and acidaemia would herald the worst outcome. Indeed, several authors have suggested that birth asphyxia is best identified among those with a low (≤ 3) Apgar score, a need for resuscitation and severe acidaemia (Low, 1988; Gilstrap *et al.* 1989; American College of Obstetricians and Gynecologists, 1991).

Follow up studies of acidaemic infants have generally included only a handful of children with a very low Apgar score and an extreme degree of acidaemia (pH < 7.00), so that the prognostic significance of this combination of signs is not clear (Ruth & Raivio, 1988; Fee *et al.* 1990). However, two studies using less stringent definitions of acidaemia have found, contrary to expectations, that neurological abnormality among children born at term is most frequent among those with the combination of a low Apgar score and normal acid-base status at birth. This was

observed both in the neonatal period (Dijxhoorn *et al.* 1986) and at age 4½ years (Dennis *et al.* 1989). In the former study, neurological abnormality was defined as hypo- or hyperkinesia, hypo- or hypertonia, hemi-syndrome, apathy syndrome, or hyperexcitability syndrome; that is, the presence of some signs of newborn encephalopathy. In the latter study, infants with a low (≤ 3) one-minute Apgar score and normal acid-base status had significantly lower scores on locomotor and hearing/speech tests and were more behaviour disordered than control children. Both these studies included small numbers (<20) in the group having a low Apgar score and normal acid-base values, and their findings need to be further explored.

3.6 Summary

It is important to gain a better understanding of how birth asphyxia affects neurological outcome. Because this understanding is hazy, it is still not known to what extent neurological damage can be prevented by obstetric or paediatric intervention, nor is it clear how potentially treatable children should be identified. Further, there is confusion, both ethical and legal, about the responsibility of the obstetrician for a child's neurological impairment.

Certain links between markers of asphyxia and neurological outcome are generally accepted. Severe cerebral depression at birth, as reflected in a prolonged low Apgar score, is associated with both death and later cerebral palsy. Moderate or severe neonatal encephalopathy is a strong predictor of both death and serious impairment, including cerebral palsy, and the more severe the encephalopathy, the more likely are these devastating outcomes. It also seems that children who survive moderate neonatal encephalopathy without serious impairment may nonetheless be developmentally delayed. Early neonatal seizures are closely associated with death and serious handicap, although they appear to be important as part of the complex of signs constituting encephalopathy, rather than as a separate entity.

Some of these links are understood only in general terms, and much detail needs to be filled in. This is particularly true of low Apgar score, perhaps because the huge NCPP cohort, which has provided most of our knowledge about Apgar score, predated the classification of neonatal encephalopathy and the common use of acid-base measurement and FHR monitoring. Moreover, this study concentrated on death and cerebral palsy, and provided much less information about milder forms of impairment.

It is widely agreed that cerebral depression at birth - that is, a low Apgar score - must be present if neurological damage is to ensue (Nelson & Ellenberg, 1987). The longer the depression lasts, the worse the outlook. A persistent low Apgar score may progress to neonatal encephalopathy, or it may resolve without further abnormal signs. We know that the combination of a low Apgar score and other signs of encephalopathy portends a far worse outcome than a low Apgar score alone (Ellenberg & Nelson, 1988). Indeed, one study observed that a low Apgar score led to serious neurological impairment only if additional signs of encephalopathy were present (Levene *et al.*1986). This observation needs to be confirmed, not only for severe impairment, but also for less severe.

As we have seen, the most direct marker of birth asphyxia is fetal acidaemia (as reflected in umbilical arterial blood). Extreme acidaemia increases the risk of neonatal death and seizures, but as would be expected from the foregoing, acidaemia alone, without cerebral depression at birth, does not carry a poor prognosis for the long term. However, acidaemia is associated with low Apgar score, and given the separate significance of each of these markers, one might expect their combination to herald an adverse outcome. It would be illuminating to know whether those infants with a persistent low Apgar score, encephalopathy and a poor outcome also exhibit acidaemia. If they do not, an acute intrapartum asphyxial insult could not be impli-

cated in their condition.

Long-term outcome after a low Apgar score and acidaemia has not been systematically investigated. However, two studies have reported that neurological abnormality among children born at term is most frequent among those with a low Apgar score and a normal acid-base status at birth (Dijxhoorn *et al.* 1986; Dennis *et al.* 1989). In both studies, this conclusion was based on a small number of children, and it needs to be further examined. If confirmed, it would again suggest that some of the adverse outcomes associated with low Apgar score are not due to acute intrapartum asphyxia.

Finally, FHR patterns of infants with a low Apgar score have never been studied. Indeed, although it has been observed that particular ominous FHR patterns may precede death and neonatal seizures, there is little direct information about the relation between abnormal FHR patterns and long-term outcome in any group of babies.

3.7 **Introduction to present study**

The purpose of this investigation was to address the following questions:

(i) Can we confirm that a low Apgar score only heralds a poor outcome if accompanied by other signs of neonatal encephalopathy?

(ii) Among infants with a low Apgar score, is neonatal encephalopathy associated with acidaemia? Or does it more often occur with a normal acid-base status?

(iii) Is the combination of low Apgar score and acidaemia more favourable (as has been suggested) than low Apgar score with a normal acid-base status?

(iv) Among infants with a low Apgar score, what is the long-term significance of abnormal FHR patterns in labour?

Because almost all infants with prolonged cerebral depression at birth are depressed at one minute (Nelson & Ellenberg, 1981), the study cohort was a consecutive series of births with a one-minute Apgar score ≤ 3. We set out to measure acid-base

status in umbilical arterial blood for all these infants, and to retrieve details of their FHR patterns where they had been monitored in labour. We planned to trace the infants at the age of five years and to give them a range of developmental tests, in order to identify any impairment, whether severe, moderate or mild.

This was the first follow-up study to collect such comprehensive information about a group of infants with low Apgar score. The combination of detailed FHR analyses, acid-base status at delivery, perinatal details and neurodevelopmental function at the age of five was unique.

CHAPTER II

OUTCOME AT AGE FIVE YEARS OF A COHORT OF TERM INFANTS WITH ONE-MINUTE APGAR SCORE ≤3: MATERIALS AND METHODS

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CHAPTER II

FOLLOW-UP AT AGE FIVE YEARS OF A COHORT OF TERM INFANTS WITH ONE-MINUTE APGAR SCORE ≤3: MATERIALS AND METHODS

1. SUMMARY

Ethical approval for the study was obtained from the Central Oxford Research Ethics Committee.

During 1984 and January-September 1985 we planned to measure the acid-base status of umbilical cord blood of all babies delivered at the John Radcliffe Hospital, Oxford, who had a one-minute Apgar score ≤3. There were 273 such infants (2.8% of total deliveries), 191 of whom were singletons born at or after 37 weeks' gestation. Seven of these infants had specific anomalies leading to neonatal death (six congenital malformations; one rhesus disease) and were excluded from further consideration. The remaining 184 infants, originally thought to be normally formed, constituted the full study cohort. They included three further neonatal deaths, ascribed on autopsy to "birth asphyxia", and 181 survivors.

We set out to trace the 181 survivors at age 5 years. 161 consented to a detailed neurodevelopmental assessment by a paediatrician; for a further eight children a broad assessment of neurodevelopmental outcome was obtained from other sources. Of these 169 children two were excluded from the analysis because of congenital abnormalities apparent at the time of follow-up. The remaining 167, together with the three whose neonatal death was ascribed to "birth asphyxia", were the subject of the analysis.

2. MEASUREMENT OF ACID-BASE STATUS IN UMBILICAL CORD BLOOD

2.1. Collection and analysis of cord blood samples for infants with one-minute Apgar score ≤3

At the end of 1983, staff on Delivery Suite were asked to collect and analyse umbilical cord blood for all infants who had a one-minute Apgar score of 3 or less. Since routine cord blood collection and analysis had not previously been carried out in

this hospital, the request was made by a consultant clinical physiologist (Dr Paul Johnson), who explained the study, and subsequently made regular visits to Delivery Suite to encourage compliance. A prominent notice reminding staff of the study was posted in Delivery Suite.

The Apgar score (Apgar, 1953) ranges from 0 (the infant with no sign of life) to 10 (the vigorous infant with no sign of depression). (Table 1.1). The score is usually assigned by the midwife who takes the baby from the accoucheur immediately after delivery, but if a paediatrician is present, he or she will assign the score.

At delivery, the umbilical cord is clamped near the baby and the cord cut. To obtain a segment of cord for blood sampling, a second set of clamps was placed further along the cord and the cord again cut. The segment was placed in a dish and a blood sample was drawn anaerobically into a polyethylene syringe containing a solution of heparin and sodium fluoride, as described above. The samples were analysed immediately with an ABL3 Acid-Base Laboratory (Radiometer, Copenhagen), or if this was not possible, placed in ice, and stored at 5°C until measurement. The median time from collection to analysis was 18 minutes, with a range of 1 to 168 minutes. Of the 124 blood samples measured, only six (4.8%) were stored for more than 60 minutes before analysis.

Collection and analysis of cord bloods took place from the beginning of January 1984 until the end of September 1985.

The results of the cord blood analyses were obtained each working morning from Delivery Suite, and details recorded in a book. As a check on the completeness of coverage, the identities of babies for whom results were expected (all those with one-minute Apgar score ≤ 3) were obtained daily from the Delivery Suite registers, in which Apgar scores were recorded. Details of missing measurements were noted, and brought to the attention of Delivery Suite staff, in an effort to improve their rate of measurement.

2.2. **Effect of delay in measurement**

The acid-base composition of blood samples changes progressively with the time between collection and measurement (Sigaard Andersen, 1961; Strickland *et al.* 1984). Because we could not guarantee immediate analysis of umbilical cord blood samples in a busy clinical setting, we investigated ways of counteracting this problem. Of the various methods previously proposed, the most promising was that of Nhan *et al.* (1980), who redistributed samples into syringes containing sodium fluoride and stored the samples on ice. Their results however were inconsistent, possibly because the redistribution of blood increased gaseous exchange, or because the concentration of sodium fluoride used was insufficient to inhibit glycolysis. We therefore tested the effect of adding a higher concentration of sodium fluoride to the heparin solution used as an anticoagulant, and storing samples at 5°C. Our results showed that in blood samples stored at 5°C with 20mM sodium fluoride, only small changes in blood gas measurements were observed over 24 hours (Farrow *et al.* 1987). Most of the changes occurred within the first two hours after collection; thus the mean fall in pH observed after two hours was 0.019 (95% CI 0.013,0.025), and after 24 hours 0.028 (95% CI 0.016,0.040). In samples stored without sodium fluoride, blood gas measurements showed continuous and substantial changes over a 24-hour period.

For this study, we used the method described above, and are confident that such changes did not occur.

3. IDENTIFICATION OF STUDY COHORT

3.1. **The Oxford Obstetric Data System (ODS)**

To avoid the confounding effects of prematurity and multiple birth (see Chapter I, Section 1.2), the study cohort consisted of singletons born at term. It was therefore necessary to identify the full-term singletons from among all the infants with a low (≤ 3) one-minute Apgar score.

A detailed listing of the singletons born in the study period with a one-minute

Apgar score ≤ 3 was obtained from the Oxford Obstetric Data System (ODS) (Yudkin & Redman, 1990). The ODS is a computerised system for storing and retrieving obstetric data, based at the John Radcliffe Hospital. For all women delivering in the hospital at 20 weeks' gestation or later, the system records a wealth of clinical and other information about the pregnancy, delivery and newborn baby. At the time of the study, this information was entered into the ODS after each woman's discharge by a team of coding clerks. To check that all deliveries had been covered, the identification details on each coded case-note were checked against the entries in the Delivery Suite registers. The coding clerks were thus alerted to missing case-notes, and conversely to the rare cases where a delivery had been inadvertently omitted from the Delivery Suite registers. This checking system ensured that the total number of deliveries entered on the ODS was as accurate as possible.

The accuracy of the clinical data within the ODS was originally established by comparison with manual records which were kept concurrently. Later, accuracy was maintained by frequent use of the system, particularly by selecting mothers or babies with certain characteristics or diagnoses, and inspecting their case-notes (Yudkin & Redman, 1990).

Of the 273 deliveries between January 1984 and September 1985 with a record of a one-minute Apgar score ≤ 3, 251 were singletons. The full-term infants were identified from the print-out containing details of these cases.

3.2. **Calculation of gestational age**

Term was defined as a gestational age of 37 or more completed weeks at birth.

Gestational age was assessed as follows. The ODS records the obstetrician's "best estimate" of the expected date of delivery (EDD). This is derived from the date of the last menstrual period (LMP), or, especially where this date is unknown or uncertain, from the result of an ultrasound scan.

Because gestational age estimated by ultrasound scan is most accurate when the scan assessment is 20 weeks' gestation or less (The British Medical Ultrasound Socie-

ty, 1990) we recalculated EDD in the cases where such an early scan had occurred. This recalculated EDD did not always agree with the obstetrician's "best estimate". If it differed by more than 14 days from the obstetrician's estimate, the scan prediction of EDD was preferred. Gestational age was then based on the difference between the EDD and the actual date of delivery. A baby born on the EDD would have gestational age exactly 40 weeks; one born 7 days after the EDD a gestational age of 41 weeks and so on.

An assessment of gestational age is generally made by a paediatrician after birth; this is likely to be more careful and accurate if the baby is apparently preterm. Thus if birthweight was less than 2000g and the baby was admitted to the Special Care Baby Unit, the paediatrician's estimate was accepted if it differed by more than 21 days from the previous calculation of gestational age. For other babies, the paediatrician's estimate was accepted only if it differed by more than 28 days from the previous calculation. By taking the paediatrician's estimate of gestational age into account we avoided serious errors that would otherwise have arisen in some cases without an early ultrasound scan and with an uncertain date for the LMP.

Of the 251 singleton infants with one-minute Apgar score ≤ 3, 191 were born at or after 37 weeks' gestation.

3.3. **Neonatal deaths**

Ten of the 191 children died in the first month; eight had an autopsy. Six of the deaths were due to congenital anomalies: (i) Edward's syndrome (no autopsy) (ii) situs inversus with persistent fetal circulation (no autopsy) (iii) multiple congenital abnormalities (iv) pulmonary hypoplasia (v) transposition of the great vessels (vi) pulmonary agenesis with VACTERL sequence. The seventh death was ascribed to Rhesus haemolytic disease. These seven infants were excluded from further consideration.

The other three infants who died neonatally were included in the study cohort.

The cohort thus comprised 181 survivors and three neonatal deaths ascribed on autopsy to "birth asphyxia".

4. TRACING CHILDREN FOR FOLLOW-UP AT AGE 5 YEARS

4.1. Tracing children

General method

We aimed to assess the 181 surviving children between the ages of 4 years and 9 months and 5 years and 3 months. Since they had been born over a period of 21 months, efforts to trace them were staggered appropriately.

Identification details of the mothers and of their general practitioners at the time of delivery were obtained from the case-notes. The GP was contacted by a letter (Appendix 1) explaining the study, and asking whether there were any reasons why we should not contact the family involved. The name and N.H.S. number of the index child, and the mother's present address, were also sought. A stamped addressed envelope was always included whenever a reply was expected. Replies were obtained from all the GPs, sometimes after one or more written reminders or telephone calls.

Difficulties

Difficulties arose in tracing families when the mother had changed her name, or when the family had changed their GP or moved house (often several times) since the baby's birth. Service families who had moved house could reliably be traced through the Soldiers', Sailors' and Airmen's Families Association. In most other cases, the family's new address (or name) was obtained from the original GP or from the practice receptionist or health visitor. Once the family's current address was known, a letter requesting the name and address of their present GP was sent to the local Family Practitioner Committee (now known as the Family Health Service Authority), or, in Scotland, to the relevant Area Health Board (Appendix 2).

If the Family Practitioner Committee failed to identify the GP, his or her name and address could generally be obtained from the pre-school section of the local Child

Table 2.1

Numbers in study

	Total
Total in cohort	184
Neonatal death - "birth asphyxia"	3
Survivors	181
Not approached -	
not traced	1
multiple congenital anomalies	1
abroad	6
impending lawsuits	4
Approached	169
Refused	8
Assessed	161
Excluded before analysis -	
*congenital anomalies	2
Detailed outcome analysis	159
Not assessed, but Impairment Rating assigned	8
Total with Impairment Rating or "asphyxial" neonatal death	170

*1 Turner's mosaic syndrome, 1 dysmorphic features and global delay.

Health Department. This Department (or the Family Practitioner Committee itself) occasionally provided both the current address of the family and the details of their GP. In one case in which none of the above sources produced the required information, we contacted the Office of Population Censuses and Surveys (OPCS) which informed us of the mother's death, and of the child's present address.

Families not traced

Six families were living abroad, at unknown addresses, and we were unable to contact them. One family of travellers was not traced. After normal channels had failed, we approached the Gypsy Council, the Save the Children Fund, several local Gypsy Education Units in areas where the family had been sighted, health visitors and clergy. Although telephone contact was established with a relative of the mother concerned, the mother herself was never traced.

4.2. **Arranging for assessments**

Of the 174 survivors who were traced, the families of five were not approached (Table 2.1). One child was reported by the GP to have multiple congenital anomalies causing severe impairment; four families were considering lawsuits against the hospital, and we were advised not to contact them. (Detailed assessment would anyway have been precluded for three of these children, known to have severe cerebral palsy.)

An approach was made to the remaining 169 families. In one case, where the child was in the process of being adopted, the approach was made to the child's social worker. A letter was sent explaining the study, and asking consent for the child to be given an assessment by a developmental paediatrician (Appendix 3). Parents were asked to return a form giving contact details, and stating whether they would prefer the assessment to be done at home or at the John Radcliffe Hospital. All the families contacted replied, sometimes after written reminders or follow-up telephone calls. Where consent was given, an appointment for the assessment was made, and a confirmation letter sent.

The social worker and seven parents did not agree to the child's participation. Thus 161 of the 181 survivors in the cohort were assessed (Table 2.1). Because of the wide variation in the time taken to make contact, it proved impossible for all the children to be assessed within the age range we had originally planned (57 months to 63 months). Nevertheless 145/161 children (90.1%) were assessed within the target age range, and 12 others were seen between 55.5 months and 57 months. Three children who returned from living abroad during the course of the study were tested late (aged 66 months, 68 months and 72 months). One child whose mother failed repeatedly to keep appointments was finally seen at the age of 71 months.

5. THE NEURODEVELOPMENTAL ASSESSMENTS

Each assessment lasted about 1½ hours, and was generally carried out with a parent present. All but two of the assessments were carried out by the same paediatrician (Dr Ann Johnson). Two children living in Scotland were assessed by a second paediatrician (Dr Lesley Mutch) who had previously carried out similar assessments in a collaborative study with Dr Johnson.

After each child had been assessed, a summary of the paediatrician's findings was sent to the GP.

5.1. Assessment of controls

To improve the objectivity of the assessments, 22 "control" children, singletons born at term during the study period and with a one-minute Apgar score of 7 or more, were also assessed. The paediatricians were unaware of the perinatal history or cord blood measurements of any of the children. Results for the "control" children were not used in this study.

5.2. Griffiths developmental scales

Description

Five of the six subscales of the Griffiths Developmental Scales (Griffiths, 1970)

were used: locomotor, personal/social, hearing/speech, eye-hand co-ordination, and performance. The sixth scale - practical reasoning - was not employed because the paediatrician felt it to be too dependent on the child's social background and experience. It includes, for instance, ability to count, and knowledge of the value of different coins.

Each subscale consists of groups of six tasks, each group being graded according to year of age. For instance, on the locomotor subscale, the six tasks set for the fifth year (i.e. between the ages of 48.0 and 59.9 months) are: (i) can run to kick a ball (ii) walks downstairs with one foot on each step, in an adult manner (iii) touches toes with the knees straight (iv) jumps a 6 inch high rope with both feet together (v) can climb on and off a bus unaided (vi) can run upstairs. (The ability to perform some items can be accepted by report.) The six tasks at the sixth year level (ages 60.0 to 71.9 months) are: (i) can bounce and catch ball (ii) can run fast out of doors (iii) can hopskip four or more times (iv) can jump off three steps (v) can hop once on one foot.

Appendix 4 shows a completed Griffiths test book for one of the children in the study. This contains details of the tasks demanded on each subscale.

Scoring

A child is taken through successive levels of the test until three failures occur. Mental Age is then calculated according to the age-level of the tasks achieved. For instance, a child who can perform all tasks up to and including those for the fifth year, but none above this, would have a Mental Age of 60 months. A child able to perform three of the six tasks at the sixth-year level (and all tasks at lower levels) would have a Mental Age of 66 months.

The Griffiths score for each subscale is Mental Age (months) x 100/Calendar Age (months). Thus a child aged 4 years 9 months who has a Mental Age of 62 months on a particular subscale would score (62 x 100/57) = 109. The Griffiths

score can therefore identify equally well both the unusually able and the unusually poor performer.

Norms for Griffiths subscale scores

When the Griffiths tests were originally devised, the mean score for each subscale was set at 100. Norms for children aged 2 to 7 years were based on the performance of 1397 children, tested in 1960 (Griffiths, 1970). Application of the tests in 1980, to a sample of 217 children in the same age range, showed an increase in the mean score achieved on all the subscales, of between 7 and 15 points (Hanson & Aldridge Smith, 1987).

In the present study, the scores achieved by children in the cohort were not compared with external standards. Rather, scores achieved by subgroups of the cohort were compared with one another.

5.3. **Movement Assessment Battery for Children (Movement ABC)**

Description

The Movement Assessment Battery for Children (Movement ABC) (Henderson & Sugden, 1992) was formerly known as the Test of Motor Impairment (Stott *et al.* 1984). In contrast to the Griffiths Test, it is designed specifically to measure motor impairment in children, and the score indicates the extent to which a motor-impaired child falls below the level of age-peers. No attempt is made to provide a scale of performance that falls above the normal range.

Four areas of motor ability are tested: manual dexterity, ball skills, static balance and dynamic balance. The set tasks are graded in two-year age-bands with the results being scored according to the exact year of age. Thus although children in the age-band five to six years all attempt the same tasks, six-year olds are scored at a more demanding level. Unlike the Griffiths Developmental Scales, the scoring is not graduated to take account of the child's age in months.

The tasks set in our study were those for the age-band five to six years, and the

scores assigned those appropriate for five-year olds, even though some of the children in our cohort were tested before their fifth birthday. Of the following eight tasks set, numbers 1,2 and 3 test manual dexterity, numbers 4 and 5 test ball skills, number 6 tests static balance, and numbers 7 and 8 test dynamic balance.

1. *Posting coins*

Equipment: a money box, and twelve plastic coins. At the stopwatch signal, the child drops the coins through the slot one at a time, but may not change hands during the trial. The tester stops timing when the last coin strikes the bottom of the box. The preferred hand is tested first, followed by the other hand. The number of seconds taken to complete the task is recorded. If the pass criterion is not achieved, a second trial is allowed.

2. *Threading beads*

Equipment: a lace and twelve cube-shaped beads. At the stopwatch signal, the child threads the beads, one at a time, as quickly as possible. The tester stops timing when the child moves the last bead into position. The number of seconds taken to complete the task is recorded. If the pass criterion is not achieved, a second trial is allowed.

3. *Bicycle trail*

Equipment: a picture of a narrow, curving bicycle trail. The child draws a continuous line, following the trail without crossing its boundaries. Only the preferred hand is tested. The picture should not be rotated during the test, and the child must continue in the same direction throughout. One trial only is allowed. The tester records the number of times the drawn line moves outside one of the boundaries of the track. An additional fault is counted for each centimetre that the line stays outside the track.

4. *Catching a bean bag*

Equipment: bean bag and tape, to mark a distance of 6 feet between the tester and child. The tester throws the bean bag so that it comes down between the child's

waist and shoulder. The child catches the bean bag with both hands, without gathering it to the body. Five practice throws are allowed. The test consists of ten throws and catches. The number of clean catches out of ten is recorded.

5. *Rolling a ball into goal*

Equipment: two jumping stands placed 16 inches apart, and tape to mark a distance of 6 feet between the child and the jumping stands. With the preferred hand, the kneeling child rolls a ball along the floor between the stands, to score a "goal". Five practice rolls are allowed. The test consists of ten attempts at scoring a goal. The number of goals out of ten is recorded. It is permissible for the ball to touch one of the stands as long as it goes through the goal.

6. *One leg balance*

The child stands on one leg, with the arms held freely by the sides, for up to 20 seconds. Both legs are tested. The number of seconds the child maintains balance is recorded. If the pass criterion is not achieved, a second trial is allowed.

7. *Jumping over cord*

Equipment: two jumping stands with pins and cord; the cord is fixed at the child's knee height. From a stationary position with two feet together, the child jumps over the cord; the feet must be together for take-off and landing. Three attempts to clear the cord are allowed. If the child fails at the third attempt, the cord is lowered by one hole, and three more attempts are allowed.

8. *Walking with heels raised*

Equipment: a 15-foot line of tape is laid on the floor. The child walks along the line with heels raised, and without stepping off the line. Three attempts to walk the length of the line are allowed.

Scoring

A pass criterion is set for each of the tasks. If this is achieved, the child scores zero. If it is not achieved, the child scores 1 or 2. For each item, a score of 1 is

intended to apply to the lowest 15% of the population; a score of 2 to the lowest 5%.

The norms on which the criteria are based were derived from a parallel study of British and American children. The British sample consisted of 29-36 children of each sex, in each year group; the American sample of 30 children in each sex/year group (Stott *et al.* 1984). At the time of our study, there was no scoring system available for four-year olds, so we used the five-year old criteria for all the children in the study.

These criteria were as follows:

Posting coins (score for each hand)

Pass (score 0)	Preferred hand:	≤21 secs
	Other hand :	≤22 secs
Borderline (score ½)	Preferred hand:	22-23 secs
	Other hand :	23-25 secs
Fail (score 1)	Preferred hand:	24+ secs
	Other hand :	26+ secs

Threading beads

Pass (0)	≤58 secs
Borderline (1)	59-65 secs
Fail (2)	66+ secs

Bicycle trail

Pass (0)	≤12 deviations
Borderline (1)	13-18 deviations
Fail (2)	19+ deviations

Catching a bean bag

Pass (0)	6+ catches (out of 10)
Borderline (1)	4-5 catches
Fail (2)	≤3 catches

Rolling a ball into goal

Pass (0)	5+ goals (out of 10)
Borderline (1)	3-4 goals
Fail (2)	≤2 goals

One leg balance (score for each leg)

Pass (0)	9+ secs
Borderline (½)	6-8 secs
Fail (1)	≤5 secs

Jumping over cord

Pass (0)	Clear cord at knee height
Borderline (1)	Clear cord at lower height
Fail (2)	Fail to clear cord

Walking with heels raised

Pass (0)	13+ steps
Borderline (1)	7-12 steps
Fail (2)	≤6 steps

When the study was almost completed, a revised scoring system became available. It differed considerably from the one we had used, in that each item was graded in more detail, producing a range of scores of 0 to 5, instead of 0 to 2. Moreover, a set of criteria for four-year olds as well as for five-year olds was produced. However, we decided against rescoring the tests using these new standards, since it became clear at this time that scores in our study were significantly higher than the published norms, to the extent that we suspected a systematic error in the application of the test (see Chapter III, Section 5.2).

5.4. **Behaviour disorder**

As a measure of behaviour disorder, we used a questionnaire developed for five-year olds (Watt *et al.* 1980) (Appendix 5) based on the Rutter behaviour screening questionnaire (Rutter *et al.* 1970) which was originally intended for older children. This 15-item questionnaire was completed by the parents during the child's assessment session.

The questionnaire assesses both neurotic disorder (e.g. anxiety, fear, obsessiveness) and conduct disorder (e.g. lack of concentration, fighting, telling lies). The former is assessed by 6 questions (Nos. 6,8,9,12,13,15); the latter by 9 questions (Nos. 1,2,3,4,5,7,10,11 and 14). Each aspect of behaviour is rated by the parent as 0, 1 or 2. These ratings are added to give the Rutter score, which can thus range from 0 (no behaviour disorder) to 30 (extreme behaviour disorder).

The standards for the Rutter score for five-year olds were based on a sample of

282 children (146 boys and 136 girls). The mean (SD) score was 5.9 (4.1) and the median score 5 (Watt *et al.* 1980). A score of 12 or more was the cut-off point for identifying the most behaviour-disordered 10% of children.

5.5. **Impairment Rating**

Overall performance was summarised by an Impairment Rating based on review of the total outcome information available for each child, including the paediatrician's clinical impression. The Impairment Rating was developed in a previous study in this hospital (Dennis *et al.* 1989) during which it was recognised that numerical scores on developmental tests could not adequately reflect a child's overall level of impairment (Illingworth, 1989).

Three levels of impairment were defined:

(1) No impairment or nonspecific poor performance on single items, but overall appeared normal

(2) definite identified area(s) of impairment, not necessarily needing referral

(3) serious impairment, needing referral, and including global delay, lateralising signs, and severe deficit in a specific area.

For the children undertaking the battery of neurodevelopmental tests, the Impairment Rating was assigned by the paediatrician as soon as the test session was completed. An Impairment Rating could also be assigned for eight children not assessed: three whose families were considering lawsuits against the hospital, and five whose families refused assessment.

The three children with families considering lawsuits against the hospital all had cerebral palsy. Details of the neurodevelopmental outcome of these children were obtained from the Oxford Region Register of Early Childhood Impairment (Johnson & King, 1989). One had died at the age of four; all were rated as seriously impaired (Rating 3).

The five children whose families refused assessment included one with an

Impairment Rating of 3, assigned on the basis of reports from the Children's Assessment Unit of the Royal Bucks Hospital. This child was noted to be developmentally delayed, and to have difficulties with expressive language, described as oro-pharyngeal dyspraxia. Although at a mainstream school, he was receiving regular speech therapy and physiotherapy at the Assessment Unit.

The other four children were all rated as unimpaired (Rating 1). Three were assigned this Rating on the basis of their school medical records. Information about the fourth child (who was in the care of the Social Services) came from a recent school medical report, and from contact with the Senior Clinical Medical Officer of the Health Authority where he lived.

Since the Rating includes a subjective element, and cannot be defined in very precise terms, its repeatability was checked. After all the children had been assessed (but before analysis of the study results) the paediatrician reassigned each Rating, on review of the child's notes and test results. Of the 170 Ratings, 164 (96.5%) remained the same. Of the six Ratings that were altered, one was changed from Rating 2 to Rating 1, two from Rating 1 to Rating 2 and three from Rating 3 to Rating 2. Since very few children received a Rating of 3, this reflects a particular difficulty in distinguishing between serious impairment (Rating 3) and some impairment (Rating 2).

5.6. **Social and personal information**

Information about (i) the occupation and marital status of the parents (ii) the child's attendance at school or playgroup and (iii) the child's intercurrent illnesses or hospital admissions was gathered from a second questionnaire completed by the parent(s) during the assessment session (Appendix 6). Social class was assigned, based on the occupation of the head of household, according to the OPCS Classification of Occupations (Office of Population Censuses and Surveys, 1980).

The height, weight and occipito-frontal head circumference of the child was recorded by the paediatrician. Centiles were assigned by reference to the charts of

Tanner *et al.* (1966) and Ounsted *et al.* (1985).

6. RECORDING OF PERINATAL EVENTS

6.1. Final cohort for analysis

Of the 161 children assessed by the paediatrician, two were found to have congenital anomalies affecting their performance: one Turner's mosaic syndrome, and the other dysmorphic features and global developmental delay. These two children were therefore excluded from the analysis, leaving 159 with full assessment details.

Outcome information was known for an additional eight children, making 167 in all. With the addition of the three infants who died neonatally with a diagnosis of birth asphyxia, there were 170 children in the final analysis (Table 2.1).

6.2. Electronic fetal monitoring in labour

Of the 170 infants in the final analysis, six were delivered by caesarean section before labour. Of the 164 born after labour, 23 (14.0%) were monitored by intermittent auscultation, eight (4.9%) received a brief period of electronic monitoring on admission only, and 133 (81.1%) were continuously monitored in labour. Cardiotocographic (CTG) traces from 130 of the 133 continuously monitored infants were found.

The traces were analysed by an obstetrician with considerable experience in detailed CTG analysis (Dr Karl Murphy). Before analysis, as an aid to interpretation, the traces were marked with the times of membrane rupture, onset of labour, onset of the second stage, administration of oxytocin, epidural anaesthesia, and delivery. All other information, including the mode of delivery, Apgar score and acid-base status, was concealed. To improve the objectivity of the exercise, the traces were mixed with a further 80 "control" traces, taken from singleton, term infants with a one-minute Apgar score ≥ 7, and similarly prepared.

Ten main types of fetal heart rate (FHR) abnormality were defined (Parer,

Table 2.2

Fetal Heart Rate (FHR) Changes

Grade	Type
	Tachycardia (FHR in bpm)
1	Mild: 150-159
2	Moderate: 160-179
3	Severe: ≥180
	Bradycardia (FHR in bpm)
2	Moderate: 100-109
3	Severe, with recovery: <100 for >3 min
3	Severe until delivery: <100 for >3 min, no recovery
	Baseline variability (amplitude in bpm)
2	Reduced: 2-4
1	Increased: 16-24
3	Very increased: ≥25
3	Absent: <2
	Variable decelerations: amplitude ≥50 bpm
1	Mild: lasting <30 sec
2	Moderate: lasting 30-59 sec
3	Severe: lasting ≥60 sec, with <50% of contractions
3	Very severe: lasting ≥60 sec, with ≥50% of contractions
	Slow recovery or overshoot after decelerations
2	Slow recovery: return to baseline >1 min from end of contraction
2	Overshoot: post-deceleration acceleration, amplitude >15 bpm above baseline
	Late decelerations: amplitude >10 bpm, lag phase >20 sec
3	Severe: lasting >30 sec, with <50% of contractions
3	Very severe: lasting >30 sec, with ≥50% of contractions
	Uterine hyperstimulation
3	≥30 contractions in 60 min
	Sinusoidal pattern
3	Amplitude >5 bpm, frequency <5 cycles/min.
	Non-accelerative FHR pattern
1	Fewer than 6 accelerations per hour (of >15 bpm, lasting >15 sec)
	Poor quality recording
2	Artefact or inadequate data - interpretation limited

bpm: beats per minute
Assessment of baseline variability allows for physiological cyclical sleep states (Spencer & Johnson, 1986).

1983; Murphy *et al.* 1991) and some of them were subdivided according to severity (Table 2.2). Each abnormality was classified as Grade 1 (mild), Grade 2 (moderate) or Grade 3 (severe). The simultaneous occurrence of two or more Grade 2 abnormalities was counted as a Grade 3 abnormality. The abnormalities were graded the same whether they occurred during the first or second stage of labour.

For each infant, the duration of each FHR abnormality was noted, each stage of labour being analysed separately. A summary record was made of (i) the total duration of the trace (ii) the duration free of any abnormality ("time reassuring") (iii) the duration of each grade of FHR abnormality (more severe grades taking precedence over less severe where both occurred together).

Based on these details, and particularly on the combination of different abnormalities, the obstetrician gave an overall assessment of each trace. The purpose was to identify the most ominous traces, namely those that were judged by the obstetrician to predict acidaemia at delivery (umbilical arterial pH ≤ 7.10 and base deficit > 12 mmol/l), and/or a low (≤ 3) one-minute Apgar score. This was essentially a subjective judgement, based on the obstetrician's knowledge and experience, and was akin to the assignment of an Impairment Rating by the paediatrician (Section 5.5). It was thus not equivalent to a formal set of criteria. Each CTG was labelled by the obstetrician as either "ominous" or "not ominous".

Of the 130 traces available for scrutiny, 5 could not be classified: 3 short traces of poor quality, and 2 vaginal breech deliveries with no trace in the second stage. The remaining 125 traces all continued to within 10 minutes of delivery, and were considered of adequate quality to be classified by the obstetrician.

6.3. **Other perinatal events**

The obstetric (and where applicable, paediatric) case-notes of all the infants in the cohort were found. For the four families considering lawsuits against the hospital the notes were obtained from the Health Authority's Administrative Department.

Information about the pregnancy, delivery and neonatal period was extracted

from the notes and from the ODS printout, and was recorded on a structured coding form (Appendix 7). A consultant neonatologist (Dr Peter Hope) gave advice on the interpretation of complicated paediatric notes, and determined the grading of neonatal encephalopathy, which was defined according to Sarnat and Sarnat (1976).

7. DATA MANAGEMENT

7.1. Data entry

As the data were gathered, they were transferred to the structured coding form (Appendix 7). Some of the paediatric assessment data had to be transformed before entry onto the form (e.g. results of the Movement ABC tests had to be converted into scores).

The data were then keyed into the Oxford University VAX computer via a modem link from the John Radcliffe Hospital.

7.2. Accuracy of data

The acid-base values were checked individually for plausibility, and advice on questionable results was given by a consultant clinical physiologist (Dr. Paul Johnson). Occasionally, the recorded values showed the venous blood to be more acidaemic than the arterial blood. This was assumed to be a recording error, and the values were reversed. In a few other cases, the recorded values for the vein and artery were identical, showing that two samples had mistakenly been drawn from the same vessel. In these cases, a decision as to the most likely source of the blood was made by Dr Johnson.

As the data were entered into the computer, regular printouts of the file were obtained, and the new entries checked by eye against the original coding forms.

After all the data had been entered, the frequency distributions of all the variables were checked for outliers or impossible values, and errors corrected. A number of crosstabulations were carried out to check consistency of recording. For

example, mode of delivery was crosstabulated against the reason for operative delivery; type of monitoring in labour against the obstetrician's prediction of a poor outcome.

Some errors came to light during the analysis. These were most likely to be spotted when primary sources (e.g. the obstetrician's detailed CTG data; the Griffiths record book) were examined for detailed information not recorded on the coding sheet.

7.3. **Statistical methods**

Computer packages

The main analysis was carried out using SPSS-X (SPSS Inc. Chicago, IL 1988), on the Oxford University VAX computer. Confidence intervals were calculated using the package CIA (Confidence Interval Analysis; Gardner S.B., Winter P.D., Gardner M.J. 1991). Exact probabilities for contingency tables were calculated using the package StatXact (CYTEL Software Corporation, Cambridge MA 1989).

Study size

In a previous follow-up study in this hospital (Dennis *et al.* 1989) the small group of children with a one-minute Apgar score ≤ 3 and no acidaemia had a mean locomotor score of 103.2, 8.7 points lower than the mean for children with a low Apgar score and accompanying acidaemia. This finding generated the original hypothesis for this study, which was that mean locomotor Griffiths score among non-acidaemic children would be 8.7 points lower than the mean for acidaemic children.

An opportunity to test this hypothesis was presented by the availability of data from a cohort of children born in 1984 and 1985. The cohort - of consecutive deliveries with a one-minute Apgar score ≤ 3 - had originally been studied for the purpose of describing and classifying the possible causes of a low Apgar score. The number of term singletons in the cohort was large enough to detect the hypothesised difference in Griffiths locomotor score with a power of 80%, at the 0.05 level of

significance (two-tailed test).

As well as enabling this hypothesis to be tested, the data presented a unique opportunity to draw together specific information about the peripartum period and long-term outcome. No previous study had examined the relationships between fetal heart rate changes in labour, acid-base status at delivery, neonatal signs, and neurodevelopmental function at the age of five. For this purpose, there was no formal sample size requirement.

Comparisons between groups

In examining the association between outcome and acid-base status, three groups of infants were considered: an acidaemic group, a non-acidaemic group, and a group with unknown acid-base status. For completeness, and to maintain constant numbers, the results are presented throughout for all three groups. However, in line with the study hypothesis, formal comparisons using significance tests were made only between the acidaemic and non-acidaemic groups. Similarly, in considering the effect of an ominous CTG in labour, statistical comparisons were made between the group with an ominous CTG and the group with a non-ominous CTG, although results for the group with unknown FHR changes in labour are always presented.

Statistical tests

Where variables were approximately normally distributed, comparisons between means were made using the t test. The version of the test making allowance for a difference in variance between the two groups was used where appropriate.

Scores on some of the tests (e.g. the Movement ABC) had a limited range and were far from normally distributed. For comparisons between the two groups, the Mann-Whitney U test was used; results were however presented in terms of means and standard deviations. This was partly because these summary measures were more informative than the median and range, and partly to facilitate comparison with the test standards, which were presented in terms of means and standard deviations.

In the multiple regression analysis, a step-up procedure was used. Variables entered the equation one at a time, and were included if they were statistically significant at least at the 0.05 level. To assess the fit of each equation, the distribution of residuals was checked for normality. In practice, the fit was always judged to be adequate.

CHAPTER III

OUTCOME AT AGE FIVE YEARS OF A COHORT OF TERM INFANTS WITH ONE-MINUTE APGAR SCORE ≤3: RESULTS

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6. **Fetal heart rate (FHR) monitoring in labour**

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6.2. Details of FHR traces

6.3. FHR changes in labour and acid-base status

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7. **Neonatal death, outcome at age five, and FHR changes**

7.1. "Asphyxial" neonatal death

7.2. Spastic quadriplegia

7.3. Impairment Rating

7.4. Test scores

8. **Discussion**

CHAPTER III

OUTCOME AT AGE FIVE YEARS OF A COHORT OF TERM INFANTS WITH ONE-MINUTE APGAR SCORE ≤3: RESULTS

1. STUDY COHORT: PERINATAL FACTORS

1.1. Description of cohort

Sex, birthweight and gestational age

As explained in the previous chapter, follow-up results were analysed for 170 children in the study cohort. There were 95 males and 75 females. Gestational age was symmetrically distributed around a median of 40 weeks:

Gest. age (wk)	Number	Percent
37	7	4.1
38	19	11.2
39	30	17.6
40	67	39.4
41	29	17.1
42	16	9.4
43	2	1.2
Total	170	100.0

The distribution of birthweight was:

Birthweight (g)	Number	Percent
<2500	4	2.4
2500-2999	36	21.2
3000-3499	65	38.2
3500-3999	44	25.9
≥4000	21	12.3
Total	170	100.0

Birthweight was appropriate for gestational age, being below the tenth centile

for 20 infants (11.8%) and below the third centile for three (1.8%). Birthweight was above the 90th centile for 18 infants (10.6%) and above the 97th centile for eight (4.7%) (Yudkin *et al.* 1987).

Head circumference tended to be large for gestational age. It was below the tenth centile for 12/166 infants (7.2%) and below the third centile for 3/166 (1.8%). (Head circumference was unknown for four infants). 26 infants (15.7%) had a head circumference above the 90th centile, and nine (5.4%) a head circumference above the 97th centile (Yudkin *et al.* 1987).

Mode of delivery

There was a high rate of operative deliveries: 73/170 (42.9%) of the infants were delivered either by caesarean section or forceps. This compares with an operative delivery rate for the whole hospital during 1984 and 1985 of 22.7% (11.1% by forceps or ventouse and 11.5% by caesarean section). A further 10 infants in the cohort (5.9%) were vaginal breech deliveries, compared with 2.0% in the hospital as a whole.

The full breakdown by mode of delivery was:

Delivery Mode	Number	Percent
Spontaneous	87	51.2
Low forceps	27	15.9
Mid/high forceps	10	5.9
Ventouse	1	0.6
Vaginal breech	10	5.9
C/S before labour	6	3.5
C/S in labour	29	17.1
Total	170	100.0

The most common indication for operative delivery was fetal distress. This was the case in 19 of the 38 vaginal operative deliveries, and in 18 of the 35 caesarean sections. Delay or disproportion was the indication for 15 of the vaginal opera-

tive deliveries and for 10 caesarean sections.

31/170 infants (18.2%) were delivered under general anaesthetic: six by caesarean section before labour and 25 by caesarean section in labour.

Apgar scores

The distribution of one-minute Apgar scores was:

Score	Number	Percent
0	6	3.5
1	17	10.0
2	58	34.1
3	89	52.4
Total	170	100.0

The majority of infants were vigorous by the age of five minutes, with only 30 (17.6%) having a five-minute Apgar score <7.

The distribution of five-minute scores was:

Score	Number	Percent
0	1	0.6
1	1	0.6
2	1	0.6
3	3	1.8
4	4	2.4
5	11	6.5
6	9	5.3
7	15	8.8
8	16	9.4
9	31	18.2
10	78	45.9
Total	170	100.0

38 infants had an Apgar score recorded at 10 minutes or later; in only six cases was the score 7 or less. These low ten-minute scores were: 0,5,5,6,7,7.

The three infants who died neonatally never established spontaneous regular

respiration. Of the other 167 infants, 120 (71.9%) had established spontaneous regular respiration by five minutes, and 159 (95.2%) by ten minutes. The longest recorded time to establish spontaneous regular respiration was 30 minutes.

A heart rate of >100 beats per minute was established within five minutes by 155/170 (91.2%) infants. All infants had established this heart rate by 16 minutes.

Maternal details

Mean maternal age at delivery was 27.4 years (S.D. 5.2) with a range of 17 to 41 years.

Four of the mothers were taking medication for an existing disease: one with diabetes, one with essential hypertension, one with psychiatric problems, and one with thyroid dysfunction.

There was a high proportion of primiparae: 105/170 (61.8%), considerably higher than the proportion for the hospital as a whole in 1984-85 (43.2%). The distribution of parity was:

Previous deliveries	Number	Percent
0	105	61.8
1	41	24.1
2	13	7.6
3	5	2.9
4	6	3.5
Total	170	100.0

None of the 65 multiparae had a previous stillbirth or neonatal death; two had a previous preterm (<37 week) delivery.

The onset of labour was spontaneous for 112 (65.9%) of the mothers; 52 (30.6%) were induced, and six (3.5%) were delivered by caesarean section before labour.

2. ACID-BASE STATUS

2.1. Comparison between infants with and without blood gas measurements

Of the 170 infants, 124 (72.9%) had pH and base deficit measured in the umbilical vein, and 122 (71.8%) had these measurements in the umbilical artery. Since acidaemia in this study was defined in terms of pH and base deficit in the umbilical artery, these 122 infants formed the subgroup with known acid-base status.

A comparison was made between these 122 infants and the remaining 48 with unknown acid-base status. The purpose was to examine whether immediate neonatal management differed between the two groups. If this were the case, and if it is assumed that neonatal management affects long-term outcome, it could be argued that results relating to long-term outcome, which are based only on the subgroup of infants with arterial blood gas measurements, are biased.

In making the comparison, any differences observed between the groups, whether statistically significant or not, may be relevant. However, the level of statistical significance will suggest whether an observed difference has arisen for reasons other than chance.

The following table shows the rates (%) of various neonatal interventions and responses in the two groups.

	Infants with measurements N=122	Infants without measurements N=48	p value
Operative delivery	56.6	29.2	0.002
*Paediatrician called	81.1	74.4	0.49
One-minute Apgar score < 3	50.0	41.7	0.65
Five-minute Apgar score < 7	18.9	14.6	0.66
Intubation for meconium aspiration	50.8	64.6	0.15
Resuscitation by:			
intubation	78.7	72.9	0.55
bag and mask	8.3	19.7	0.12
THAM/bicarb	7.4	2.1	0.29
cardiac massage	8.3	10.4	0.89
Time to spont. reg. resp. ≥ 10 min.	13.9	16.7	0.83
Time to heartrate > 100 bpm > 5 min.	8.3	10.4	0.89
Admission to Special Care Baby Unit	16.4	14.6	0.95

* Not known for 11 infants

Infants with blood gas measurements were nearly twice as likely as others to have had an operative delivery. On the other hand, those without measurements were somewhat more likely to be intubated for meconium aspiration, and to be resuscitated by bag and mask. Otherwise, both the immediate neonatal management, and the response to it, appeared to be similar in the two groups. It seems therefore that an analysis of the relationship between acid-base status and long-term outcome, based inevitably on the subgroup of infants with cord blood gas measurements, is unlikely to

be biased.

2.2. **Cord blood gas values**

Mean values

The means and standard deviations of the blood gas values measured in the artery and vein were:

		Artery N=122	Vein N=124
pH	Mean	7.16	7.28
	SD	0.14	0.12
Base deficit (mmol/l)	Mean	10.9	8.0
	SD	5.9	4.8
CO_2 (mm Hg)	Mean	54.8	41.5
	SD	14.3	12.2
O_2 (mm Hg)	Mean	11.1	24.0
	SD	6.6	7.3

In a previous series of deliveries in this hospital (Sykes *et al.* 1982) mean (S.D) pH in the umbilical artery for 34 infants with a one-minute Apgar score ≤ 3 was 7.12 (0.12), slightly but not significantly lower than the mean value obtained in this study.

Rate of acidaemia

Acidaemia was defined following previous studies as umbilical arterial pH ≤ 7.10 and base deficit > 12 mmol/l (Sykes *et al.* 1982; Dennis *et al.* 1989). Based on these criteria, 28/122 (23.0%) of infants were acidaemic, and 94 (77.0%) were not.

This rate of acidaemia was similar to the rate of 29.4% (10/34) previously observed among infants in this hospital with a one-minute Apgar score ≤ 3 (Sykes *et al.* 1982).

Infants in the acidaemic group exhibited a significant degree of acidaemia; their mean pH was 6.97 and 13/28 infants (46.4%) had pH < 7.00. Excluding these very

acidaemic infants, it was notable that the mean pH and base deficit of the non-acidaemic group was almost identical to those previously recorded in an unselected series of births in this hospital (Sykes *et al.* 1982). Mean blood gas values in the two groups were:

		Acidaemic N=28	Not Acidaemic N=94
pH	Mean	6.97	7.22
	SD	0.12	0.07
Base deficit (mmol/l)	Mean	19.3	8.5
	SD	5.0	3.4
CO_2 (mm Hg)	Mean	71.5	50.0
	SD	14.7	10.0
O_2 (mm Hg)	Mean	9.3	11.6
	SD	7.4	6.2

2.3. **Prolonged low Apgar score and acid-base values**

A five-minute Apgar score <7 was recorded for 30/170 (17.6%) of the whole cohort, and for 23/122 (18.9%) of the infants with blood gas measurements. Infants with this persisting low Apgar score were more acidaemic than others:

		5 min. Apgar <7 N=23	5 min. Apgar ≥7 N=99	p value
pH	Mean	7.02	7.19	<0.001
	SD	0.19	0.10	
Base deficit (mmol/l)	Mean	16.4	9.7	0.001
	SD	8.0	4.6	
CO_2 (mm Hg)	Mean	64.7	52.6	<0.01
	SD	17.9	12.4	
O_2 (mm Hg)	Mean	9.8	11.4	0.31
	SD	6.6	6.6	

Of the 23 infants with a five-minute Apgar score <7 and known acid-base status, 10 had Ua pH <7.00. Thus of the 13 infants with pH <7.00, 10 had this low five-minute Apgar score. (The other 3 infants had scores of 7,9 and 9).

An Apgar score ≤3 for longer than five minutes has been suggested as one marker of potentially damaging hypoxia (American College of Obstetricians and Gynecologists, 1991). A score of 3 or under at five minutes occurred in only six infants. Three had Ua pH <7.00, one had pH 7.10, and two had unknown acid-base status.

2.4. **Encephalopathy and acid-base values**

As mentioned in Chapter I (Section 2.5), a number of studies have reported that most infants with neonatal encephalopathy are not acidaemic at birth (Huisjes *et al.*1980; Low *et al.*1985; Dijxhoorn *et al.*1986; Gilstrap *et al.*1989).

In the study cohort encephalopathy was diagnosed for 12 infants. Five were

graded as Stage 1 (mild), three as Stage 2 (moderate), and four as Stage 3 (severe) (Sarnat & Sarnat, 1976). Five-minute and ten-minute Apgar scores, and Ua pH and base deficit for these infants were:

	5 min. Apgar	10 min. Apgar	pH	Base deficit (mmol/l)
Stage 1				
1.	9	N.K.	7.22	7
2.	6	N.K.	6.87	24
3.	5	7	6.79	27
4.	3	7	7.13	11
5.	4	8	6.90	16
Stage 2				
6.	4	N.K.	6.71	29
7.	2	5	6.93	23
8.	4	4	6.97	20
Stage 3				
9.	5	5	6.70	26
10.	1	N.K.	6.90	19
11.	3	N.K.	7.10	14
12.	0	0	6.74	30

Thus most of the infants (9/12) were severely acidaemic, with pH < 7.00. However, this extreme level of acidaemia was not necessary for encephalopathy to occur, even in its severe form. The variation in the stage of encephalopathy with a given acid-base status and five-minute Apgar score was striking. For example, Case 4 and Case 11 had similar acid-base values and a five-minute Apgar score of 3, yet Case 4 had mild encephalopathy and Case 11 severe. Again, a similarity in acid-base status and Apgar score with a disparity in the stage of encephalopathy was seen in Cases 3 and 9.

3. NEONATAL DEATH, IMPAIRMENT, AND MARKERS OF HYPOXIC DAMAGE

In Chapter I (Section 3.7) a number of questions were posed, including the following:

(i) Can we confirm that a low Apgar score only heralds a poor outcome if accompanied by other signs of neonatal encephalopathy?

(ii) Is the combination of low Apgar score and acidaemia more favourable (as has been suggested) than low Apgar score with a normal acid-base status?

These questions will first be addressed by examining the perinatal details of infants with a poor outcome; that is, those who died or were seriously impaired.

3.1. "Asphyxial" neonatal death

Three infants in the cohort died in the neonatal period with a diagnosis at autopsy of birth asphyxia; they are described below. G.A. stands for gestational age; Apgar scores are at one and five minutes. Birthweight centiles were based on the tables of Yudkin *et al.* (1987); unless otherwise stated, birthweight was appropriate for gestational age.

Case A.

Female. Birthweight 3870g. G.A. 40 wk.
Delivery by Keillands forceps for fetal distress
Apgar scores 0,3
Ua pH 7.10, base deficit 14 mmol/l
Severe encephalopathy
Seizures starting within first hour of life
CT scan at age 3 days showed cerebral oedema with compressed ventricles
Generalised oedema aged 3 days, associated with reduced urinary output
Died aged 5 days
At autopsy: bilateral tentorial tears
cerebral oedema and hypoxic change

Case B.

Female. Birthweight 2780g. G.A. 40 wk.
Weight approx. at 10th centile for G.A. (2760g)
Spontaneous delivery
Apgar scores 0,0
Ua pH 6.74, base deficit 30 mmol/l
Severe encephalopathy
Seizures starting at age one hour
Ultrasound scan on first day showed cerebral oedema
Very poor peripheral perfusion; never passed urine
Cardiac ischaemia; two cardiac arrests
Died aged 40 hours
At autopsy: cerebral oedema and widespread
ischaemic changes

Case C.

Female. Birthweight 2955g. G.A. 40 wk.
Vaginal breech delivery
Apgar scores 0,1
Ua pH 6.90, base deficit 19 mmol/l
Severe encephalopathy
Seizures starting at age one hour
Cardiac arrhythmia
Died aged 32 hours
At autopsy: bilateral tentorial tears
cerebral oedema and contusions
cord contusion

Thus all three infants had a five-minute Apgar score ≤ 3, seizures starting within the first two hours of life, and severe encephalopathy. At autopsy, although they all exhibited cerebral oedema, they did not present a uniform picture. One infant (Case A) was only moderately acidaemic, and showed both hypoxic changes and evidence of birth trauma. The other two infants were severely acidaemic, with pH <7.00. One (Case B) showed widespread hypoxic changes at autopsy, while the other (Case C) showed evidence of considerable trauma, with bruising of the brain and spinal cord.

3.2. **Severe impairment**

An Impairment Rating was assigned to each child, based on review of the total outcome information available (see Chapter II). Three levels of impairment were

assigned:

(1) No impairment or nonspecific poor performance on single items, but overall appeared normal

(2) definite identified area(s) of impairment, not necessarily needing referral

(3) serious impairment, needing referral, and including global delay, lateralising signs, and severe deficit in a specific area.

There were 167 children with an Impairment Rating, eight of whom were assigned a Rating of 3. These were four children with cerebral palsy, and four with severe developmental delay. Details of the four children with cerebral palsy were:

Case 1.

Male. Birthweight 2280g. G.A. 37 wk.
Weight < 10th centile for G.A.
Mother admitted for raised B.P.; fetal distress diagnosed on antepartum CTG; delivery by caesarean section before labour
Apgar scores 3,10
Ua pH 7.13; base deficit 12 mmol/l
Polycythaemia; two partial exchange transfusions
Extensive necrotising enterocolitis at age 3 days; discharged at 22 days
Right hemiplegia
Griffiths subscale scores:

Locomotor:	45
Social:	94
Hearing/speech:	115
Eye/hand:	118
Performance:	97

Case 2.

Female. Birthweight 3155g. G.A. 41 wk.
Caesarean section in labour for fetal distress
Apgar scores 0,4
Ua pH 6.97; base deficit 20 mmol/l
Seizures starting at 2 hours; moderate encephalopathy
CT scan aged 14 days showed diffuse white matter damage
Low urinary output for first few days; hypotension, coagulopathy in 2nd week
Spastic quadriparesis; optic atrophy; epilepsy
Profound developmental delay
Died aged 4 yrs 4 mths.

Case 3.

Male. Birthweight 3466g. G.A. 39 wk.
Forceps delivery for fetal distress
Apgar scores 3,5
Ua pH 6.70; base deficit 26 mmol/l
Seizures starting at 8 hours; severe encephalopathy
CT scan aged 11 days showed suspected white matter damage; at 13 weeks severe white matter destruction
Neonatal anuria; hyperkalaemia
Spastic quadriparesis; cortical blindness
Microcephalus; profound developmental delay; epilepsy
Untestable

Case 4.

Female. Birthweight 3726g. G.A. 39 wk.
Spontaneous delivery
Apgar scores 2,2
Ua pH 6.93; base deficit 23 mmol/l
Seizures starting at 2 hours; moderate encephalopathy
CT scan aged 16 days showed suspected white matter damage; ultrasound scan at 28 days showed cerebral atrophy and left periventricular leukomalacia
Spastic quadriparesis; visual impairment
Profound developmental delay
Untestable

Thus three of the four children were severely acidaemic (pH < 7.00) and had moderate or severe encephalopathy. All three had spastic quadriplegia, with visual impairment and profound global developmental delay.

The fourth child with cerebral palsy had a different perinatal history and type of cerebral palsy. He was mildly acidaemic at birth and showed no signs of encephalopathy. In the early neonatal period, he developed necrotising enterocolitis. At the age of five, he had a diagnosis of right hemiplegia, but apart from the locomotor subscale, scored appropriately on the Griffiths tests.

The other four children with Impairment Rating 3 all had global developmental delay:

Case 5.

Female. Birthweight 3710g. G.A. 40 wk.
Apgar scores 2,6
Ua pH 7.16; base deficit 9 mmol/l
No neonatal problems; discharged home in good condition
Global developmental delay
Griffiths subscale scores:

Locomotor:	88
Social:	92
Hearing/speech:	54
Eye/hand:	68
Performance:	71

Case 6.

Male. Birthweight 3800g. G.A. 40 wk.
Apgar scores 3,10
Ua pH 7.15; base deficit 9 mmol/l
No neonatal problems; discharged home in good condition
Global developmental delay; no expressive language
Griffiths subscale scores:

Locomotor:	40
Social:	38
Hearing/speech:	Untestable
Eye/hand:	63
Performance:	73

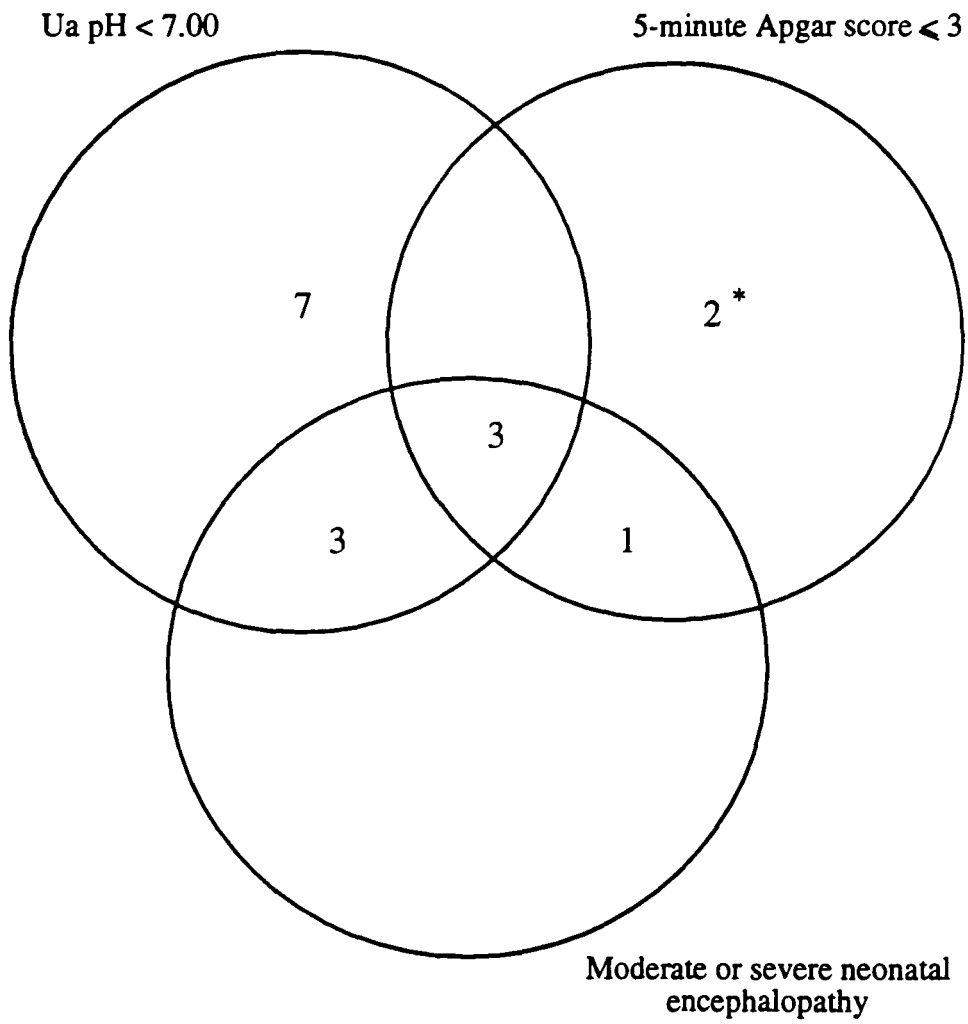
Case 7.

Male. Birthweight 3080g. G.A. 38 wk.
Apgar scores 3,9
Acid-base status not known
No neonatal problems; discharged home in good condition
Global developmental delay
Griffiths subscale scores:

Locomotor:	72
Social:	85
Hearing/speech:	79
Eye/hand:	68
Performance:	79

Figure 3.1

Numbers with different signs of hypoxic damage



* Unknown acid-base status

Case 8.

Male. Birthweight 3280g. G.A. 42 wk.
Apgar scores 2,4
Ua pH 6.90; base deficit 16 mmol/l
Mild encephalopathy; in Special Care for 2 days
Global developmental delay;
oro-pharyngeal dyspraxia
Parent refused child assessment; information came
from a Children's Assessment Unit where
this child receives treatment

Three of these children had no neonatal problems. Two were not acidaemic, and the third had unknown acid-base status. The fourth child was severely acidaemic at birth, had a low five-minute Apgar score and subsequently exhibited mild encephalopathy.

3.3. **Summary: death and severe impairment**

To summarise the relationship between neonatal death, severe impairment and markers of hypoxic damage, I shall use three of the criteria for potentially damaging hypoxia set out by the American College of Obstetricians and Gynecologists (1991). These criteria are: (i) umbilical arterial pH < 7.00 (ii) a five-minute Apgar score ≤ 3 and (iii) moderate or severe neonatal encephalopathy. (A fourth criterion - evidence of multiorgan system dysfunction - is considered later.)

There were 16 infants with one or more of these signs, as displayed in Figure 3.1.

Table 3.1. shows the relationship between the signs and later impairment (or death). The first four columns of the table include double counting. Because of the small numbers involved, these results must be considered tentative.

Moderate or severe encephalopathy occurred in seven infants, a hospital rate of 0.75 per 1000 term singleton livebirths. Three of the infants died neonatally and three had spastic quadriplegia. The seventh was unimpaired at the age of five. Six of these seven infants had pH < 7.00, including the child who was later unimpaired.

Table 3.1

Death and impairment after severe acidaemia, prolonged low Apgar score, and encephalopathy

	Moderate or severe NE	Ua pH <7.00	Moderate or severe NE and Ua pH <7.00	5-minute Apgar score ≤3	None of these signs	TOTAL
"Asphyxial" neonatal death	3	2	2	3	0	3
Severe impairment (Rating 3)						
Spastic quadriplegia	3	3	3	1	0	3
Hemiplegia	0	0	0	0	1	1
** Developmental delay	0	1	0	0	3	4
Some impairment (Rating 2)	0	0	0	*1	20	21
No impairment (Rating 1)	1	7	1	*1	130	138
TOTAL	7	13	6	6	154	170

NE : neonatal encephalopathy.
* : acid-base status unknown.
** : acid-base status unknown for one child.

Severe acidaemia (pH <7.00) occurred in 13 infants: the six with encephalopathy and seven others. Of these seven, six were unimpaired at the age of five; the seventh had global developmental delay and was rated as seriously impaired (Case 8 above).

A five-minute Apgar score ≤ 3 occurred in six infants, including the three who died neonatally. A fourth had spastic quadriplegia (Case 4 above). All four of these infants had moderate or severe encephalopathy. The remaining two children did not have encephalopathy, and had unknown acid-base status; one was unimpaired at the age of five and the other had a moderate degree of impairment (Rating 2). He was noted to have poor fine motor control and difficulty with visuo-spatial tasks, as well as disordered behaviour (showing restlessness, destructiveness and frequent temper tantrums).

In summary, moderate or severe encephalopathy was the single marker most predictive of a poor outcome; in practice it nearly always occurred with pH <7.00. Severe acidaemia on its own had a more favourable outcome. There was not enough information to draw any conclusions about the outcome of a prolonged low Apgar score occurring as an isolated sign.

In addition to the combination of markers considered above, the American College of Obstetricians and Gynecologists (1991) suggested that evident multiorgan system dysfunction (such as cardiovascular, haematological, pulmonary or renal) would be a necessary concomitant of damaging hypoxia. I therefore sought signs of multiorgan damage among the infants who died or who were seriously impaired.

Two of the infants who died neonatally (Cases A and B) had multiorgan system dysfunction, indicated by low or absent urinary output, and by cardiac ischaemia (Case B). The third infant who died had cardiac arrhythmia, probably also reflecting multiorgan damage.

Two of the three children with spastic quadriplegia (Cases 2 and 3) also showed

multiorgan damage. One (Case 2) had reduced urinary output for the first few days of life; the other exhibited anuria and hyperkalaemia, resulting in cardiac ventricular arrhythmia and collapse. Case 4 did not show such signs.

Thus a cluster of hypoxic signs was a strong predictor of death and cerebral palsy. The three infants with neonatal death and the three with spastic quadriplegia all had moderate or severe neonatal encephalopathy and at least one of the other suggested markers of damaging hypoxia (pH <7.00, five-minute Apgar score ≤ 3, and signs of multiorgan system dysfunction). However, all four suggested markers were not uniformly present. Can we nevertheless state with confidence that these six infants were damaged by birth asphyxia?

Additional evidence, not yet considered, is provided by autopsy reports and cerebral scans. The three infants who died neonatally all showed cerebral oedema at autopsy. In one case, this was attributed solely to hypoxic damage, in one to a combination of asphyxia and trauma, and in the third mainly to severe birth trauma. All three children with spastic quadriplegia showed white matter destruction on CT or ultrasound scan; in two of these children repeated scans showed evolving cystic change consistent with asphyxial damage.

Birth asphyxia supposes an asphyxial event or episode during labour. To search for such an event, the pregnancy and labour histories of these six infants, including their fetal heart rate changes in labour, were investigated. The results are presented in Section 6.

Suppose that we make a provisional diagnosis of birth asphyxia for these children. Their case histories suggest considerable variation in the way in which damaging hypoxia might present. For instance, one child with spastic quadriplegia and persuasive clinical and scan evidence of asphyxial brain damage (Case 4) did not show any signs of multiorgan system dysfunction. Another infant who died neonatally (Case A) exhibited many features of asphyxia, including cerebral oedema with hypox-

Table 3.2

Acid-base status and impairment

	Acidaemic		Not acidaemic		Acid-base status unknown		Total	
	N	%	N	%	N	%	N	%
Impairment Rating								
1:Unimpaired	19	76.0	77	81.9	42	87.5	138	82.6
2:Some impairment	2	8.0	14	14.9	5	10.4	21	12.6
3:Serious impairment	4	16.0	3	3.2	1	2.1	8	4.8
TOTAL	25	100.0	94	100.0	48	100.0	167	100.0

ic changes at autopsy, but nevertheless had only a moderate degree of acidaemia at birth (Ua pH 7.10 and base deficit 14 mmol/l). There was also variation in the five-minute Apgar score of these infants, although all had a five-minute score of 5 or less.

As a basis for comparison, how many of the children without severe impairment had perinatal signs of asphyxial damage associated with their low Apgar score? Table 3.1. shows that of the 21 with some impairment (Rating 2), one (4.8%) had a five-minute Apgar score ≤ 3. Of the 138 infants with no impairment (Rating 1) eight (5.8%) had at least one asphyxial sign, including one child with moderate encephalopathy and pH < 7.00.

3.4. **Impairment after less severe acidaemia**

One of the hypotheses to be tested in this study was that the combination of a low Apgar score and acidaemia heralded a more favourable outcome than did a low Apgar score with a normal acid-base status. This hypothesis related to acidaemia defined as umbilical arterial pH ≤ 7.10 and base deficit > 12 mmol/l (Dennis *et al.* 1989). In this section, therefore, Impairment Rating at the age of five is related to acidaemia defined in this way. The analysis excludes the three infants who died in the neonatal period.

Table 3.2 shows the proportion of children with each Impairment Rating in three groups: acidaemic, not acidaemic, and acid-base status unknown. As explained in Chapter II, formal comparisons were made between the acidaemic and non-acidaemic groups, but the group with unknown acid-base status is shown throughout for completeness. There was no evidence of a more favourable outcome in the acidaemic group. On the contrary, the rate of serious impairment was higher in this group (comparison of the distributions with an exact test gave $p=0.065$). As we have seen, the four acidaemic children with severe impairment all had an extreme degree of acidaemia, with pH < 7.00. The proportion of unimpaired children was similar in

Table 3.3

Acid-base status and social and personal factors: children assessed

	Acidaemic N=21	Not acidaemic N=93	Acid-base status unknown N=45	Total N=159
Male (%)	57.1	60.2	51.1	57.2
Social Class (%)				
1 and 2	38.1	45.2	35.6	41.5
3	38.1	32.3	48.9	37.7
4,5, unclassified	23.8	22.6	15.6	20.8
Single-parent family (%)	14.3	*6.5	11.1	8.9
Started school (%)	19.0	30.1	31.1	28.9
Age at testing (mths)				
Mean	58.8	58.6	59.1	58.8
SD	1.6	1.9	3.0	2.3
Height at testing (cm)				
Mean	109.6	109.4	109.5	109.4
SD	4.2	4.7	3.9	4.4
Head circumference at testing (cm)				
Mean	51.9	52.0	*51.7	51.9
SD	1.1	1.7	1.6	1.6
Weight at testing (kg)				
Mean	18.3	18.3	18.2	18.3
SD	2.5	3.0	2.5	2.8

* Information missing for one child.

the acidaemic and non-acidaemic groups.

There was also no difference in the rate of moderate impairment (Rating 2) in the two groups (8.0%: 2/25 compared with 14.9%: 14/94). The two acidaemic children with moderate impairment both had difficulties with fine motor and visuo-spatial tasks. Of the 14 non-acidaemic children with moderate impairment, five had difficulties with visuo-spatial tasks, one had global delay, and eight had gross motor delay, usually with poor balance, clumsiness, and posturing.

A limitation of the Impairment Rating is its lack of detail; it places children in three categories only. To examine associations between more subtle aspects of neurodevelopment and acid-base status, scores on the Griffiths Developmental Scales were analysed.

4. GRIFFITHS SUBSCALE SCORES AND ACID-BASE STATUS

As described in Chapter II, five of the six Griffiths subscales were used: locomotor, personal/social, hearing/speech, eye-hand co-ordination, and performance. A full set of Griffiths scores was recorded for all 159 children assessed, except for three children with no score on the hearing/speech subscale. This subscale could not be completed by the child with no expressive language (Case 6 above), nor by two other children whose first language at home was not English. These two children were not considered by the paediatrician to be hampered by language difficulties on the other subscales.

4.1. Characteristics of children assessed

The primary analysis to be performed on the Griffiths subscale scores was a comparison of mean scores between the acidaemic and non-acidaemic groups. Of the 159 children assessed, 114 had known acid-base status; 21 were acidaemic and 93 were not.

Table 3.4

Acid-base status and Griffiths subscale scores

	Acidaemic N=21	Not acidaemic N=93	Acid-base status unknown N=45	Total N=159
Locomotor				
Mean	112.1	109.9	111.6	110.7
SD	11.7	16.4	13.0	14.9
Personal/social				
Mean	107.0	106.9	105.7	106.6
SD	8.6	13.2	6.5	11.1
*Hearing/speech				
Mean	116.2	121.5	114.5	118.8
SD	8.9	14.5	13.5	13.9
Eye/hand				
Mean	105.3	110.7	108.8	109.4
SD	14.5	17.2	15.9	16.5
Performance				
Mean	104.8	108.5	107.7	107.8
SD	16.4	16.8	18.5	17.2

* Sig. diff. between acidaemic and non-acidaemic groups; $p<0.05$.
In acidaemic group, 1 non-English speaking child not tested.
In non-acidaemic group, 1 non-English speaking child not tested; 1 child with no expressive language untestable.

Characteristics known to affect performance on developmental tests, such as social class and school attendance (Hanson & Aldridge Smith, 1987; Dennis *et al.* 1989) were therefore first compared between the two groups (Table 3.3). As before, results for the group with unknown acid-base status are also presented for completeness. The social and personal characteristics of the children were similar, and none of the differences between them was statistically significant. However slightly fewer children in the acidaemic group had started school.

4.2. Griffiths mean scores and acid-base status

Mean scores were similar in the two groups on the locomotor and personal/social subscales (Table 3.4). On the eye/hand and performance subscales the acidaemic group had a somewhat lower mean score than the non-acidaemic group, but these differences were not statistically significant ($p=0.19$ and $p=0.36$ respectively). On the hearing/speech subscale the acidaemic group (mean 116.2; S.D.8.9) performed significantly worse ($p=0.038$) than the non-acidaemic group (mean 121.5; S.D. 14.5).

To investigate whether the depressed hearing/speech scores in the acidaemic group occurred among the most acidaemic children, scores for the seven children with umbilical arterial pH <7.00 were examined. Their mean score was 115.4, marginally lower than the mean of 116.5 achieved by the remaining children in the acidaemic group. This result should however be judged against the fact that the worst hearing/speech scores (mean 114.5) were in the group with unknown acid-base status. It is highly unlikely that acid-base derangement in this group was more extreme than in the acidaemic group; it most likely contained a mix of acidaemic and non-acidaemic infants (see Section 2.1). If hearing/speech scores were related to the degree of acidaemia one would therefore expect the score for the group with unknown acid-base status to lie between the scores for the other two groups.

On the other four Griffiths subscales, the seven infants with Ua pH < 7.00 performed well in relation to the whole cohort. Their results were:

		pH < 7.00 N=7	Total cohort N=159
Locomotor			
	Mean	109.3	110.7
	SD	11.4	14.9
Personal/social			
	Mean	109.3	106.6
	SD	6.0	11.1
Hearing/speech			
	Mean	115.4	118.8
	SD	10.5	13.9
Eye/hand			
	Mean	106.7	109.4
	SD	12.7	16.5
Performance			
	Mean	112.0	107.8
	SD	16.9	17.2

The five children with encephalopathy (four mild and one moderate) who were able to be assessed also showed mean scores similar to the mean for the whole cohort. Their mean (SD) scores were: Locomotor 108.6 (12.2); personal/social 108.0 (3.9); hearing/speech 118.2 (7.2); eye/hand 107.4 (15.1); performance 109.4 (10.9).

4.3. **Regression of Griffiths scores on acid-base values**

Introduction

The comparison of mean scores between the acidaemic and non-acidaemic groups is a simple analysis, which may have failed to show up real associations between Griffiths scores and acid-base status. One reason for this is the arbitrary distinction into two groups, on the basis of Ua pH and base deficit. Another is that

the observed differences between the two groups in social class, school attendance etc., although not statistically significant, may nevertheless have obscured a real effect of acid-base status.

Although these problems cannot be perfectly resolved by statistical manipulation, they can be addressed by the use of multiple regression analysis. Such an analysis allows the effect of a variable of interest (e.g. pH, base deficit) to be isolated, after the effects of associated variables (e.g. social class) have been taken into account. Moreover, pH and base deficit may be considered singly or in combination, and either as continuous or binary variables; the analysis need not be tied to a fixed, arbitrary, definition of acidaemia.

The regression analysis also allows an exploration of the relationships between Griffiths scores and factors other than acid-base status. The effect of variables such as social class, which are known to be related to outcome, can be quantified.

Method and results

Before carrying out the multiple regression analysis, a series of two-way scatter plots were examined, to seek obvious associations between each blood gas measurement and each Griffiths subscale score. Had there been any striking linear or non-linear relationships between these variables, they would have been obvious on such plots; in fact, no clear relationships were observed. However, a theoretical possibility remained that real relationships were obscured by confounding variables. To test this possibility, and to seek variables other than acid-base values that were related to Griffiths scores, a number of multiple regression analyses were performed. Separate regressions were run for each Griffiths subscale score.

The analyses were carried out first for the 114 children who had known acid base status. A step-up approach was used, each variable entering the regression equation only if it was statistically significant at least at the 0.05 level. Apart from

the values of pH and base deficit, all the explanatory variables offered were defined as binary variables. They were included in the analysis only if there were at least 10 cases; this was an arbitrary cut-off designed to avoid chance associations due to very small numbers. Variables which were omitted from the analysis because of small numbers included five-minute Apgar score ≤ 5 (N=8), cardiac massage (N=4) and head circumference $<$ 10th centile (N=7). Social class was grouped in various ways during the analysis; the grouping shown produced the closest associations with outcome.

The explanatory variables included were:

Ua pH

Ua base deficit (mmol/l)

Acidaemia (pH ≤ 7.10 and base deficit $>$ 12 mmol/l) (N=21)

Male sex (N=68)

Birthweight $<$ 10th centile (N=15)

Intubation for meconium aspiration (N=62)

Resuscitation by intubation (N=89)

Resuscitation by bag and mask (N=22)

Spontaneous regular respiration after $\geq$ 10mins (N=11)

Social class I or II (N=50)

Social class IV, V, unclassified (N=21)

Started school (N=32)

Table 3.5

Statistically significant explanatory variables in the regression analyses of Griffiths subscale scores

Variable	Regression Coefficient,b	95% CI for b	p value
Children with known acid-base status; N=114			
Locomotor score:			
None			
Personal/Social:			
Birthweight < 10th centile	-9.4	-15.9, -2.8	0.006
Resuscitation by intubation	-5.4	-10.8, -0.1	0.05
Hearing/Speech:			
Soc. Class I,II	7.6	2.6, 12.5	0.004
Eye/Hand			
Started school	12.9	6.5, 19.4	0.0002
Performance			
Started school	10.0	3.4, 16.6	0.004
Soc. Class I,II	7.4	1.5, 13.4	0.02
All children assessed; N=159			
Locomotor score:			
None			
Personal/Social:			
Birthweight < 10th centile	-6.8	-11.9, -1.7	0.01
Hearing/Speech:			
Soc. Class I,II	9.5	5.4, 13.7	<0.0001
Eye/Hand			
Started school	7.8	2.2, 13.4	0.007
Soc Class I,II	6.4	1.2, 11.6	0.02
Performance			
Soc. Class I,II	8.7	3.4, 14.0	0.002
Started school	7.0	1.2, 12.8	0.02

Explanatory variables that were statistically significant are shown in Table 3.5. None of the variables was significantly related to the locomotor score. Both high social class and attendance at school were associated with an increase in the mean score on three of the subscales. In the case of high social class, the increase was about 7.5 points on both the hearing/speech and performance subscales. The increase associated with having started school was at least 10 points on both the eye/hand and performance subscales. Birthweight below the tenth centile for gestational age was associated with a reduction of 9 points in the mean personal/social score. A reduction in this score was also weakly associated with resuscitation by intubation. Neither pH, base deficit, nor acidaemia were significantly associated with any of the subscale scores.

To confirm that these associations held for the whole cohort of 159 children, the regressions were run again, offering the same explanatory variables. The results are shown in Table 3.5.

The associations were similar for the whole cohort. Again, there were no significant associations with the locomotor subscale score. High social class showed an even more pervasive effect, being significantly associated with the eye/hand score as well as the hearing/speech and performance scores. The significant negative association between resuscitation by intubation and the personal/social score was no longer seen.

4.4. Griffiths scores compared with previous study results

The lack of association between acid-base status and scores on the Griffiths subscales refuted the hypothesis being tested: that children with a low Apgar score and normal acid-base status have a worse outcome than those with a low Apgar score and acidaemia. The hypothesis was generated by observations made in a previous study of 4-5 year olds born in this hospital in 1981 (Dennis *et al.*1989); these obser-

vations were compared with the results of the present study.

The previous study included a control group of children with normal acid-base status at birth, and one-minute Apgar score >3. This control group showed similar mean scores to those achieved by the total cohort in the present study:

		Study Cohort N=159	Previous controls N=64
Locomotor			
	Mean	110.7	112.0
	SD	14.9	9.1
Personal/social			
	Mean	106.6	108.3
	SD	11.1	10.8
Hearing/speech			
	Mean	118.8	118.3
	SD	13.9	15.9
Eye/hand			
	Mean	109.4	111.4
	SD	16.5	17.8
Performance			
	Mean	107.8	111.2
	SD	17.2	19.8

Children in the previous study with acidaemia and a one-minute Apgar score ≤3 also performed similarly to their counterparts in the present study:

		Study Cohort N=21	Previous Study N=8
Locomotor			
	Mean	112.1	111.9
	SD	11.7	14.7
Personal/social			
	Mean	107.0	107.9
	SD	8.6	10.7
Hearing/speech			
	Mean	116.2	117.0
	SD	8.9	21.4
Eye/hand			
	Mean	105.3	103.5
	SD	14.5	20.8
Performance			
	Mean	104.8	104.5
	SD	16.4	24.0

However, the non-acidaemic low-Apgar group in the previous study performed worse on some subscales than children in the study cohort:

		Study Cohort N=93	Previous study N=10
Locomotor			
	Mean	109.9	103.2
	SD	16.4	11.7
Personal/social			
	Mean	106.9	103.9
	SD	13.2	7.3
Hearing/speech			
	Mean	121.5	107.1
	SD	14.5	13.7
Eye/hand			
	Mean	110.7	106.3
	SD	17.2	24.0
Performance			
	Mean	108.5	110.5
	SD	16.8	23.0

The previous study group had a lower mean score on the hearing/speech subscale (difference 14.4, 95% CI 4.9,23.9; p=0.003) and a somewhat lower mean score on the locomotor subscale (difference 6.7, 95% CI -3.9,17.3; p=0.21).

The low scores recorded on the hearing/speech and locomotor subscales by the 10 low-Apgar, non-acidaemic children in the previous study gave rise to the present study hypothesis. This hypothesis has not been substantiated, suggesting that the previous study results were chance findings resulting from the small numbers of children involved. There is no evidence from the present study that, among children with a low one-minute Apgar score who are testable, acid-base status is related to mean Griffiths scores at age five.

4.5. **Range and variation of Griffiths scores**

One of the findings in the previous follow-up study in this hospital was that children with a low (≤ 3) one-minute Apgar score performed less consistently across the five Griffiths subscales than did children with a higher Apgar score (Dennis *et al.* 1989). Since the present study was limited to children with a low one-minute Apgar score this result could not be re-examined, but it was possible to see whether, within the low-Apgar group, the degree of acidaemia affected consistency of performance across the range of Griffiths tests.

Mean scores on the five subscales differed considerably, ranging from 106.6 on the social/personal subscale to 118.8 on the hearing/speech subscale (Table 3.4). The standard deviations of the scores also differed between the subscales. Thus a given score on one subscale did not denote the same level of achievement, relative to other children, as the same score on another subscale. To compare relative achievement across all five subscales, the scores were therefore standardised; that is, each score was expressed as a number of standard deviations from the mean of that subscale. For example, a score of 115 on the social/personal scale (mean 106.6, SD 11.1) would become (115-106.6)/11.1=0.757. The same score on the hearing/speech subscale would convert to a standardised score of (115-118.8)/13.9= -0.273. These standardised scores will be referred to (as is conventional) as z-scores.

Consistency of performance was measured in two ways: by the range of the five z-scores (the difference between the highest and the lowest) and by their standard deviation. Children who performed consistently on all the subscales had a small range and standard deviation of z-scores; more erratic performers had a larger range and standard deviation.

Comparisons were made between the acidaemic and non-acidaemic groups, with acidaemia defined as before, as umbilical arterial pH ≤ 7.10 and base deficit > 12 mmol/l. The three children with no score on the hearing/speech subscale (one in the

acidaemic group, two in the non-acidaemic group) were omitted from this analysis.

The results are shown below:

	Acidaemic N=20	Not acidaemic N=91	p value
Range of z-scores			
Mean	1.65	1.93	0.06
SD	0.52	0.85	
Standard deviation of z-scores			
Mean	0.67	0.76	0.11
SD	0.21	0.33	
Maximum z-score			
Mean	0.74	1.02	0.17
SD	0.66	0.83	
Minimum z-score			
Mean	-0.90	-0.91	0.95
SD	0.54	1.05	

The range of z-scores was slightly higher in the non-acidaemic group, with the difference between the groups approaching the conventional level of statistical significance. The wider range was due to a higher maximum z-score in the non-acidaemic group (although the difference between groups was not statistically significant); minimum z-scores were the same in both groups. Inspection of the maximum and minimum z-scores showed that there was no tendency, in either group, for them to attach to any particular subscale.

To explore these associations further, regression analyses were performed, with the range, standard deviation, maximum and minimum z-scores as the outcome variables. The same explanatory variables were offered as in the regressions on the Griffiths scores.

Variables that were statistically significant were:

Variable	Regression Coefficient,b	95% CI for b	p value
Children with known acid-base status; N=111			
Range of z-scores:			
None			
Standard deviation of z-scores:			
None			
Maximum z-score:			
Soc. Class I,II	0.44	0.17, 0.71	0.002
Minimum z-score:			
Started school	0.44	0.08, 0.80	0.02
Birthweight < 10th centile	-0.61	-1.11, -0.12	0.02
All children assessed; N=156			
Range of z-scores:			
None			
Standard deviation of z-scores:			
None			
Maximum z-score:			
Soc. Class I,II	0.48	0.25, 0.71	0.0001
Minimum z-score:			
Started school	0.37	0.07, 0.66	0.02
Soc. Class IV,V unclassified	-0.36	-0.71, -0.01	0.05

High social class and having started school were the only variables that were consistently significant in the regressions. High social class was associated with a mean increase of nearly 0.5 in the maximum z-score; having started school with a mean increase of about 0.4 in the minimum z-score.

Low social class was weakly associated, in the whole cohort, with a reduction in the minimum z-score; this association was not observed for the subgroup with known acid-base status. In this subgroup, birthweight below the tenth centile for

gestational age was associated with a reduction in the minimum z-score, an association not seen for the cohort as a whole.

Neither pH, base deficit nor acidaemia were significantly associated with any of the outcome variables. The tendency noted above for the non-acidaemic children to show a greater range of scores than the acidaemic children was therefore apparently explicable in terms of social factors. This result confirms the overriding influence of social class and schooling on performance in neurodevelopmental tests at the age of five.

5. OTHER TEST RESULTS AND ACID-BASE STATUS

5.1. Movement ABC scores and acid-base status

As described in Methods, the Movement ABC was formerly known as the Test of Motor Impairment (TOMI), and the published instructions and norms relate to this latter test (Stott *et al.*1984). The test battery consists of eight tasks, in which four types of skill are tested: manual dexterity, ball skills, static balance and dynamic balance. A pass criterion is set for each of the tasks, and if this is achieved, the child scores zero. If it is not achieved, the child scores 1 or 2. For each task, a score of 1 is intended to apply to the lowest 15% of the population; a score of 2 to the lowest 5%. Thus the higher the score, the worse the performance. Because, at the time of our study, there was no scoring system available for four-year olds, we applied the scores appropriate for five-year olds.

A number of children were unable to perform some of the tests; for instance, 10 children could not walk along a line, with heels raised, and six children were unable to stand on one leg. Failure to perform a test resulted in a score of 2. Thus scores were recorded for all the children.

Table 3.6 shows the mean Movement ABC scores, and the proportion of children with a score of 9 or more, in each acid-base group. The acidaemic and non-

Table 3.6

Acid-base status and Movement ABC scores

	Acidaemic N=21	Not acidaemic N=93	Acid-base status unknown N=45	Total N=159
Total score				
Mean	5.26	5.33	5.68	5.42
SD	3.00	2.96	2.93	2.94
Score ≥9: N	2/21	9/93	7/45	18/159
%	9.5	9.7	15.6	11.3
Manual dexterity				
Mean	2.83	2.45	2.44	2.50
SD	1.58	1.42	1.28	1.40
Ball skills				
Mean	0.57	0.63	1.04	0.74
SD	0.98	1.01	1.31	1.11
Static balance				
Mean	0.76	0.93	0.92	0.90
SD	0.72	0.72	0.62	0.69
Dynamic balance				
Mean	1.10	1.32	1.29	1.28
SD	0.70	0.96	0.76	0.87

acidaemic children had very similar scores. The table also shows the results for each group of items in the test battery. There were no statistically significant differences between the acidaemic and non-acidaemic groups in any of the test results.

These results together with those of the Griffiths locomotor subscale fail to reveal any association between acid-base status and motor ability among testable children.

5.2. Movement ABC scores compared with published norms

The test results allowed comparison between the acidaemic and non-acidaemic children in the study cohort; it was not our primary purpose to compare the cohort results with external standards.

Nevertheless, it was noted that the study results were very different from the published standards for children of the same age. The published mean overall scores for five-year olds were: in Britain 1.7 (SD 1.4) for boys and 1.8 (SD 1.7) for girls; and in America 1.6 (SD 1.6) for boys and 2.3 (SD 2.5) for girls (Stott *et al.* 1984). The mean score for the 159 children assessed in our study cohort was 5.4 (SD 2.9) (Table 3.6).

To explore the reason for these differences, we compared the results achieved on each separate task with the published results for five-year old British children (Stott *et al.* 1984). There was no British standard available for the bicycle trail.

The results were as follows:

		Study cohort		British
		Age 4 yr N=126	Age 5 yr N=33	standard Age 5 yr
Posting coins (secs)				
Preferred hand:	Mean	22.7	22.5	19.0
	SD	4.1	4.8	2.4
Other hand:	Mean	26.6	26.4	19.8
	SD	4.7	6.1	2.6
Threading beads (secs)				
	Mean	71.9	62.3	51.2
	SD	20.7	13.5	10.8
Catching a bean bag (number of catches)				
	Mean	6.7	7.5	7.5
	SD	2.2	1.9	2.0
Rolling a ball into goal (number of goals)				
	Mean	5.4	6.2	6.6
	SD	2.0	1.7	2.2
One leg balance (secs)				
Right leg:	Mean	8.2	9.2	15.2
	SD	2.8	3.1	5.8
Left leg:	Mean	6.9	7.4	16.2
	SD	2.8	3.2	5.4
Jump over cord (fault score)				
	Mean	0.26	0.18	1.3
	SD	0.55	0.46	2.0
Walking with heels raised (number of steps)				
	Mean	9.9	10.4	14.0
	SD	2.7	2.3	2.6

On all the tasks except for posting coins, the five-year olds in the study cohort performed better than the four-year olds. It might therefore be imagined that the high (poor) scores achieved by the study cohort arose from the application of a scoring system suitable for older children. However, the five-year olds in the study cohort also performed worse than the British standards for five-year olds in nearly all

areas. For example, they took much longer than expected on posting coins and threading beads, and they could maintain balance on one leg for much less than the standard time.

There were two exceptions to this overall tendency. Firstly, the study children achieved the expected mean scores on both of the tasks involving ball skills. Secondly, they achieved a much lower fault score for jumping over a cord. This task involved jumping over a cord, with feet together, either at knee height (score 0) or at a height one notch lower (score 1). Failure to clear the rope at the lower height resulted in a score of 2. While the mean fault score for the British standard was 1.3, the mean for five-year olds in the study cohort was only 0.18. Indeed, 28 of the 33 five-year olds cleared the rope at knee height, and only one child failed to clear the rope at the lower height.

One explanation for the generally poorer results achieved by the children in the study, compared with the expected standards, might be that the children in the cohort were motor impaired. However, the level of their Griffiths scores argues against this conclusion. Moreover, the erratic nature of the Movement ABC scores, some of them exceptionally poor, and some exceptionally good, suggests an artefact relating to the test itself.

After the assessments were completed, a set of scoring criteria suitable for four-year olds became available. Although we considered rescoring the tests for the four-year olds in the study, we decided against doing so, because of the ambiguities of our results. The reason for these ambiguities is not clear, but they highlight a potential difficulty in using a test of performance on children.

5.3. **Rutter behaviour scores and acid-base status**

Table 3.7 shows Rutter behaviour scores by acid-base status. Information was missing for one child in the non-acidaemic group whose parent failed to fill in the

Table 3.7

Acid-base status and Rutter behaviour scores

	Acidaemic N=21	Not acidaemic N=92	Acid-base status unknown N=45	Total N=158
Total score				
Mean	5.9	5.6	6.2	5.8
SD	3.1	4.2	4.8	4.2
Score ≥ 12: N	1/21	9/92	6/45	16/158
%	4.8	9.8	13.3	10.1
Conduct score				
Mean	4.2	3.5	3.8	3.7
SD	2.6	3.0	3.5	3.1
Neurotic score				
Mean	1.7	2.1	2.4	2.1
SD	1.3	2.1	2.2	2.0

Score missing for one child in non-acidaemic group

questionnaire.

Total Rutter score consists of two parts: a Conduct score (reflecting the extent of fighting, aggression, tempers etc.) and a Neurotic score (reflecting shyness, fearfulness etc.). There was no significant difference either in these subscores or in total Rutter score between the acidaemic and non-acidaemic groups (Table 3.7).

High scores on this test indicate more disordered behaviour. In the whole cohort 16/158 (10.1%) children scored a total of 12 or more, the expected cut-off point for the top 10% (Watt *et al.* 1980). There was no significant difference in this proportion between the acidaemic and non-acidaemic groups.

5.4. **Test results and acid-base status: summary**

Of the 170 children in the cohort, three died neonatally and three had spastic quadriplegia with profound developmental delay. These latter three children could not have undertaken the tests administered to the others (although, in practice, the families of the children were not contacted because they were considering lawsuits against the hospital). Thus 164 children were testable, of whom five refused to participate, leaving 159 children who were actually assessed.

Their results failed to support the hypothesis being tested: that non-acidaemic children with a low one-minute Apgar score would perform worse than acidaemic children. In spite of a careful and thorough analysis, there was no evidence that acid-base status was associated with any of the areas of function tested. Nor was it associated with consistency of performance across a range of abilities.

There was only one statistically significant result, in the opposite direction to that hypothesised: the acidaemic children had a lower mean score on the Griffiths hearing/speech subscale than did the non-acidaemic children. Confusingly, an even lower mean score on this subscale was achieved by the children with unknown acid-base status. This suggested that, if acid-base status was indeed associated with ability

in hearing and speech, this unknown group was in fact more acidaemic than the acidaemic group, but the available perinatal data countered this suggestion. Further, regression analyses designed to detect associations between Griffiths scores and acid-base values, while taking account of confounding variables such as social class, consistently failed to show any effect of acid-base status. It seems therefore that the single significant ($p < 0.05$) result could be explained by confounding.

While acid-base status at birth was shown to bear no relation to scores on developmental tests at the age of five, the strong influence both of social class and of starting school was consistently seen. These social factors affected the child's ability to perform language and visuo-perceptual tasks. However, neither social class, starting school, nor any other factor considered in this analysis was associated with gross motor ability.

6. FETAL HEART RATE (FHR) MONITORING IN LABOUR

6.1. Comparison between infants with and without FHR traces

In Section 2.1. a comparison was made between the infants with and without acid-base measurements, to examine whether immediate neonatal management differed between the two groups. It was argued that if this were the case, and if it is assumed that neonatal management affects long-term outcome, results based only on the subgroup of infants with arterial blood gas measurements could be biased. For a similar reason, a comparison was made between the 125 infants with a complete CTG trace and the 45 without.

However, a major difference between continuous FHR monitoring and acid-base measurement at delivery is that the former is an aspect of obstetric management, and its application is by no means random. For instance, during the study period, it was hospital policy to monitor continuously after induction of labour, and where the pregnancy was thought to be at increased risk. It has therefore to be considered

whether the indication for monitoring, or the monitoring itself, could have changed the relationship between FHR changes in labour and outcome - the relationship being analysed here.

A biased result would be obtained if, for example, the association between FHR abnormalities in labour and outcome were different in induced and non-induced labours. Or if FHR abnormalities detected by CTG led to more vigorous (and successful) obstetric and neonatal intervention than did FHR abnormalities detected by auscultation. The apparent relationship between FHR abnormalities and outcome would also be affected if FHR abnormalities remained undetected in infants not continuously monitored.

Evidence from the Dublin randomised trial of continuous FHR monitoring in labour suggests that long-term outcome is not improved by continuous monitoring compared with intermittent auscultation, at least as far as death and cerebral palsy are concerned (MacDonald *et al.* 1985). Nevertheless, in view of the foregoing, results relating to FHR abnormalities should be interpreted carefully.

The following table shows the rates (percent) of various obstetric and neonatal interventions and responses among those with and without continuous FHR monitoring:

	Infants with complete CTG N=125	Infants without complete CTG N=45	p value
Operative delivery	53.6	35.6	0.06
*Paediatrician called	84.3	65.9	0.02
One-minute Apgar score <3	46.4	51.1	0.71
Five-minute Apgar score <7	16.8	20.0	0.80
Intubation for meconium aspiration	58.4	44.4	0.15
Resuscitation by:			
intubation	79.2	71.1	0.37
bag and mask	14.4	22.2	0.33
THAM/bicarb.	7.2	2.2	0.40
cardiac massage	5.6	11.1	0.37
Time to spont. reg. resp. ≥10 min	12.8	20.0	0.36
Time to heartrate >100 b.p.m. >5 min	8.8	8.9	1.00
Admission to Special Care Baby Unit	12.8	24.4	0.11

* Not known for 11 infants

Infants with a complete CTG were much more likely to have a paediatrician called to the delivery and to be delivered operatively; they were somewhat more likely to be intubated for meconium aspiration. On the other hand, they were less likely to be admitted to Special Care and to receive cardiac massage, and fewer showed a delay in establishing spontaneous regular respiration.

These differences suggest that infants with a complete CTG were less seriously compromised than others, or were more vigorously managed at birth.

Table 3.8

Grades of Fetal Heart Rate (FHR) change by CTG group

	CTG ominous N=45	CTG not ominous N=80	Total N=125
Duration of trace (min):			
Median	320	285	300
Range	(12-1020)	(18-960)	(12-1020)
Mean (SD) percentage time in each grade			
Reassuring : Mean	19.0	33.3	28.1
: SD	(27.6)	(30.5)	(30.2)
Grade 1 changes : Mean	22.8	40.8	34.3
: SD	(27.9)	(31.3)	(31.2)
Grade 2 changes : Mean	8.9	16.2	13.6
: SD	(18.3)	(26.0)	(23.7)
Grade 3 changes : Mean	49.3	9.7	23.9
: SD	(34.1)	(16.2)	(30.7)
Total	100.0	100.0	100.0

6.2. **Details of FHR traces**

Of the 125 infants with a complete CTG trace, 45 (36.0%) were classified as "ominous" and 80 as "not ominous" (see Chapter II). The median length of the CTG trace was similar in the two groups: 320 mins in the "ominous" group and 285 min in the "not ominous" group (p=0.32) (Table 3.8).

As explained in Chapter II, each fetal heart rate (FHR) change was classified as Grade 1 (mild), Grade 2 (moderate) or Grade 3 (severe). The simultaneous occurrence of two or more Grade 2 changes counted as a Grade 3 change. The details of these classifications (shown in Table 2.2) are reproduced below (bpm stands for beats per minute):

Grade 1

1. Mild tachycardia: 150-159 bpm
2. Increased baseline variability : amplitude 16-24 bpm
3. Mild variable decels (amplitude $\geq$50 bpm): lasting $<$30 sec
4. Fewer than 6 accelerations per hour (of $>$15 bpm, lasting $>$15 sec)

Grade 2

5. Moderate tachycardia: 160-179 bpm
6. Moderate bradycardia: 100-109 bpm
7. Reduced baseline variability: amplitude 2-4 bpm
8. Moderate variable decels: lasting 30-59 sec
9. Slow recovery after decels: return to baseline $>$1 min from end of contraction
10. Overshoot after decels: post-deceleration acceleration, amplitude $>$15 bpm above baseline
11. Artefact or inadequate data - interpretation limited

Grade 3

12. Severe tachycardia: $\geq$180 bpm
13. Severe bradycardia with recovery: $<$100 bpm for $>$3 min
14. Severe bradycardia until delivery: $<$100 bpm for $>$3 min
15. Very increased baseline variability: amplitude $\geq$25 bpm
16. Absent baseline variability: amplitude $<$2 bpm
17. Severe variable decels: lasting $\geq$60 sec, with $<$50% of contractions

Table 3.9

Grade 3 (Severe) FHR abnormalities in group with ominous CTG (N=45)

FHR abnormality	Number of occurrences	Duration of abnormality (mins)		
		Median	Minimum	Maximum
Severe tachycardia	4	85	7	230
Severe bradycardia with recovery	8	8	5	35
Severe bradycardia until delivery	16	10	3	20
Very increased baseline variability	6	12.5	5	40
Absent baseline variability	17	12	3	360
Severe variable decelerations	17	70	10	430
Very severe variable decelerations	15	30	10	225
Severe late decelerations	3	70	60	180
Very severe late decelerations	11	120	20	210
Uterine hyperstimulation	1	85	-	-
Sinusoidal pattern	3	75	40	340
Total	101	20	3	430

18. Very severe variable decels: lasting ≥60 sec, with ≥50% of contractions
19. Severe late decels (amplitude >10 bpm, lag phase >20 sec), lasting >30 sec, with <50% of contractions
20. Very severe late decels: lasting >30 sec, with ≥50% of contractions
21. Uterine hyperstimulation: ≥30 contractions in 60 min
22. Sinusoidal pattern (amplitude >5 bpm, frequency <5 cycles/min

Table 3.8. shows that on average, the "ominous CTG" group exhibited Grade 3 changes for about half of their trace, while 19% of the trace was reassuring. In contrast, the group with a non-ominous CTG showed Grade 3 changes for only 10% of their trace, while a third of the trace was classified as reassuring.

The nature and duration of the severe (Grade 3) FHR changes in the ominous CTG group are shown in Table 3.9. The 45 infants in this group showed severe FHR changes on 101 occasions - a mean of 2.2 different abnormalities per infant. Most of the infants (35/45) showed at least two different Grade 3 abnormalities.

FHR abnormalities are extremely difficult to summarise, since they may vary in timing, overlap, duration and severity. The information shown in Tables 3.8 and 3.9 is therefore far from comprehensive, but because the FHR analysis was not central to this study, I have not attempted more complex classifications of FHR changes. Computer analysis of CTG traces would seem to be called for, but while there have been considerable advances in handling CTG information by computer (Pello *et al.*1991), this facility was not available to us.

6.3. **FHR changes in labour and acid-base status**

Of the 122 infants for whom acid-base measurements were known, 38 had an ominous CTG, 53 had a non-ominous CTG, and 31 had no trace, or an incomplete one. There was a gradient of acidaemia across the three groups (Table 3.10), infants with an ominous CTG being the most acidaemic, those with a non-ominous CTG the least, and those with unknown FHR changes showing acid-base values in between the

Table 3.10

CTG group and umbilical arterial acid-base status

		CTG ominous N=38	CTG not ominous N=53	*FHR changes unknown N=31	Total N=122	ANOVA for trend p value
pH	Mean	7.09	7.23	7.14	7.16	<0.001
	SD	0.15	0.08	0.16	0.14	
Base deficit (mmol/l)	Mean	13.8	8.5	11.7	10.9	<0.001
	SD	6.4	3.6	6.9	5.9	
CO_2 (mmHg)	Mean	60.3	50.0	56.0	54.8	0.003
	SD	17.7	10.1	13.4	14.3	
O_2 (mmHg)	Mean	11.4	11.8	9.3	11.1	0.25
	SD	7.9	6.2	5.2	6.6	

* Includes four infants delivered before labour.

two extremes. The gradient was apparent for pH, base deficit and CO_2 (ANOVA test for linear trend $p < 0.005$ in each case), but not for O_2.

If cut-off points rather than mean acid-base values were considered, a similar gradient was seen. The group with an ominous CTG included 16/38 (42.1%) infants who were acidaemic (Ua pH ≤ 7.10 and base deficit > 12 mmol/l) and 8/38 (21.1%) with pH < 7.00. In the group with a non-ominous CTG 4/53 (7.5%) infants were acidaemic; none had pH < 7.00. In the group with unknown FHR changes 8/40 (20.0%) infants were acidaemic and 5/40 (12.5%) had pH < 7.00.

From these observations two separate conclusions can be drawn. Firstly, severe FHR abnormalities were strongly associated with acidaemia at delivery; of the 20 acidaemic infants with known FHR patterns in labour, 80% had an ominous CTG, compared with 31% of non-acidaemic infants. Secondly, the group of infants with no CTG (four of whom were delivered by caesarean section before labour) appeared to be a mix of the other two groups, and most likely included some infants with severe FHR changes, and some without.

6.4. **FHR changes in labour and markers of hypoxic damage**

As recorded in Section 3.3, there were 16 infants with one or more of the signs suggested by the American College of Obstetricians and Gynecologists (1991) as indicating potentially damaging hypoxia. Considering each sign separately, seven infants had moderate or severe neonatal encephalopathy, 13 had pH < 7.00 and six had a five-minute Apgar score ≤ 3.

Among infants continuously monitored, these hypoxic markers were almost invariably preceded by an ominous CTG. Ten of the 16 infants had continuous monitoring; 9 showed an ominous CTG. The one with a non-ominous CTG had a five-minute Apgar score ≤ 3, unknown acid-base status and no encephalopathy. Among the six infants not continuously monitored, one had an operative delivery for

fetal distress. In the remaining infants there was no record of serious FHR abnormalities leading to operative delivery, but that is not an assurance that serious FHR abnormalities did not occur.

In comparison, of the 154 infants with none of the signs of hypoxia (including those without pH measurements), 115 were continuously monitored, and 36 (31.3%) had an ominous CTG. Of the 39 not continuously monitored, five (12.8%) had an operative delivery for fetal distress.

7. NEONATAL DEATH, OUTCOME AT AGE FIVE, AND FHR CHANGES

7.1. "Asphyxial" neonatal death

As discussed in Section 3.3, neonatal death and spastic quadriplegia, observed in six children, were strongly associated with a cluster of hypoxic signs, such as neonatal encephalopathy, acidaemia, prolonged cerebral depression and multiorgan system dysfunction. To investigate whether these signs might have resulted from a hypoxic insult or episode during labour, the pregnancy and intrapartum details of the six infants, including their fetal heart rate changes detected by CTG, were examined. All three infants who died neonatally had a complete CTG; details of these infants, shown in Section 3.1, are reproduced again below. The FHR abnormalities described are those observed retrospectively by the obstetrician in this study.

Case A.

Female. Birthweight 3870g. G.A. 40 wk.
Delivery by Keillands forceps for fetal distress
Apgar scores 0,3
Ua pH 7.10, base deficit 14 mmol/l
Severe encephalopathy
Seizures starting within first hour of life
CT scan at age 3 days showed cerebral oedema with compressed ventricles
Generalised oedema aged 3 days, associated with reduced urinary output
Died aged 5 days
At autopsy: bilateral tentorial tears
cerebral oedema and hypoxic change

The mother (a 22-year old primigravida) had an uneventful pregnancy until three days before delivery, when a Flying Squad call was initiated because of an increase in diastolic blood pressure to 110 mm Hg, associated with severe frontal headache and proteinuria. A reduction in fetal movements was also observed. The mother was treated with hydralazine and admitted to hospital. Spontaneous rupture of the membranes occurred two days later, and labour was induced with oxytocin.

Electronic fetal monitoring continued for 18 hours, covering the first stage of 16 hours 40 minutes and the second stage of 30 minutes. Severe FHR changes were recorded for 220 minutes in the first stage and for the whole of the second stage. These changes were:

First stage: severe tachycardia: 220 mins; very severe late decelerations: 20 mins.

Second stage: severe tachycardia: 10 mins; severe bradycardia until delivery: 15 mins; absent baseline variability: 15 mins.

Case B.

Female. Birthweight 2780g. G.A. 40 wk.
Weight approx. at 10th centile for G.A. (2760g)
Spontaneous delivery
Apgar scores 0,0
Ua pH 6.74, base deficit 30 mmol/l
Severe encephalopathy
Seizures starting at age one hour
Ultrasound scan on first day showed cerebral oedema
Very poor peripheral perfusion; never passed urine
Cardiac ischaemia; two cardiac arrests
Died aged 40 hours
At autopsy: cerebral oedema and widespread ischaemic changes

The pregnancy, in a 35-year old primigravida, was uneventful, and labour started spontaneously. ARM gave a normal volume of clear liquor. Electronic fetal monitoring continued for the full length of the labour: a first stage of 7 hours 10 minutes and a second stage of 120 minutes. Severe FHR changes were recorded for 20 minutes in the first stage and 100 minutes in the second:

First stage: very severe variable decelerations: 20 mins.

Second stage: absent baseline variability: 10 mins; very severe variable decelerations: 90 mins.

Case C.

Female. Birthweight 2955g. G.A. 40 wk.
Vaginal breech delivery
Apgar scores 0,1
Ua pH 6.90, base deficit 19 mmol/l
Severe encephalopathy
Seizures starting at age one hour
Cardiac arrhythmia
Died aged 32 hours
At autopsy: bilateral tentorial tears
cerebral oedema and contusions
cervical cord contusion

The mother (a 21-year old primigravida) had an uneventful pregnancy until 6 days before delivery, when there was a suspected membrane rupture, with leaking liquor. Five days later, labour started spontaneously, with the infant in the breech position. The first stage lasted 15 hours 20 minutes and the second stage 75 minutes; electronic fetal monitoring was carried out for 12 hours 25 minutes.

Severe FHR changes were recorded for 90 minutes in the first stage and for the whole of the second stage. These changes were:

First stage: severe tachycardia: 90 mins; severe variable decelerations: 70 mins.

Second stage: severe tachycardia: 60 mins; severe bradycardia until delivery: 15 mins; very severe variable decelerations: 60 mins.

Thus two of the three infants had obstetric complications which could have given rise to birth asphyxia (Case A: pre-eclampsia, Case C: vaginal breech delivery). The third infant had no apparent obstetric complications. All three showed evidence of serious fetal compromise in labour, with multiple FHR abnormalities on the CTG.

7.2. **Spastic quadriplegia**

Only one of the children with spastic quadriplegia had a complete CTG:

Case 2.

Female. Birthweight 3155g. G.A. 41 wk.
Caesarean section in labour for fetal distress
Apgar scores 0,4
Ua pH 6.97; base deficit 20 mmol/l
Seizures starting at 2 hours; moderate encephalopathy
CT scan aged 14 days showed diffuse white matter damage
Low urinary output for first few days;
hypotension, coagulopathy in 2nd week
Spastic quadriparesis; optic atrophy; epilepsy
Profound developmental delay
Died age 4 yrs 4 mths.

This was the fourth pregnancy of a 27-year old mother, with two previous normal deliveries and one abortion. Pregnancy was uneventful, and labour was induced at 41 weeks for post-term pregnancy.

Electronic fetal monitoring continued for 4 hours and 5 minutes, from the onset of labour until delivery by caesarean section. Severe FHR abnormalities were observed throughout. These were:

First stage: severe bradycardia with recovery: 7 mins; severe bradycardia until delivery: 20 mins; absent baseline variability: 20 mins; severe variable decelerations: 160 mins; sinusoidal patterns: 40 mins.

One of the other children with spastic quadriplegia was delivered operatively for fetal distress, although not continuously monitored.

Case 3.

Male. Birthweight 3466g. G.A. 39 wk.
Forceps delivery for fetal distress
Apgar scores 3,5
Ua pH 6.70; base deficit 26 mmol/l
Seizures starting at 8 hours; severe encephalopathy
CT scan aged 11 days showed suspected white matter damage; at 13 weeks severe white matter destruction
Neonatal anuria; hyperkalaemia
Spastic quadriparesis; cortical blindness
Microcephalus; profound developmental delay; epilepsy
Untestable

The mother was a 31-year-old primipara, with one previous abortion. Labour started spontaneously; the first stage was 4 hours 20 minutes; the second stage 105 minutes. There was no concern in labour until 1 hour 25 mins before delivery, when the FHR was observed to drop from 140 bpm to 100 bpm. It remained between 110 bpm and 90 bpm until delivery by forceps, with manual rotation of the head.

Case 4.

Female. Birthweight 3726g. G.A. 39 wk.
Spontaneous delivery
Apgar scores 2,2
Ua pH 6.93; base deficit 23 mmol/l
Seizures starting at 2 hours; moderate encephalopathy
CT scan aged 16 days showed suspected white matter damage; ultrasound scan at 28 days showed cerebral atrophy and left periventricular leukomalacia
Spastic quadriparesis; visual impairment
Profound developmental delay
Untestable

This was an uneventful pregnancy to a 26-year old mother with one previous normal delivery. Labour started spontaneously; the first stage was 4 hours 10 minutes, and the second stage 25 minutes.

There were no concerns about the FHR throughout labour. Auscultation every three or four minutes recorded a FHR between 110 and 140 until delivery.

In summary, two of the infants were compromised in labour; one showed severe FHR changes on the CTG for more than 4 hours, and the other, monitored by intermittent auscultation, had bradycardia lasting 1½ hours. The third had no recording of any FHR abnormalities in labour, nor of any clinical event that might have caused hypoxic damage.

7.3. **Impairment Rating**

One of the issues to be addressed by this study was the long-term significance of abnormal FHR patterns in labour (Chapter I, Section 3.7). The relationship between an ominous CTG and Impairment Rating at age five is shown in Table 3.11.

Table 3.11

CTG group and impairment

	CTG ominous		CTG not ominous		*FHR changes unknown		Total	
	N	%	N	%	N	%	N	%
Impairment Rating								
1:Unimpaired	34	81.0	70	87.5	34	75.6	138	82.6
2:Some impairment	7	16.7	7	8.8	7	15.6	21	12.6
3:Serious impairment	1	2.4	3	3.8	4	8.9	8	4.8
TOTAL	42	100.0	80	100.0	45	100.0	167	100.0

* Includes four infants delivered before labour.

There was no difference in the proportions of children with each Impairment Rating in the two CTG groups. Details of the children with Impairment Rating 2 and 3 were:

Ominous CTG:

Rating 3: spastic quadriplegia (one)

Rating 2: central motor deficit (three)

visuo-spatial delay (two)

poor static/dynamic balance (two)

CTG not ominous:

Rating 3: global developmental delay (three)

Rating 2: central motor deficit (one)

visuo-spatial delay (three)

poor balance, clumsiness (one)

language delay (one)

global developmental delay (one)

Thus there was no relationship between the type of impairment evident at the age of five and the occurrence of an ominous CTG in labour.

7.4. **Test scores**

Griffiths scores and FHR changes

Of the 159 children assessed by the paediatrician, 41 had an ominous CTG in labour, 76 had a non-ominous CTG and 42 had unknown FHR changes. Characteristics known to affect performance on developmental tests, such as social class and school attendance (Hanson & Aldridge Smith, 1987; Dennis *et al.* 1989), were first examined in the two CTG groups (data not shown). The social and personal characteristics of the children with and without an ominous CTG were very similar, giving confidence in a direct comparison between these groups.

Table 3.12

CTG group and test scores

	CTG ominous N=41	CTG not ominous N=76	FHR changes unknown N=42	Total N=159
Griffiths subscale scores				
Locomotor Mean	109.2	111.3	111.1	110.7
SD	14.9	14.3	16.4	14.9
Social Mean	105.5	107.3	106.3	106.6
SD	9.9	12.2	10.3	11.1
*Hearing/speech Mean	121.2	117.5	118.8	118.8
SD	10.6	15.2	14.4	13.9
Eye/hand Mean	111.3	108.2	109.9	109.4
SD	13.6	18.1	16.3	16.5
Performance Mean	109.1	108.0	106.0	107.8
SD	16.1	18.7	15.4	17.2
Movement ABC total score				
Mean	5.2	5.4	5.6	5.4
SD	3.2	2.9	2.9	2.9
Score ≥9 N	6/41	8/76	4/42	18/159
(%)	14.6	10.5	9.5	11.3
#Rutter total score				
Mean	5.7	5.8	6.0	5.8
SD	4.0	4.0	5.0	4.2
Score ≥12 N	4/40	5/76	7/42	16/158
(%)	10.0	6.6	16.7	10.1

* In non-ominous CTG group one child with no expressive language not testable.
In group with unknown FHR changes two non-English speaking children not tested.
Score missing for one child in ominous CTG group.

Mean scores on all the Griffiths subscales differed only slightly between the two CTG groups (Table 3.12); none of the differences approached statistical significance. The lack of association between Griffiths subscale scores and the occurrence of an ominous CTG was confirmed by regression analysis. Using data for the 117 infants who had a complete CTG, the only statistically significant explanatory variables were high social class (positively associated with the hearing/speech, eye/hand and performance subscales) and having started school (positively associated with the eye/hand and performance subscales). The occurrence of an ominous CTG was not significant in any of the regressions, and there were no significant associations with the locomotor or social/personal subscales. These results accord with those obtained using data from all 159 children assessed (Section 4.3).

A detailed comparison of all aspects of the Movement ABC scores and of the Rutter behaviour scores also showed no significant differences between the CTG groups. Total scores on these tests are shown in Table 3.12.

8. DISCUSSION

This study, an intensive analysis of a small group of infants, has thrown some light on the confusing relationships between a low Apgar score, acidaemia, neonatal encephalopathy, and long-term outcome. Because of its small size, and the possibility of bias (see Sections 2.1 and 6.1) the conclusions drawn from the study must be considered as provisional; nevertheless, they form a coherent picture.

Previous studies have shown that infants with severe acidaemia (umbilical arterial pH < 7.00) are more likely than others to show a persistent low Apgar score (Gilstrap *et al.* 1989; Goldaber *et al.* 1991; Winkler *et al.* 1991). This relationship was confirmed, and our study also showed that infants who developed moderate or severe neonatal encephalopathy usually exhibited both these signs. Thus of the seven

infants in our cohort with moderate or severe encephalopathy, six had pH <7.00, and all had a five-minute Apgar score of 5 or less.

Among infants who were continuously monitored, both severe acidaemia and moderate or severe encephalopathy were invariably preceded by an ominous CTG. This association was observed for the nine continuously monitored infants with neonatal encephalopathy, pH <7.00, or both. These observations are consistent with a sequence of: serious fetal compromise in labour → severe acidaemia → prolonged cerebral depression → neonatal encephalopathy, although the initiating insult may have occurred well before labour.

Since not all infants received continuous FHR monitoring in labour, a doubt must persist as to whether these observations are biased. It could be that infants with encephalopathy or severe acidaemia who were not continuously monitored did not experience FHR abnormalities. The fact that only one of five such infants had an operative delivery for fetal distress supports this view. On the other hand, it is also possible that abnormalities occurred, but were either not detected or not acted upon appropriately. This issue is being investigated (Dr. Ann Johnson, personal communication) but is beyond the scope of this study.

Our data also confirmed the link between encephalopathy and neonatal death or cerebral palsy, particularly spastic quadriplegia (Robertson & Finer, 1985; Levene *et al.* 1986). Of the seven infants with moderate or severe encephalopathy, six had these outcomes. A close inspection of their pregnancy and intrapartum details, cerebral scans and autopsy reports suggested that all six infants were damaged by asphyxia. As regards the timing of the asphyxial insult, there was evidence of intrapartum compromise in five of the six cases; in the sixth (who was not continuously monitored) no FHR abnormalities were detected. Notably, only two of the infants (both of whom died neonatally) had overt obstetric complications: pre-eclampsia in one case and a vaginal breech delivery in the other.

The relationships just described, between an ominous CTG and severe acidaemia, and between severe acidaemia and a low five-minute Apgar score, were observed beyond the small group of severely compromised infants. Thus in general, infants with an ominous CTG were more acidaemic at delivery than those with a non-ominous CTG; and the more acidaemic infants tended to take longer to achieve a satisfactory Apgar score. However, beyond the six severely damaged infants just described, evidence of fetal compromise during labour or at delivery was not related to long-term outcome. Our study was too small to investigate the long-term outcome of infants who survived neonatal encephalopathy without severe impairment. But among infants who exhibited only short-lived cerebral depression there was no association between scores on a battery of neurodevelopmental tests and the occurrence of an ominous CTG, or between test scores and acid-base status.

While our study provides detailed evidence of a damaging asphyxial process leading to neonatal death or cerebral palsy, there was no evidence for a so-called continuum of reproductive casualty, in which "a small amount of asphyxia causes a small amount of damage" (Low *et al.* 1988).

CHAPTER IV

A STUDY OF CEREBRAL PALSY IN THE OXFORD HEALTH DISTRICT: JANUARY 1984 - SEPTEMBER 1985

1. **Introduction**

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3. **Frequency of cerebral palsy in residents of the Oxford Health District: singleton births from January 1984 to September 1985**

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CHAPTER IV

A STUDY OF CEREBRAL PALSY IN THE OXFORD HEALTH DISTRICT: JANUARY 1984 - SEPTEMBER 1985

1. INTRODUCTION

Earlier in the thesis, I discussed the way in which clinical markers of asphyxia have been used to investigate the link between birth asphyxia and later neurological impairment. One type of neurological impairment that has often been observed to follow birth asphyxia is cerebral palsy. This observation concurs with the results of experiments on fetal monkeys subjected to imposed asphyxia.

Although the connection between birth asphyxia and cerebral palsy is established, opinions differ as to its strength and importance. A study of cerebral palsy in the Oxford Health District was therefore undertaken, to assess the contribution of birth asphyxia in term infants to the overall rate of cerebral palsy in the population. The starting point was the follow-up study already described - of term singletons born at the John Radcliffe Hospital between January 1984 and September 1985 with a one-minute Apgar score ≤ 3.

In that study it turned out that there were four children who had cerebral palsy. All of them were born to mothers resident in the Oxford Health District. The way in which these four cases fitted into the overall picture of cerebral palsy in the Oxford District during the study period was examined.

Specifically, the following questions were posed:

(i) How many cases of cerebral palsy occurred in singletons born to Oxford District residents during the study period? How many of these were in term children? What proportion of all cerebral palsy cases did the four children in my follow-up study represent?

(ii) What was the rate of cerebral palsy among total livebirths? What was the

rate among term livebirths?

(iii) Were these rates in line with the rates estimated by other studies?

(iv) How many of the cases of cerebral palsy might have been due to birth asphyxia? Was the proportion of cases possibly attributable to birth asphyxia in line with the proportion suggested by previous authors?

(v) Did the four children in my study differ from others with respect to the aetiology or type of their cerebral palsy?

2. BACKGROUND

2.1. What is cerebral palsy?

Cerebral palsy is not a single entity, but rather a miscellany of clinical syndromes, with various causes, that occur in young children. The diversity of these syndromes has led, over a long period, to difficulties in defining and classifying cerebral palsy (Ingram, 1984; Mutch *et al.*1992). However, it is now widely agreed that all the syndromes involve motor deficit, are persistent but non-progressive, and are due to a brain lesion, and it is the combination of these three elements that forms the basis of currently used definitions of cerebral palsy. One such definition was arrived at by a small working group under the chairmanship of Bax. This group described cerebral palsy as 'a disorder of movement and posture due to a defect or lesion of the immature brain' and added that disorders due to progressive disease were excluded from this definition (Bax, 1964). Similarly, Ingram defined cerebral palsy as 'an inclusive term to describe a group of chronic, non-progressive disorders occurring in young children, in which disease of the brain causes impairment of motor function' (Ingram, 1964). As will be seen later, this definition is not always straightforward to apply in practice.

While the overall definition of cerebral palsy may be agreed, the classification

of cerebral palsy by type continues to present problems. Various approaches have been suggested: aetiological, pathological and clinical. Some of the early classifications included reference to the presumed underlying pathology or aetiology of the condition, although there were criticisms of this approach. Freud, writing in 1897, listed three objections. Firstly, it was often impossible to identify the timing or nature of the insult which caused brain damage. Secondly, multiple causes might operate in the prenatal, perinatal and postnatal periods. Thirdly, classification on the basis of presumed aetiology was of little clinical value (Ingram, 1984). Nevertheless, such classifications persisted. In a paper published in 1952, Perlstein (1952) advanced the view that classification according to aetiology was "one of the most useful classifications of cerebral palsy, since specific etiological factors often cause characteristic clinical syndromes". He stated, for example, that prematurity was commonly associated with spastic paraplegia; toxaemia of pregnancy with spastic hemiplegia; anoxia with "athetoid or rigidity" and a precipitate or caesarean delivery with spastic quadriplegia or rigidity. In 1953, members of the American Academy for Cerebral Palsy voted to include aetiology as one aspect of their classification system (Minnear, 1956).

Later workers however echoed Freud's reservations about basing classification on presumed aetiology (Bax, 1964; Isler, 1971), and the emphasis shifted towards clinically-based classifications.

Such an approach also presents difficulties. One problem is that classifications may be based on clinical syndromes or on separate clinical signs. If it is based on syndromes it can only be applied by the neurologist who knows how a clinical picture presents in early childhood. If based on signs, the changes in signs likely to occur as the child grows older may necessitate changes in classification (Bax, 1964). Moreover, classifications based on signs have led in the past to complex and sometimes contradictory terminology (Ingram, 1955).

In practice, several different clinical classifications, based on a combination of

syndromes and signs, have been proposed (Balf & Ingram, 1955; The Little Club, 1959; Hagberg *et al.* 1975). As an example, that of Hagberg *et al.* specified three main groups of syndromes: spastic (hypertonic), ataxic, and dyskinetic. Each group was further subdivided: the spastic syndromes into hemiplegia, tetraplegia, and diplegia; the ataxic syndromes into ataxic diplegia and congenital ataxia; the dyskinetic syndromes into athetosis and dystonia. A simplified version of this classification has recently been proposed which matches the information actually available in epidemiological studies (Mutch *et al.* 1992).

In spite of the availability of such classifications, there appears to be a low level of concordance between clinicians about diagnosing specific types of cerebral palsy. The main underlying problem is that the same term may be used to mean different things by different people. This problem was vividly described by Bax (1964), reporting on the meeting (mentioned above) to discuss the terminology and classification of cerebral palsy. He wrote that after accepting a basic definition of cerebral palsy, "the group ran into considerable difficulty when they went on to discuss the classification of various types of cerebral paresis. Indeed, they barely got beyond discussing the word 'spastic'". Similarly, Jarvis *et al.* (1985) commented on the different interpretations of the term 'diplegia' used by various authors. In their own study, Jarvis and colleagues avoided the term, preferring to use the categories 'quadriplegia' and 'paraplegia' in combination.

Blair and Stanley carried out a study to assess the level of agreement between clinicians in categorising cerebral palsy (Blair & Stanley, 1985). A number of clinicians were asked to classify the motor type (athetoid, dystonic, spastic etc.) and severity (mild, moderate, severe) of cerebral palsy in about 20 children. Two classifications were performed a year apart: before and after a seminar on diagnostic systems, in which use of the system of Hagberg *et al.* (1975) was recommended.

Before the seminar, the kappa coefficient of agreement between the clinicians for motor type was 0.10, indicating very poor agreement (Altman, 1991). The coefficient for severity was 0.38, indicating fair agreement. After the seminar, the kappa coefficients were 0.35 (fair) and 0.40 (fair) respectively. In general, several factors are thought to contribute to the diagnostic variation between clinicians, including the temporal variations in a child's clinical signs, and the different training and interests of the specialists (paediatricians, neurologists and physiotherapists) who may be involved in the diagnosis (Blair & Stanley, 1985).

The fact that a given term means different things to different clinicians has been one of the factors hindering epidemiological studies of cerebral palsy, which require comparison of the same disorder between countries, areas or treatments (Evans & Alberman, 1985; Evans *et al.*1986). Mainly for epidemiological purposes, a standard form for recording central motor deficit has been produced, based on clinical observations, and eschewing clinical terms (Evans *et al.*1989). The aim is not to label the child as having a particular type of cerebral palsy, but rather to describe how the child functions. Thus the form separates "motor" and "other" involvement, and describes each of these aspects in some detail. For instance, motor involvement includes seven elements: observed unwanted movements; tone; distribution of involvement; mouth; functional severity of head, neck and trunk; lower limb function; upper limb function. Each of these elements is then graded, so that, for example, lower limb function can take one of four grades: (i) walks fluently (ii) gait functional but non-fluent (iii) gait obviously abnormal, reducing mobility and/or restricting life style (iv) no independent walking. This form has been criticised on the grounds that consistency of recording of neuromotor impairment can only be achieved using a structured examination, with defined standards (Stewart, 1989). Therefore a precise scheme for assessing and recording neurological deficit, for children aged from 9 months to 5 years, and based on a structured examination, has been produced (Amiel-

Tison & Stewart, 1989).

2.2. Measures of frequency relevant to cerebral palsy

Even when the definition and classification of cerebral palsy are agreed, there are still problems in determining the rate of cerebral palsy in the population. The problems are both conceptual and practical.

There are two commonly used measures of disease frequency in a population: incidence and prevalence. In the calculation of incidence the numerator is the number of new cases arising in a certain period. In calculating prevalence the numerator is the number of cases present during a certain period. This number must be less than the number of new cases arising because of intervening deaths. The denominator for both rates is the number in the population at risk of the disease.

For cerebral palsy, the most commonly used measure of frequency is *birth prevalence*, defined as the number of cases of a given age per 1000 livebirths (or per 1000 neonatal survivors) (Alberman, 1984; Paneth & Kiely, 1984). It is usual to include children who were diagnosed with cerebral palsy but who died before the given age, although (as discussed below) this may present problems. The resulting rate is sometimes termed the cumulative incidence rate (Paneth & Kiely, 1984; Rosen & Dickinson, 1992). This rate necessarily excludes children who would have developed cerebral palsy, but who died before any diagnosis could be made. As ultrasound and other imaging techniques become increasingly accurate in predicting outcome, true prevalence rates may also become more accurate (Johnson & King, 1989).

In practice, it is sometimes difficult to distinguish cases of cerebral palsy from non-cases. Some children who are diagnosed as having cerebral palsy later appear to "outgrow" the disorder. For example, in the NCPP cohort, 51% of children diagnosed with cerebral palsy at the age of one were free of this disorder by the time they

were seven (Nelson & Ellenberg, 1982). If it is accepted that cerebral palsy is a persisting disorder, such children should not be included in any frequency rates. Since most diagnoses of cerebral palsy are firm by the age of five, some registers of cerebral palsy make their final ascertainment at this age (Stanley, 1982; Johnson & King, 1989). If children are diagnosed as having cerebral palsy at an earlier age, and die before the age of five, it may be questioned whether they should be counted as cases. Since the children who outgrow cerebral palsy are virtually always those with a mild disorder (Nelson & Ellenberg, 1982), the inclusion of children who die with severe cerebral palsy seems reasonable.

An opposing difficulty is that some children with very mild cerebral palsy may be missed, especially if they have no contact with the health care services. Indeed, the distinction between clumsiness and mild cerebral palsy is not always clear (Stanley, 1982; Johnson & King, 1989).

2.3. **Observed frequency of cerebral palsy**

Details of studies

The frequency of cerebral palsy among infants born since 1970 has been reported in eleven studies (Cussen *et al.* 1978; Jarvis *et al.* 1985; Dowding & Barry, 1988; Emond *et al.* 1989; Holst *et al.* 1989; Hagberg *et al.* 1989; Riikonen *et al.* 1989; Meberg, 1990; Pharoah *et al.* 1990; Grether *et al.* 1992; Stanley & Watson, 1992). The results of ten of these studies are summarised in Table 4.1. Data from Cussen *et al.* were not included because their period of follow up was less than three years.

Five of the studies related to mothers resident in a geographically-defined area at the time of delivery. These areas were in the U.K. (Jarvis *et al.* 1985; Emond *et al.* 1989; Pharoah *et al.* 1990), Ireland (Dowding & Barry, 1988) and California (Grether *et al.* 1992). Five related to infants born in a geographically-defined area, in Denmark (Holst *et al.* 1989), Sweden (Hagberg *et al.* 1989), Finland (Riikonen *et*

Table 4.1

Rate of cerebral palsy in birth cohorts born since 1970

	Years of birth	Follow-up (yr)	Total			Birthweight < 2500g			Birthweight ≥ 2500g		
			CP	Live births	CP rate per 1000	CP	Live births	CP rate per 1000	CP	Live births	CP rate per 1000
Jarvis *et al.* 1985	1972-75	5	72	39076	1.84	19	*2736	6.94	53	*36340	1.46
Dowding & Barry 1988	1979-81	4	145	76506	1.90	46	*3900	11.79	99	*72606	1.36
Emond *et al.* 1989	1970	5	41	#16136	2.54	16	*1043	15.34	25	*15093	1.66
Holst *et al.* 1989	1978	4	20	4138	4.83	8	*146	54.79	12	*3992	3.01
Hagberg *et al.* 1989	1979-82	4	151	74666	2.02	*59	*2990	19.73	*92	*71676	1.28
Riikonen *et al.* 1989	1978-82	5	70	27643	2.53	35	1110	31.53	35	26533	1.32
Meberg 1990	1980-84	4	22	10334	2.13	6	390	15.38	16	9944	1.61
Pharoah *et al.* 1990	1983-84	5	123	63442	1.94	62	4147	14.95	61	59295	1.03
Grether *et al.* 1992	1983-85	3	192	*156100	1.23	-	-	-	-	-	-
Stanley & Watson 1992	1983-85	5	150	68855	2.18	66	3998	16.51	84	64857	1.30
Total			986	536,896	1.84						
Total excl. Grether *et al.*			794	380,796	2.09	317	20,460	15.49	477	360,336	1.32

* Numbers estimated. # Survivors at 28 days.

*al.*1989), Norway (Meberg, 1990), and Western Australia (Stanley & Watson, 1992). All reported a follow-up period of four or five years, except for Grether *et al.*, who followed up infants for only three years.

The rates presented are cumulative incidence rates; that is, they are based on all cases of cerebral palsy, and include children who did not survive for the full follow-up period. (This is clear for eight of the studies, and is assumed for the other two (Holst *et al.*1989; Stanley & Watson, 1992).) The lower age limit for inclusion of children who died was not usually made explicit, although Hagberg *et al.* (1989) and Meberg (1990) stated that they included children who died after the age of two, whereas Grether *et al.* (1992) included only those who died after the age of three.

Postnatally acquired cerebral palsy was assumed to have been excluded from all the studies, although this was not made explicit in one case (Holst *et al.*1989). Again, what was meant by "postnatal" was not always defined, although in three studies it referred to insults after the 28th day of life (Jarvis *et al.*1985; Pharoah *et al.*1990; Grether *et al.*1992), and in two studies to insults after the first eight days (Hagberg *et al.*1989; Riikonen *et al.*1989).

The denominators on which the rates in Table 4.1. were based were livebirths, except for the study of Emond *et al.* (1989), who based rates on neonatal survivors. The numbers shown in the table as estimates were based on the rates reported in each paper. In most studies high birthweight was defined as $\geq$2500g; in the studies of Hagberg *et al.* (1989) and Pharoah *et al.* (1990) it was defined as >2500g.

Results

The pooled rate of cerebral palsy was 1.84 per 1000 livebirths (95% CI 1.72 to 1.95). Eight of the studies reported rates between 1.84 per 1000 and 2.54 per 1000, although there were two outlying rates: 1.23 per 1000 (Grether *et al.*1992) and 4.83

per 1000 (Holst *et al.*1989). The sheer size of the Grether *et al.* study (it accounted for 29% of all the livebirths observed) pulled down the average rate. The impact made on the pooled rate by the small study of Holst *et al.* was, however, minimal.

The low rate reported by Grether *et al.* (1992) can be explained by two factors. Only moderate or severe cases of cerebral palsy were included in this study, while other authors included all grades of severity. Also, Grether *et al.* used more stringent criteria than did some other authors for the inclusion of children who died. A third factor which distinguished their study from the others was their short (three-year) follow-up period. This would probably be expected to increase, rather than lower, the number of cerebral palsy cases observed, as children would be included as cases who were later found not to have the disorder. However, this effect may have been negligible, because such children generally have mild cerebral palsy (Nelson & Ellenberg, 1982), and they were already excluded.

The overall pooled rate of cerebral palsy excluding the study of Grether *et al.* was 2.09 per 1000 (95% CI 1.94 to 2.23)

From Table 4.1 there was no indication of any trend in the cerebral palsy rate over time.

Cerebral palsy rate by birthweight

Table 4.1. also shows the cerebral palsy rate by birthweight.

In children of birthweight <2500g, the overall rate was 15.49 per 1000 (95% CI 13.80 to 17.18). In six studies the rate ranged between about 12 and 20 per 1000, but a rate as low as 6.94 per 1000 was reported by one study (Jarvis *et al.*1985), and as high as 54.79 per 1000 by another (Holst *et al.*1989).

In term (≥2500g) infants, the pooled rate was 1.32 per 1000 (95% CI 1.20 to 1.44), ranging from 1.03 per 1000 (Pharoah *et al.*1990) to 3.01 per 1000 (Holst *et al.*1989). Children of birthweight ≥2500g represented 58.6% of all cases of cerebral palsy.

Since birthweight information for total livebirths was not reported by Grether *et al.* (1992), the birthweight specific rates relate to a pooled overall rate which excludes this study, of 2.09 per 1000 (95% CI 1.94 to 2.23).

Singletons/multiples

The table shows rates for singletons and multiples combined. The relative risk of cerebral palsy in twins compared with singletons was reported only by Dowding & Barry (Dowding & Barry, 1988) and Grether *et al.*, who observed relative risks of 3.0 and 5.9 respectively. Assuming a relative risk of 4.0, and an incidence of multiple births of 1 in 50 livebirths (Macfarlane & Mugford, 1984), the cerebral palsy rate in singletons would be expected to be 6% lower than the overall rate. Taking the composite overall rate of 1.84 per 1000, this would suggest a rate of 1.73 per 1000 in singletons.

In term (≥2500g) livebirths, the incidence of multiple births is only about 1 in 100 (Macfarlane & Mugford, 1984). The estimated rate of cerebral palsy in term singletons would therefore be 3% lower than the overall rate of 1.32 per 1000; i.e. 1.28 per 1000.

2.4. **Proportion of cerebral palsy cases thought to be due to birth asphyxia**

Estimates based on relative risk and prevalence of birth asphyxia

The proportion of cases of a disease that can be attributed to a so-called "risk factor" is termed the population attributable risk, or PAR. This quantity depends on two values: the relative risk of the disease associated with the factor (r), and the preva-

lence of the factor in the population (b) (Kahn & Sempos, 1989).

$$PAR = [b(r-1)/1+b(r-1)] \times 100$$

Application of this formula to the risk factor birth asphyxia is problematical since (as discussed in Chapter I) birth asphyxia cannot be directly identified. The occurrence of asphyxia can be recognised only through proxy markers, such as fetal acidaemia, low Apgar score or neonatal encephalopathy. Each of these markers is likely to carry its own PAR.

In their estimate of the PAR of asphyxia for cerebral palsy, Blair & Stanley (1988) used as asphyxial markers the occurrence of fetal distress followed by a one-minute Apgar score <7; or a time to spontaneous respiration of more than 2 minutes; or both. These markers are clearly not specific for birth asphyxia, and would be likely to occur in a substantial proportion of the population. Using the Western Australia Cerebral Palsy Register to identify children with cerebral palsy born between 1975 and 1980, they estimated the PAR of birth asphyxia for cerebral palsy at 14%.

I have made a further estimate for term singleton infants, using data from the NCPP study (Nelson & Ellenberg, 1987). This study covered the period 1959 to 1966 and any estimate based on it may not be wholly relevant to present practice.

I identified birth asphyxia by the combination of three markers: (i) obstetric complications (e.g. placental abruption, breech delivery, cord prolapse or fetal bradycardia) (ii) sustained abnormal neurological signs (e.g. decreased activity after the first day of life, need for incubator care for more than three days, feeding problems or seizures) (iii) a five-minute Apgar score <6. This combination of signs occurred in 68/41,012 term ($\geq$2500g) singleton infants, a rate of 1.7 per 1000. Their risk of cerebral palsy was 176.5 per 1000, a relative risk of 63.9 compared with babies who did not exhibit this combination of signs.

The PAR of birth asphyxia for cerebral palsy in term singleton infants was calculated as

$$[0.0017(62.9)/1+0.0017(62.9)] = 0.097, \text{ or } 9.7\%.$$

Estimates based on examination of case records of infants with cerebral palsy

The PAR estimates the proportion of cases of a disease that is "attributable to" the risk factor only in the sense of being associated with it. If the association has arisen through intermediate or confounding variables the risk factor itself would not be responsible for any cases of the disease, and there would be no corresponding benefit if the risk factor were removed. The PAR calculated for birth asphyxia assumes that all the cases of cerebral palsy occurring together with birth asphyxia were actually caused by the asphyxia. It thus estimates the maximum contribution that birth asphyxia could have made to the sum of cerebral palsy.

A more direct approach to measuring the risk attributable to birth asphyxia was taken by Blair and Stanley (1988). They examined the obstetric and neonatal records of all the infants in their cohort with cerebral palsy, to assess the likelihood that intra-partum asphyxia had led to their brain damage. This mechanism of brain damage was judged to be very likely only if stringent criteria were met. There had to be abnormal neurologic signs "of the required type, severity, onset, and duration", and no definite evidence that brain damage had occurred at times other than labour or delivery (for instance, evidence of periventricular leukomalacia on ultrasonography at birth). If there had been an uncomplicated delivery, without evidence of fetal distress, and the baby was in good condition at birth, intrapartum asphyxial damage was judged very unlikely. After applying these criteria, birth asphyxial damage was considered to be very likely in only 5% (9/183) of the cases, and possible in a further 3% (6/183). Thus it was estimated that at most 8% of all cases of cerebral palsy could be attributed

to intrapartum asphyxia.

A similar method was used by Hagberg *et al.* (1989) on their cohort of infants born between 1979 and 1982. However, an important difference between the two studies was that Blair and Stanley looked specifically for intrapartum asphyxial damage, while Hagberg *et al.* sought a much wider group of cases: those with an "obviously perinatal" origin. The term "perinatal" covered the period up to one week after birth, and events occurring during this time, including intracerebral haemorrhage, CNS infection, or a need for mechanical ventilation, were included among the "obviously perinatal" causes. In preterm infants (<37 weeks of gestation) Hagberg *et al.* considered that 35/70 (50%) had an obvious perinatal cause for their cerebral palsy, while among term infants, the proportion was 14/92 (15.2%). Overall, the proportion ascribed to a perinatal cause was therefore 30.2%, a much higher rate than that suggested by Blair and Stanley.

From the data given by Hagberg *et al.* it is possible to refine this estimate for term (≥37 weeks gestation) infants. Among the 14 term infants whose cerebral palsy was assigned to an "obviously perinatal" cause there were five with an Apgar score (time not stated) of 8 or more. On the grounds that infants damaged by birth asphyxia are unlikely to be vigorous at birth (see Chapter I), these infants may be excluded. This would leave 9 infants at most for whom birth asphyxia was the likely cause of their cerebral palsy - a rate of 9/92 or 9.8%. All these infants were reported as having had intrauterine asphyxia (details not given), an Apgar score of 4 or less, a need for mechanical ventilation, and seizures.

Other estimates

Using data from the NCPP cohort, Nelson and Ellenberg used a third method to estimate the proportion of cerebral palsy cases caused by birth asphyxia (Nelson & Ellenberg, 1986). The method involved predicting the likelihood of cerebral palsy

with a logistic regression model; first entering variables known before the onset of labour and then assessing the impact of additional perinatal variables. The variables entered into the model were selected as having the strongest association with cerebral palsy among all the variables available. It turned out that the best predictors among variables determined before labour began were: maternal mental retardation, proteinuria, motor deficit in a sibling, thyroid and oestrogen use, third trimester bleeding, microcephaly, major non-CNS malformation, gestational age ≤ 32 weeks, birthweight ≤ 2000g and breech presentation. Based on these factors, the 5% of pregnancies at the highest risk for cerebral palsy predicted 34% of cerebral palsy cases. A number of perinatal variables were then entered: placental complications, chorionitis, time to cry ≥ 5 minutes, asymmetric Moro reflex, and neonatal seizures. Using the full model, the 5% of pregnancies at highest risk predicted 37% of all cerebral palsy cases; a gain of only 3%.

Nelson interpreted this result as estimating that the proportion of cerebral palsy cases associated with birth asphyxia was 3% (Nelson, 1988). This conclusion seems rather arbitrary. If, for instance, the 10% of pregnancies at the highest risk of cerebral palsy had been considered instead of the 5% at highest risk, the conclusion might have been different. Moreover, it seems surprising that variables previously identified by Ellenberg and Nelson as important associates of cerebral palsy - particularly abnormal neonatal neurological signs other than seizures (Ellenberg & Nelson, 1988) - did not enter the regression equation. It also appeared that variables were treated individually in the equation, while the occurrence of birth asphyxia is probably best represented by a combination of markers. The 3% figure estimated by this method is thus rather uncertain.

Summary

It is clear that only a small fraction of cerebral palsy cases is caused by birth asphyxia. The size of this fraction is difficult to estimate, partly because of the difficulty of identifying birth asphyxia, and partly because of the difficulty of distinguishing cause from simple association. The most plausible estimates suggest that the fraction is between 8% and 14%. The same fraction has been estimated for all infants, and for term infants only.

There is insufficient information available to investigate whether birth asphyxia is linked with particular types of cerebral palsy. Working with the 45,500 births of known outcome in the NCPP cohort, Nelson and Ellenberg stated that "limitations of sample size prevented a definitive test of this question", but they did not observe qualitative differences in the major antecedents of the various types of cerebral palsy (Nelson & Ellenberg, 1986).

3. FREQUENCY OF CEREBRAL PALSY IN RESIDENTS OF THE OXFORD HEALTH DISTRICT: SINGLETON BIRTHS FROM JANUARY 1984 TO SEPTEMBER 1985

3.1. Methods

Identification and details of children with cerebral palsy

Full details of all singleton children with cerebral palsy, born between 1st January 1984 and 30th September 1985 to mothers resident in the Oxford Health District, were obtained from the Oxford Region Register of Early Childhood Impairment (Johnson & King, 1989). Permission to use data from the register was obtained from Dr Valerie Harpin, on behalf of the Register's Management Group.

The Oxford Region Register of Early Childhood Impairment uses multiple sources to identify children with serious impairment in early childhood, including cerebral palsy. In principle, all children resident in the Oxford Health Region at the

time of birth are included, although some may move out of the Region before their impairment is picked up, and these children will be missed.

The sources of information for the register are assessment centres, paediatricians, teachers, community health visitors, community physicians and local handicap registers. An active search for new cases is made every three months. At the age of three, the child's case status (e.g. definite cerebral palsy; cerebral palsy suspected) is provisionally assigned on the basis of a standard form (Evans *et al.* 1989), completed by the professional most closely in touch with the child. Final ascertainment of the child's status is obtained at the age of five, again using the standard form. In spite of the difficulties previously discussed, it is found useful to record a diagnosis for each child, by type and severity of cerebral palsy. This is based on the opinion of the professionals involved.

The register records the birthweight and gestational age of each child, but not the Apgar scores or other details of the perinatal period. It turned out that all except two of the children pertinent to this study were born in the John Radcliffe Hospital, and details of their Apgar scores and perinatal course were obtained from the obstetric or paediatric notes. For one child born (at term) at Wantage Hospital detailed information could not be obtained; however, it was known that this child did not encounter any perinatal problems. Apgar score was also missing for one preterm child born before arrival in hospital; again, there were no perinatal problems recorded.

Number of livebirths

The total number of singleton livebirths to mothers resident in the Oxford Health District during the study period, and the breakdown of these births by birthweight and one-minute Apgar score, was obtained from the Oxford Record Linkage Study (ORLS) (Gill *et al.* 1993). This computer-based system records and links hospital data for all residents of Oxfordshire and West Berkshire. Permission to use data from the ORLS was obtained from its director, Dr Michael Goldacre.

The breakdown of livebirths by gestational age was obtained by combining information from the ORLS and the Oxford Obstetric Data System (ODS) (Yudkin & Redman, 1990). A combination of sources was used because gestational age was often missing on the ORLS. This was due partly to poor reporting by some of the smaller hospitals, but mainly because gestational age was based entirely on the date of the last menstrual period, and this date was commonly unknown or unrecorded. In contrast, gestational age was known for all deliveries on the ODS, since it was calculated from a range of information, including the results of ultrasound scans and the paediatrician's assessment of gestational age at delivery (see Chapter II). Although the ODS relates to births only in the John Radcliffe Hospital, it covered about three-quarters of all births to Oxford District residents during the study period.

3.2. **Results 1. Frequency of cerebral palsy**

Overall rate of cerebral palsy

The Oxford Region Register identified 33 singleton children with a diagnosis of cerebral palsy, who had been born during the study period to residents of the Oxford District.

On further examination of their records, it appeared that two of these children had a diagnosed progressive neurological disorder. Since the definition of cerebral palsy excludes disorders due to progressive disease (Bax, 1964; Ingram, 1964), these children were excluded from our study. Their details were as follows:

Case A.

Female. Birthweight 3460g. G.A. 41 wk.
Apgar scores 5,8
Said to have "evolving" cerebral palsy
Non-ketotic hyperglycinaemia diagnosed;
sibling also affected
Spastic quadriparesis; visual disability;
hearing loss; seizures; profound developmental delay
Died age 3 yrs 7 mths.

Case B.

Female. Birthweight 2930g. G.A. 40 wk.
Apgar scores 8,10
Apparently normal until the age of 7 months, then progressive neurological disease
Leukodystrophy (of unknown type) diagnosed
One sibling and one cousin with the same disorder; another sibling (who died) also probably affected
Spastic quadriplegia; severe truncal hypotonia
Profound developmental delay; visual disability

Postnatally acquired cerebral palsy was defined as that arising from an insult after the 28th day of life. One child came into this category:

Case C.

Male. Birthweight 3340g. G.A. 40 wk.
Apgar scores 6,10
Complex cyanotic heart disease
At age 2 years, sustained brain damage following cardiac catheterisation
Right hemiplegia; loss of speech; visual impairment

Thus there were 30 children with cerebral palsy not of postnatal origin.

There were 11682 singleton livebirths in the period to mothers resident in the Oxford District. Thus the cumulative incidence rate for cerebral palsy was 30/11682, or 2.57 per 1000 livebirths (95% CI 1.65 to 3.49).

Cerebral palsy rate in term infants

The birthweight and gestational age breakdown of the 30 children with cerebral palsy was as follows:

	Birthweight (g)		
	<2500	≥2500	Total
Gest. age (wk)			
<37	13	2	15
≥37	1	14	15
TOTAL	14	16	30

Total livebirths by birthweight were:

Weight (g)	Number	Percent
<2500	616	5.3
≥2500	11020	94.3
N.K.	46	0.4
Total	11682	100.0

Of the total births, 8863/11682 (76%) took place in the John Radcliffe Hospital, and 2819/11682 (24%) outside it. These other hospitals accounted for 45 of the 46 cases with missing birthweight. Working with three birthweight bands (<1500g; 1500-2499g; ≥2500g), it was assumed that the unknown birthweights were distributed as the rest of the population in these other hospitals. On this assumption, the cumulative incidence of cerebral palsy by birthweight group was:

Weight (g)	Number	CP Rate per 1000
<2500	14/618	22.65
≥2500	16/11064	1.45
Total	30/11682	2.57

On the extreme assumption that all the missing birthweights were among infants weighing <2500g, this would leave the cerebral palsy rate among infants weighing ≥2500g unchanged at 1.45 per 1000, and would lower the rate among infants weighing <2500g from 22.65 per 1000 to 21.15 per 1000.

Cerebral palsy rate in infants ≥37 weeks' gestation with one-minute Apgar score ≤3

Because my original study cohort consisted of children of 37 weeks' gestation or more, with a one-minute Apgar score ≤3, the cerebral palsy rate among this group was estimated.

The breakdown of the cases with cerebral palsy, by gestational age and one-minute Apgar score was:

	Apgar score ≤3	>3	Total
Gest. age (wk)			
<37	5	10	15
≥37	4	11	15
Total	9	21	30

The two children with unknown Apgar scores - one born at Wantage Hospital, and one born before arrival in hospital - were assumed to have a score of >3.

As explained above, there were difficulties in obtaining a gestational age breakdown for all livebirths to Oxford District residents because gestational age information was very incomplete for births outside the John Radcliffe. Apgar score was also sometimes missing, both for John Radcliffe births and for others.

For 8694/8863 (98%) of the livebirths in the John Radcliffe, the Obstetric Data System provided a crosstabulation of gestational age by one-minute Apgar score. The 169 infants with unknown Apgar score were assumed to have the same Apgar score distribution as other infants of the same gestational age.

A crosstabulation of gestational age by one-minute Apgar score was available from the ORLS for 1248 of the 2819 livebirths in other hospitals. Although gestational age was unknown for the remaining 1571 births, birthweight was recorded for nearly all of them (more than 97%). Most of these births took place in general practitioner maternity hospitals and only 58/1571 (3.7%) weighed <2500g. (The proportion of low birthweight babies among those with known gestational age was 5.0%.) A crosstabulation of birthweight by one-minute Apgar score was available for 21% of these livebirths. Failing any other information, it was assumed that the remaining 79% of births showed the same Apgar score distribution in relation to their birth-

weight. For these infants with known birthweight but no gestational age information, the birthweight cut-off value of ≥2500g was used as a proxy for gestational age ≥37 weeks. Although this was rather a shaky estimate, it was the best available, and applied to only 10% of the total livebirths.

In this way, the breakdown for all Oxford District livebirths, by gestational age and one-minute Apgar score, was estimated. Cerebral palsy rates were based on the following numbers:

	Apgar score		
	≤3	>3	Total
Gestation (wk)			
<37	5/62	10/510	15/572
≥37	4/245	11/10,865	15/11,110
Total	9/307	21/11,375	30/11,682

The rates (per 1000 livebirths of each gestational age and Apgar score) were:

	Apgar score		
	≤3	>3	Total
Gestation (wk)			
<37	80.65	19.61	26.22
≥37	16.33	1.01	1.35
Total	29.32	1.85	2.57

A one-minute Apgar score ≤3 was therefore associated with a greatly increased rate of cerebral palsy, both for term and preterm children. Disregarding gestational age, the rate of cerebral palsy among children with a one-minute Apgar score ≤3 was 29.3 per 1000 (95% CI 13.5 to 54.9) while the rate among children with a score >3 was 1.8 per 1000 (95% CI 1.1 to 2.6). The highest rate (80.6 per 1000; 95% CI 26.7 to 178) was seen among preterm children with a low Apgar score.

3.3. **Results 2. Proportion of cases of cerebral palsy ascribable to birth asphyxia in children born at term**

There were 15 children with cerebral palsy (not postnatally acquired) who had been born at term ($\geq$37 weeks of gestation). The records of these children were examined to identify those who might have been damaged by birth asphyxia.

Based on the conclusions of Chapter III (Section 3.3), and on the recommendations of the American College of Obstetricians and Gynecologists (1991), birth asphyxia was considered to be a likely cause of brain damage if certain signs were present. These were: a persistent low Apgar score, moderate or severe neonatal encephalopathy, severe acidaemia measured in umbilical arterial blood, and signs of multiorgan system dysfunction, such as cardiovascular, haematological, pulmonary or renal. It was not considered reasonable to set cut-off levels for the measurable items (such as Apgar score), or to demand all of the signs to be present. While the occurrence of severe acidaemia at birth was thought to be a necessary sign of intrapartum asphyxia, it was recognised that hypoxia occurring antenatally might cause brain damage, but might correct itself before delivery, resulting in normal acid-base measurements at birth.

In the following table, the cases in bold print are those identified by my follow-up study. G.A. stands for gestational age; Apgar scores are at one and five minutes. Birthweight centiles were based on the tables of Yudkin et al. (1987). The cerebral palsy diagnosis is as recorded by the Oxford Region Register.

<u>Cerebral palsy of prenatal origin</u>

Case 1.

Female. Birthweight 3235g. G.A. 40 wk.
Apgar scores 9,10
Microcephaly; CT scan at age 12 days
showed small ventricles
Spastic quadriplegia; bilateral optic atrophy
Hearing loss; epilepsy; profound developmental delay
Brother died aged 18 mths with similar syndrome
Died age 4 yrs 6 mths.

Case 2.

Male. Birthweight 3490g. G.A. 39 wk.
Apgar scores 9,10
Spastic quadriplegia; moderately impaired vision
Epilepsy; developmental delay
Many males in the family affected with a neuro-degenerative disorder; diagnosis of "familial neurological disorder of unknown origin"

Cerebral palsy of presumed prenatal origin

Case 3.

Male. Birthweight 3770g. G.A. 40 wk.
Apgar scores 7,10
Ua pH 7.17; base deficit 12 mmol/l
No neonatal problems; discharged home in good condition
CT scan at age 10 months showed an area of infarction in the left thalamus and wall of the lateral ventricle; presumed prenatal
Monoparesis affecting the right hand

Case 4.

Male. Birthweight 3579g. G.A. 39 wk.
Spontaneous delivery, Apgar scores n.k.
No neonatal problems; discharged home in good condition
CT scan at age 8 months showed area of brain destruction in left temporo-parietal region; left cerebral hemisphere smaller than right; compatible with vascular accident during intrauterine life
Right hemiplegia

Case 5.

Male. Birthweight 3180g. G.A. 39 wk.
Apgar scores 9,10
Ua pH 7.22; base deficit 7 mmol/l
No neonatal problems; discharged home in good condition
Very mild right hemiparesis

Cerebral palsy following a postnatal event before 28 days; no signs of birth asphyxia

Case 6.

Male. Birthweight 3465g. G.A. 40 wk.
Apgar scores 9,10
No neonatal problems; discharged home in good condition
Viral meningo-encephalitis aged 3 weeks; seizures
CT scan at age 3 weeks showed widespread supratentorial damage
Spastic quadriplegia
Cortical blindness
Profound developmental delay

Case 7.

Male. Birthweight 3150g. G.A. 42 wk.
Apgar scores 9,10
Myelomeningocele; ultrasound scan at age 4 days
showed moderate hydrocephalus
Meningitis and seizures following insertion
of ventriculo-atrial shunt at 9 days
No spontaneous movement below hips as a result of
spina bifida
Spasticity of upper arms; developmental delay

Case 8.

Male. Birthweight 3140g. G.A. 40 wk.
Apgar scores 9,10
No neonatal problems; discharged home in good condition
Bruising and bleeding noted at end of third week,
consistent with haemorrhagic disease of the newborn
CT scan at age 3 weeks showed large haemorrhage
in right temporo-parietal region
Left hemiplegia; left hemianopia
Hydrocephalus; epilepsy
Moderate developmental delay

Case 9.

Male. Birthweight 3300g. G.A. 40 wk.
Apgar scores 9,10
No neonatal problems; discharged home in good condition
On 7th day of life, suddenly stopped feeding and
became unresponsive; CT scan at 11 days showed
probable cerebral oedema and thrombosis
of straight sinus and vein of Galen
Spastic quadriparesis; severe developmental delay
Hydrocephalus, epilepsy
Squint; moderately impaired vision

Cerebral palsy following seizures, but overall picture not consistent with birth asphyxia

Case 10.

Male. Birthweight 2650g. G.A. 39 wk.
Weight < 10th centile for G.A.
Apgar scores 9,10
Seizures started on first day
CT scan aged 6 days showed infarction in the
territory of the left middle cerebral artery;
similar area in the right upper parietal region
Right hemiparesis; squint

Case 11.

Female. Birthweight 3985g. G.A. 41 wk.
Apgar scores 5,10
Ua pH 7.16; base deficit N.K.
Seizures starting within 24 hours
CT scan aged 5 days showed infarction in the territory of the left middle cerebral artery
Clinical and ECG evidence of myocardial ischaemia at age 3 days
Mild right hemiparesis

Cerebral palsy with evidence of intrauterine compromise

Case 12.

Male. Birthweight 2280g. G.A. 37 wk.
Weight <10th centile for G.A.
Mother admitted for raised B.P.; fetal distress diagnosed on antepartum CTG; delivery by caesarean section before labour
Apgar scores 3,10
Ua pH 7.13; base deficit 12 mmol/l
Polycythaemia; two exchange transfusions
Extensive necrotising enterocolitis at age 3 days; discharged at 22 days
Right hemiplegia

Cerebral palsy probably attributable to birth asphyxia

Case 13.

Female. Birthweight 3155g. G.A. 41 wk.
Caesarean section in labour for fetal distress diagnosed on CTG
Apgar scores 0,4
Ua pH 6.97; base deficit 20 mmol/l
Seizures starting at 2 hours; moderate encephalopathy
CT scan aged 14 days showed diffuse white matter damage
Low urinary output for first few days; hypotension, coagulopathy in 2nd week
Spastic quadriparesis; optic atrophy; epilepsy
Profound developmental delay
Died age 4 yrs 4 mths.

Case 14.

Male. Birthweight 3466g. G.A. 39 wk.
Forceps delivery for fetal distress
diagnosed by intermittent auscultation
Apgar scores 3,5
Ua pH 6.70; base deficit 26 mmol/l
Seizures starting at 8 hours; severe encephalopathy
CT scan aged 11 days showed suspected white matter
damage; at 13 weeks severe white matter destruction
Neonatal anuria; hyperkalaemia
Spastic quadriparesis; cortical blindness
Microcephalus; profound developmental delay; epilepsy

Case 15.

Female. Birthweight 3726g. G.A. 39 wk.
Spontaneous delivery
Apgar scores 2,2
Ua pH 6.93; base deficit 23 mmol/l
Seizures starting at 2 hours; moderate encephalopathy
CT scan aged 16 days showed suspected white matter
damage; ultrasound scan at 28 days showed cerebral
atrophy and left periventricular leukomalacia
No evidence of multiorgan system dysfunction
Spastic quadriparesis; visual impairment
Profound developmental delay

Summary

There were five children (Cases 1-5) whose cerebral palsy was most likely to have been of prenatal origin (although the lesions observed in Cases 3 and 4 could possibly have occurred in intrapartum or early neonatal life). In four children (Cases 6-9) the precipitating factor was a definite postnatal event. None of these children showed any evidence of birth asphyxia. In two children with CT scan evidence of infarction in the territory of the left middle cerebral artery (Cases 10-11), the picture was complicated by the occurrence of seizures, and in one of the children (Case 11), by evidence of myocardial ischaemia. These asphyxial signs were not however accompanied by other evidence of birth asphyxia; in particular, both children were vigorous at delivery, and the one with acid-base measurements had a pH of 7.16. One child (Case 12) had a number of signs indicative of antenatal intrauterine distress. Fetal distress was diagnosed by antepartum CTG, leading to delivery by elective

caesarean section; birthweight was below the 10th centile for gestational age; the child was depressed at birth and had a degree of acidaemia; there was polycythaemia necessitating two exchange transfusions, and the child suffered extensive necrotising enterocolitis, a possible result of selective brain perfusion during intrauterine life.

In three children (Cases 13-15) there was substantial evidence of birth asphyxia, as discussed in Chapter III (Section 3.3). All had a prolonged low Apgar score, profound acidaemia and moderate or severe encephalopathy; two of the three had signs of multiorgan system dysfunction. All three showed white matter destruction on CT or ultrasound scan; in two of these children repeated scans showed evolving cystic change consistent with asphyxial damage.

These three cases represented 10% (3/30) of all cases of cerebral palsy in singletons, and 20% (3/15) of cases in term singletons.

As far as the types of cerebral palsy were concerned, there was one case of monoparesis, six of hemiparesis, one of spasticity of the upper arms, and seven of spastic quadriparesis. It was notable that all the children with spastic quadriparesis had multiple disabilities, while most of the other children did not.

The child with monoparesis, and four of the six with hemiparesis, had no other disorder. One child with hemiparesis had a squint; another, who was thought to have haemorrhagic disease of the newborn, exhibited hemianopia, hydrocephalus and epilepsy, and had moderate developmental delay.

The child with spasticity of the upper arms developed cerebral palsy following meningitis after insertion of a ventriculo-atrial shunt. He had associated developmental delay.

All seven children with spastic quadriparesis had profound developmental delay and visual impairment; two were blind. In addition, five of these children had epilepsy. Apart from the three cases probably attributable to birth asphyxia, two of these children had a familial neurological disorder, one had viral meningo-encephalitis at

three weeks, and one suffered a probable cerebral thrombosis at the age of seven days.

3.4. **Discussion**

Among 11,682 singleton livebirths born during the study period to residents of the Oxford Health District there were 30 children with definite cerebral palsy at the age of five. Thus the cerebral palsy rate among Oxford residents was 2.57 per 1000 singleton livebirths. This rate was higher than the rate of 1.84 per 1000 livebirths (singletons and multiples) derived from pooling the results of ten studies of birth cohorts born after 1970. However, the difference was not statistically significant (difference 0.73 per 1000; 95% CI -0.19 to 1.66).

It is perhaps more pertinent to compare the Oxford rate with the pooled rate excluding the study of Grether *et al.* (1992), since this latter study only included moderate or severe cases of cerebral palsy. The adjusted pooled rate was 2.09 per 1000, giving a difference from the Oxford rate of 0.48 per 1000 (95% CI -0.45 to 1.41).

In deriving the rate of cerebral palsy in Oxford, the difficulty of definition became apparent, even though a working definition of cerebral palsy has been generally accepted for the last thirty years (Bax, 1964). Two children were described as having a familial neurological disorder of unknown origin; both had spastic quadriparesis with developmental delay. In both cases, the other affected members of the family had died in childhood or early adulthood. It is questionable whether these familial disorders should have been regarded as progressive, and thus outside the definition of cerebral palsy. Because they lacked a diagnosis, and it was therefore not clear whether their underlying pathology was progressive or not, they were included.

Another problem related to postnatally acquired cerebral palsy. One child in the Oxford cohort developed spastic quadriplegia following viral meningo-encephalitis at

the age of three weeks. Some studies would have regarded this case as of postnatal origin, and would have excluded it from the calculation of a cerebral palsy rate. Because we defined "postnatal" as occurring after the first 28 days, it was included in our rate. Exclusion of these three cases from calculation of the cerebral palsy rate would have reduced our observed rate from 2.57 per 1000 livebirths to 2.31 per 1000.

Of the 30 cases of cerebral palsy, 15 were in children born at term. Thus the cerebral palsy rate among term singletons was 1.45 per 1000 (for births $\geq$2500g), and 1.35 per 1000 (for births $\geq$37 weeks). These estimates were very similar to the pooled rate for births $\geq$2500g, derived from the ten studies, of 1.32 per 1000. The estimated pooled rate for singletons only was 1.28 per 1000.

Among children born at 37 weeks' gestation or later, the cerebral palsy rate associated with a one-minute Apgar score $\leq$3 was 16 times that associated with a higher one-minute score. Children born at 37 weeks' gestation or later with a score $\leq$3 - the subjects of my follow-up study - exhibited a cerebral palsy rate of 16.3 per 1000 (95% CI 4.5 to 41.3). Four children in the follow-up study had cerebral palsy: one with hemiplegia, but normal development in non-motor areas, and three with spastic quadriparesis, profound developmental delay, and visual impairment.

The child with hemiplegia had several signs suggestive of intrauterine distress. He was growth retarded (birthweight $<$10th centile for gestational age), was delivered by caesarean section before labour because of fetal distress diagnosed by antepartum CTG, was depressed at birth, with moderate acidaemia, and subsequently suffered from polycythaemia and necrotising enterocolitis. Among the 15 term children with cerebral palsy, he was the only child with this history.

The other three children identified by my follow-up study were the only children born at term whose cerebral palsy was ascribed to birth asphyxia. It therefore turned out that selection of children on the basis of a one-minute Apgar score $\leq$3 successful-

ly identified all cases of damaging birth asphyxia in term children. This finding confirms previous observations regarding birth asphyxia, that cerebral depression at birth must be present for neurological damage to ensue (Nelson & Ellenberg, 1987). However, given the subjective nature of the Apgar score, and the variation to be expected between individual infants, it seems unreasonable to attach special significance to the cut-off value of 3 for the one-minute score.

The three children with probable birth asphyxia exhibited most of the signs stated by the American College of Obstetricians and Gynecologists to be indicative of hypoxial damage (American College of Obstetricians and Gynecologists, 1991). In addition, all three children were profoundly and multiply handicapped, with motor, intellectual and visual impairment. There were only four other children born in the Oxford District during the study period with a similar degree and range of handicap; two had a familial neurological disorder, one had viral meningo-encephalitis at the age of three weeks and one suffered a probable cerebral thrombosis at the age of seven days.

Birth asphyxia at term accounted for an estimated 10% (95% CI 2.1, 26.5) of all cases of cerebral palsy. Given the small size of the study, this estimate is uncertain, but it agrees well with the previous estimates of between 8% and 14%, based both on calculations of attributable risk, and on examination of case records (Section 2.4).

Of cerebral palsy arising in term infants, birth asphyxia accounted for an estimated 20% (95% CI 4.3, 48.1). Assuming the rate of cerebral palsy among term births is 1.3 per 1000 (the pooled estimate from ten studies), the incidence of cerebral palsy due to birth asphyxia would be about 0.26 per 1000 term livebirths, or 1 per 3800 term livebirths.

It should be stressed that attributing certain cases of cerebral palsy to birth asphyxia does not imply that the asphyxia, or the cerebral palsy, was preventable.

The issue of avoidability, and thus of responsibility, has not been addressed here, and indeed, it cannot be addressed by my study design. However, in the Oxford cohort, if the three cases of cerebral palsy attributed to birth asphyxia in term births had been prevented, the cerebral palsy rate would have been reduced from 2.57 per 1000 to 2.31 per 1000. This estimate sets in context any possibility of reducing the burden of cerebral palsy in the population by obstetric or neonatal intervention in term infants.

CHAPTER V

DISCUSSION

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CHAPTER V

DISCUSSION

1. BACKGROUND

This thesis has attempted to shed light on the link between birth asphyxia and neurological impairment, a link that has been extensively studied, and is as yet imperfectly understood. I have paid particular attention to the association between birth asphyxia and cerebral palsy, since a causal connection between them has been clearly demonstrated in animal experiments. However, a central purpose of my study was to examine possible links between birth asphyxia and milder forms of impairment.

Although the connection between birth asphyxia and cerebral palsy is established, it is not known whether cerebral palsy can be prevented by obstetric or neonatal intervention, or what types of intervention or treatment might be beneficial. Moreover, in an individual case of cerebral palsy, assigning a possible cause is a difficult and uncertain task. Regarding milder forms of impairment, it is unknown whether a child who survives birth asphyxia without cerebral palsy may nevertheless suffer some neurological damage. For all these reasons there is confusion about allocating responsibility when a child does suffer neurological damage after a difficult birth, and this has led to an unsatisfactory legal situation (Freeman & Freeman, 1992).

What has made the study of this subject particularly difficult is that neither birth asphyxia nor cerebral palsy are clear-cut entities which are easy to define and to identify. On the contrary, both terms are, in different ways, elusive. Since there is no direct measure of asphyxia, markers of asphyxia must be secondary, reflecting the fetal response to a disturbance in respiratory gas exchange, rather than the disturbance itself. Moreover, there is no agreed point at which this disturbance is judged to be

severe enough to justify the term "asphyxia".

Cerebral palsy is an elusive entity because the term covers a miscellany of different clinical syndromes, with different causes. All the syndromes, which occur in young children, are due to a brain lesion, involve motor deficit, and are persistent but non-progressive. It is these shared features that have led to the use of a single term, but it may be that grouping together such diverse disorders has hampered progress in understanding them.

Early observational studies concerning the relationship between birth asphyxia and long-term outcome centred on the Apgar score. Although it was realised that a depressed score could reflect complications other than birth asphyxia, Apgar and her colleagues stated that "biochemical studies have revealed that infants scoring 3 or less are, by and large, severely asphyxiated" (Apgar & James, 1962). Observations on the NCPP cohort of some 40,000 infants, born between 1959 and 1966, made it clear that a persistent low Apgar score was a forerunner of both neonatal death and cerebral palsy (Drage *et al.*1964; Nelson & Ellenberg, 1981).

The assumption that asphyxia could be detected with a degree of accuracy by simple neonatal clinical signs persisted in a paper by Brown *et al.*, published in 1974. This described a group of "asphyxiated" infants - identified on the basis of signs such as fetal distress, a low Apgar score, a pH (source unspecified) ≤ 7.20 and CO_2 > 60 mm Hg, and the need for mechanical ventilation (Brown *et al.*1974). These infants exhibited abnormal neurological behaviour in the early neonatal period, including difficulty with feeding, cyanotic attacks, apathy, convulsions and hypothermia. At a mean age of 21 months, a third of them had died or were severely handicapped, a third were handicapped to some degree and a third were normal. A similar (and extended) constellation of abnormal neonatal neurological signs was described later by Sarnat and Sarnat, in a group of infants with "a well-defined episode of fetal distress or an Apgar score of 5 or less at one or five minutes after delivery". The perception

that these abnormal signs were asphyxial in origin was reinforced by describing them as "postanoxic encephalopathy" (Sarnat & Sarnat, 1976). In this small series, a third of the infants had died or were diagnosed as having spastic diplegia in their first year. Subsequent studies have confirmed the poor prognosis of infants showing moderate or severe neonatal encephalopathy, and have continued to attribute all instances of this condition to birth asphyxia (Finer *et al.* 1981; Robertson & Finer, 1985; Levene *et al.* 1986). A recent paper has decried this unwarranted attribution, pointing out that "the use of an incorrect etiologic diagnosis does a disservice", and that the proportion of newborn encephalopathy cases attributable to hypoxia/ischaemia (or asphyxia) remains unknown (Leviton & Nelson, 1992). These two approaches to identifying birth asphyxia - by low Apgar score and by abnormal neonatal neurological signs - are linked, in that among infants with a low Apgar score, it is those who progress to neonatal encephalopathy who are most at risk of death or later impairment (Levene *et al.* 1986; Ellenberg & Nelson, 1988). However, as discussed below, the exact relationship between birth asphyxia, Apgar score and neonatal encephalopathy has still to be clarified.

In the 1980s, a series of studies showing the imperfect correlation between acid-base status and Apgar score questioned whether Apgar score was, in spite of its long and useful history, an appropriate indicator of asphyxia (Sykes *et al.* 1982; Fields *et al.* 1983; Silverman *et al.* 1985). Since birth asphyxia was a process involving derangement of fetal acid-base balance, it was argued that it would be best identified by biochemical means (Low, 1988; Johnson *et al.* 1990). However, the usefulness of acid-base measurements as an indicator of asphyxia was itself questioned when it became clear that acid-base values, considered on their own, bore only the weakest of relationships to long-term neurological outcome (Ruth & Raivio, 1988; Dennis *et al.* 1989; Fee *et al.* 1990). More recently, it has been suggested that signs of asphyxial

damage have been sought at too moderate a level of acidaemia, and that pathologic acidaemia requires an umbilical arterial pH less than 7.00 (Goldaber *et al.* 1991).

It has thus gradually become clear that birth asphyxia severe enough to cause neurological damage will be an extremely rare event, and will announce its presence by a cluster of seriously abnormal signs. The American College of Obstetricians and Gynecologists has suggested that four signs will be apparent: severe fetal acidaemia, a persistent low Apgar score, moderate or severe neonatal encephalopathy, and multi-organ system dysfunction (American College of Obstetricians and Gynecologists, 1991). While the exact configuration of signs will vary between individuals, at least some of them would be expected to be present in any infant with birth asphyxia.

2. STUDY RESULTS

2.1. Death and cerebral palsy after apparent birth asphyxia

Since infants with a low Apgar score and subsequent neonatal encephalopathy are those with the highest risk of hypoxic death or later impairment (Levene *et al.* 1986; Ellenberg & Nelson, 1988), I studied a cohort of infants with a one-minute Apgar score ≤ 3. The cohort consisted of all such infants born at term at the John Radcliffe Hospital between January 1984 and September 1985. Multiple births and infants with congenital anomalies were excluded. When the children were traced at the age of five, the cohort was found to include seven children with serious neurological damage. Three infants had died in the neonatal period, and four had developed cerebral palsy.

The three infants who died neonatally showed compelling signs of birth asphyxia. All of them had an ominous CTG in labour, a five-minute Apgar score ≤ 3, severe encephalopathy, and signs of multiorgan damage. Two had umbilical arterial pH < 7.00; the third a pH of 7.10 and base deficit 14 mmol/l. At autopsy, all exhibited cerebral oedema. However, while two also showed evidence of hypoxic changes

at autopsy, in the third infant, the cerebral oedema was ascribed to birth trauma. This infant (a vaginal breech delivery), and one other whose mother developed pre-eclampsia just before delivery were exposed to possibly hypoxic conditions around the time of birth. They were both of appropriate weight for their gestational age. The third infant had no obvious obstetric complication, but was growth retarded. It seems possible therefore that this third infant suffered hypoxic stress in the antepartum period, as well as intrapartum.

Of the four children with cerebral palsy, three had spastic quadriplegia, severe developmental delay and visual impairment; two of these had epilepsy. Again, the records of each child suggested that they had been damaged by birth asphyxia. All three were of appropriate weight for their gestational age, all were profoundly acidaemic at delivery, all had moderate or severe neonatal encephalopathy, and all showed lesions on cerebral scans consistent with hypoxic damage. However, only two of them showed definite evidence of intrapartum distress and were delivered operatively, while the third had a reassuring fetal heart rate recorded (by intermittent auscultation) throughout labour, and was delivered spontaneously. The two delivered operatively showed subsequent signs of multiorgan damage, while the third did not. The history of this latter child thus remains somewhat puzzling. It was also notable that all of these cases were free of obstetric complications likely to produce hypoxia, such as placental abruption, pre-eclampsia, a vaginal breech delivery or cord knot.

The fourth child with cerebral palsy had right-sided hemiplegia, and apart from his gross motor handicap, showed normal development in other areas. He did not exhibit any signs of birth asphyxia, but showed clear evidence of antepartum compromise. His birthweight was below the 10th centile for gestational age and he was delivered by caesarean section before labour because of fetal distress diagnosed by antepartum CTG. In the early neonatal period, he suffered polycythaemia and necro-

tising enterocolitis: the former a possible reflection of intrauterine compromise; the latter a possible result of selective brain perfusion during intrauterine life.

Thus of the seven infants with serious neurological damage, six were probably damaged by intrapartum asphyxia, although doubt must remain about some of them. It is clear, however, that the seventh child, with right hemiplegia, did not suffer birth asphyxia. It was notable that the three children with cerebral palsy all had spastic quadriplegia and were multiply impaired. The association between birth asphyxia and spastic quadriplegia with severe developmental delay has previously been reported (Susser *et al.* 1985) and warrants further investigation.

Identifying these children with probable asphyxial damage does no more than confirm that such a route to neurological damage exists. To be of practical use, it is necessary to know not only how frequently such a sequence of events occurs, but also whether (and how) the neurological damage could have been prevented. I was able to address the former question, but not the latter, which would involve a quite different study design. It turned out that all four children with cerebral palsy were born to mothers resident in the Oxford Health District. I therefore estimated the overall rate of cerebral palsy in this geographical area, and assessed the impact made on this overall rate by the four cases in my study cohort.

Among the 11,682 singleton livebirths in the Oxford District during the study period, there were 30 cases of cerebral palsy, giving a rate of 2.57 per 1000. This rate was a little higher (but not significantly different from) the rate of 2.09 per 1000 livebirths obtained from pooling data from nine birth cohorts born in various countries after 1970. Fifteen of the Oxford children with cerebral palsy were born at term ($\geq$37 weeks' gestation), giving a cerebral palsy rate in term livebirths in the Oxford District of 1.35 per 1000. This was similar to the rate of 1.28 per 1000 estimated for term singletons from the pooled data.

A detailed examination of the histories of these 15 children showed that only the

three identified in my study cohort were probably damaged by birth asphyxia. None of the others had, for instance, the cluster of signs indicative of birth asphyxia after a one-minute Apgar score higher than 3. (There were two children with seizures starting within 24 hours of birth, but since they had none of the other signs of birth asphyxia, this was excluded as a cause of their cerebral palsy.) Birth asphyxia in term infants was therefore responsible for an estimated 10% of all cerebral palsy cases. To put this another way, the frequency of cerebral palsy ascribed to birth asphyxia was estimated as 0.26 per 1000 term livebirths, or roughly one in 3800 term livebirths. The rarity of this complication presents an intrinsic difficulty for prevention, and also ensures that prevention could have only a small effect on the overall rate of cerebral palsy.

2.2. **Frequency of signs of birth asphyxia**

As described above, there were six children who showed compelling evidence of birth asphyxia and who died neonatally, or developed cerebral palsy. There was one further child with many signs of birth asphyxia (an ominous CTG in labour, severe acidaemia at delivery, a five-minute Apgar score of 4 and moderate neonatal encephalopathy) who survived with no impairment.

If death and cerebral palsy following birth asphyxia are potentially preventable, it is these children with a cluster of asphyxial signs who will be candidates for treatment. My study design did not allow a geographically-based estimate of the frequency of these signs, but a hospital-based estimate was made. Inevitably, any cases with a one-minute Apgar score >3 would have been excluded. The frequency of potentially damaging birth asphyxia in singletons born at term was estimated as 0.75 per 1000 (95% CI 0.20 to 1.31; seven cases in 9280 livebirths). Because of selective referral to the John Radcliffe Hospital, this is likely to overestimate the rate for a geographically-based population.

The frequency of moderate or severe neonatal encephalopathy has been estimated in other studies as 2.2 cases per 1000 term livebirths (Levene *et al.* 1985; Hull & Dodd, 1992), nearly three times my estimated rate. Part of this disparity in rates can be explained by the inclusion, in these other studies, of infants with a one-minute Apgar score >3. Further, it may be that these studies included cases of encephalopathy that were not the result of asphyxia. Although Levene *et al.* (1985) stated that "cases were excluded from the study if there was not good evidence that asphyxia was the cause of their neurological disturbance", what constituted good evidence was not stated precisely. Acidaemia at delivery does not appear to have been a requirement in either study.

2.3. **Acidaemia, ominous CTG and less severe impairment**

The original purpose of the follow-up study was to examine whether, among infants with a low one-minute Apgar score, acid-base status had any bearing on outcome at the age of five. It turned out that there was no tendency for the more acidaemic children in the study cohort to score higher (or lower) than the less acidaemic on a battery of neurodevelopmental tests. Nor did the more acidaemic children perform more (or less) consistently across the range of tests. The same lack of association was found between fetal heart rate patterns in labour and test scores. In addition, neither acid-base values nor the occurrence of an ominous CTG were related to behaviour disorder as reported by parents.

As an indicator of how well the children in the study cohort performed, their Griffiths subscale scores were compared with scores achieved by a control group in a previous study (Dennis *et al.* 1989). This control group of term singletons, born in 1981, had a one-minute Apgar score >3 and normal acid-base status. Children in the present study cohort achieved similar mean scores to the previous control group, suggesting that, in spite of their low Apgar scores, they were performing at a level

appropriate to their age.

All these observations confirm previous suggestions that asphyxia leads to neurological damage only if there are seriously abnormal neonatal neurological signs. A sequence of: serious fetal compromise in labour → severe acidaemia → short-lived low Apgar score does not appear to result in neurological impairment.

Numbers were too small to determine outcome among infants who developed moderate or severe neonatal encephalopathy and survived without serious impairment. There was only one child in this category in the study cohort, and he was rated as unimpaired at the age of five.

3. DIRECTION OF FUTURE WORK

3.1. Description and follow-up of neonatal encephalopathy

Suggested treatments to counteract the effects of asphyxial damage have to be started within hours of birth (Williams *et al.* 1990). Since waiting for definite evidence of moderate or severe encephalopathy is out of the question, there is a need to determine the earliest reliable signs of impending encephalopathy.

In order to achieve this end, neonatal encephalopathy itself needs to be better understood and more tightly defined. As Leviton and Nelson have pointed out (Leviton & Nelson, 1992), basic questions about the condition remain unanswered. For instance, some observers regard the occurrence of isolated seizures as evidence of encephalopathy, while others do not. Further, it is not clear to what extent infants move from one grade of encephalopathy to another. In the series of Sarnat and Sarnat (Sarnat & Sarnat, 1976) all infants with Stage I encephalopathy proceeded to Stage II, while the descriptions given by Fenichel (Fenichel, 1983) specifically excluded such a progression. Thus it is not known whether an infant who is vigorous at birth can "crash" to Stage II or III encephalopathy, or whether all those with Grade II or III

encephalopathy are seriously depressed at delivery. Levene *et al.* (1985) reported that not all infants with serious encephalopathy were profoundly depressed at birth; among 45 infants with moderate or severe neonatal encephalopathy, 11% had a one-minute Apgar score >3 and 31% had a five-minute score >5. Hull & Dodd (1992) reported even higher proportions with these scores. Of the 107 infants in their series with moderate or severe encephalopathy, 39% had a one-minute Apgar score >3 and 52% a five-minute score >5. These observations, if confirmed, would argue against efforts to identify impending encephalopathy on the basis of a low one-minute or five-minute Apgar score.

However, it may be that the clinical picture of neonatal encephalopathy depends to some extent on what has caused it. For instance, encephalopathy resulting from birth asphyxia may entail serious depression at delivery, while encephalopathy arising for other reasons may not. It is more likely though, given natural biological variation between individuals, that separating that fraction of encephalopathy due to hypoxia from the fraction attributable to other causes will depend on more than clinical signs. For example, abnormal fetal heart rate patterns in labour followed by severe acidaemia at delivery would suggest intrapartum hypoxia, while a normal acid-base status at delivery would exclude such a diagnosis. This issue of cause needs to be addressed because both the treatment and the prognosis of neonatal encephalopathy are likely to depend on the aetiology of the condition.

Developments in brain imaging promise the most direct and therefore the most accurate, methods of diagnosis. One such method is magnetic resonance spectroscopy, which is used to measure, in brain tissue, intracellular pH, and the concentrations of phosphorylated metabolites that are important in energy metabolism (Wyatt *et al.* 1989). These metabolites depend for their synthesis on oxidative phosphorylation, which is diminished if the oxygen supply to the brain is reduced, or if oxidative metabolism is impaired. Magnetic resonance spectroscopy can therefore detect hypox-

ic brain changes at an early stage. Using this method, it has been noted that there is often a latent period between resuscitation of an asphyxiated infant and detectable energy failure (Wyatt *et al.* 1989). It is this observation that encourages hopes that irreversible injury to the brain may be prevented or reduced in future by prompt intervention.

Early diagnosis of birth asphyxia is not the only benefit likely to emerge from new methods of brain imaging. The more accurately that birth asphyxia can be identified, graded and described, the more soundly can any future treatments be assessed. In addition to magnetic resonance spectroscopy, a number of new technologies are now being investigated in an attempt to detect and quantify incipient hypoxic damage. These include brain imaging using near infrared spectroscopy, Doppler analysis of cerebral blood flow, measurement of biochemical markers in umbilical cord blood, and sophisticated computer analysis of antenatal and intrapartum fetal heart rate patterns.

Current knowledge about the long-term prognosis of neonatal encephalopathy comes essentially from one study (Robertson *et al.* 1989). This reported that infants with moderate encephalopathy who survived without serious impairment were nonetheless developmentally delayed, while infants with mild encephalopathy were performing at the level of their age peers. This study almost certainly included infants with a range of different causes for their encephalopathy, and for this reason it needs to be updated. Future studies would relate to new, more tightly defined, grades of encephalopathy, and would group infants according to the presumed aetiology of their condition.

3.2. **Aetiology of cerebral palsy**

My study results are in line with previous findings that, at most, 10% of cases of cerebral palsy are due to birth asphyxia (Nelson, 1988). This means that the cause

in the vast majority of cases is unknown. It is more realistic to talk about causes rather than a single cause, since cerebral palsy is a group of miscellaneous syndromes and not a single disorder.

One approach to discovering the causes of cerebral palsy is through a case-control study. This can identify so-called risk factors for cerebral palsy; that is, factors that appear together with cerebral palsy more often than would be expected by chance. Case-control studies looking particularly at the birthweight, gestational age, and obstetric histories of children with cerebral palsy, were published in the early 1960s (Eastman *et al.* 1962; Alberman, 1963). However, it is only recently that such studies have been able to derive a complete list of cases from cerebral palsy registers, thereby avoiding possible bias in case selection. A recent case-control study using the Western Australian Cerebral Palsy Register (Blair & Stanley, 1993a; Blair & Stanley, 1993b) found that spastic cerebral palsy was associated with a number of factors, but that only half the cases experienced one or more factor and no single factor was experienced by more than about 10% of the cases (Blair & Stanley, 1993a; Blair & Stanley, 1993b). Possibly aetiological factors included an unhealthy placenta in a mother aged 35 or more, a precipitate delivery in the index pregnancy with a stillbirth in a previous pregnancy, and birth trauma to the head in a rural delivery. The performance of these and other factors could be examined using different cerebral palsy registers, such as that in the Oxford Region.

There are other possible aetiological factors that are not routinely recorded on cerebral palsy registers, but investigation of which will depend on registers to identify index children. Such factors include fetal coagulation disorders, maternal thyroid deficiency, maternal folic acid deficiency, and the use of assisted conception.

Interest in the genetics of cerebral palsy is increasing. Cerebral palsy registers can be used to seek families with multiple cerebral palsy cases, so that blood can be

taken for DNA analysis. Also, any familial dysmorphic features can be noted. Detailed pedigrees can be drawn up relating not only to cerebral palsy, but to any other disorders, since it may be that cerebral palsy occurs more frequently in families with other diseases or anomalies.

The method used to ascribe cause in my study - close inspection of the records of each affected individual - has previously been carried out on cases recorded by the Western Australian Cerebral Palsy Register (Blair & Stanley, 1988), in order to assess the proportion of cases thought to be due to birth asphyxia. That study did not attempt to assign causes other than possible birth asphyxia. It would seem an obvious next step to use another cerebral palsy register to inspect a large number of cases of cerebral palsy and to assign a putative cause to each of them.

The assignment of cause will become more accurate as investigations such as acid-base measurement at birth and early neonatal cerebral scans are more regularly carried out. In the longer term, understanding of the origins of cerebral palsy should benefit greatly from the newer technologies mentioned above, such as magnetic resonance spectroscopy. Using these new methods, it may finally be possible to shed light on the relationship between the putative cause and type of cerebral palsy - a subject under discussion since the last century.

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LIST OF APPENDICES

1. Letter to GP
2. Letter to Family Practitioner Committee
3. Letter to parents
4. Griffiths record book
5. Behaviour checklist
6. Parents' questionnaire
7. Coding form

APPENDIX 1

LETTER TO GP

Dear

We are carrying out a neurodevelopmental follow-up study on a sample of 200 infants born in the John Radcliffe Hospital in 1984 and 1985. Our purpose is to examine the relationships - which are at present poorly understood -between perinatal events, acid-base status in umbilical arterial blood, clinical depression at birth (as measured by one-minute Apgar score) and later outcome.

The follow-up assessments will be performed by developmental paediatricians experienced in follow-up studies. The assessments will include measurement of growth parameters, and developmental tests, with particular emphasis on motor function and cognitive development. There are no blood tests or x-rays involved.

Enclosed are the names of the patients (in your practice at the time of birth) who are eligible for inclusion in this study. We shall be sending a copy of the enclosed letter to the parents explaining the purpose of the study and requesting permission to assess the child.

Would you be kind enough to complete the enclosed form and return it to us in the stamped addressed envelope.

We will let you have a summary of the findings on your patients in due course.

Please let us know if you would like further information on the study.

Yours sincerely

Dr. A. Johnson

Mrs. P. Yudkin

FOR ENCLOSURE WITH GP'S LETTER

Follow-up Study at Age 4 to 5 Years

To Dr.

Would you kindly complete the following form, updating it where necessary. Please return it as soon as possible in the envelope provided.

Mother's name at time of delivery: Surname_____

Forename_____

Mother's date of birth: _____

Mother's address at time of delivery: _____

_____

_____

Date of delivery:_____

Child's name: Surname _____

Forenames _____

Sex of child:_____

Child's N.H.S. No:_____

Please let us know if there are any strong reasons why you would prefer us not to approach this family.

APPENDIX 2

LETTER TO FAMILY PRACTITIONER COMMITTEE

Dear Sir/Madam,

Re: _____d.o.b._____

_____

We are carrying out a neurodevelopmental follow-up study on a sample of 200 infants born in the John Radcliffe Hospital in 1984 and 1985.

We understand the above named patient and family have now moved to your area. We would like to obtain further information from the Family Practitioner regarding this child's progress and would be grateful if you would let us have the name and address of the doctor. Please complete the detachable slip below and return to us in the S.A.E. provided.

We look forward to hearing from you.

With many thanks for your help.

Yours sincerely,

Dr. A. Johnson Mrs. P. Yudkin

Name: _____d.o.b._____

NHS No._____

Name and address of family practitioner:_____

_____

Date_____

APPENDIX 3

LETTER TO PARENTS

Letter to parents of boy - similar letter for girls

Dear

We are carrying out a follow-up study on a sample of children born in the John Radcliffe Hospital in 1984 and 1985, and we are inviting you and your son to take part. We are interested in your son's overall development, including how well he is growing, his activity and play, the way he sees, hears and talks, and his general level of health.

We are doing this study to evaluate some of the routine assessments made of your baby before and after he was born. This type of follow-up study can help us understand how to provide the best possible care during labour and delivery.

We would like you to allow us about 1½ hours for this assessment and it can be done either at home or at the John Radcliffe Hospital, whichever is most convenient for you. We will, of course, reimburse you for any travel expenses. The assessment will be done by Dr Ann Johnson, a developmental paediatrician, or a medical colleague. There are no blood tests or x-rays involved. Most parents find the assessment interesting and the children enjoy it too.

We will let your family doctor have the results of the assessment, but otherwise all information gathered is confidential.

Would you please complete the attached form and return it to us in the enclosed stamped addressed envelope.

Do write to us or telephone Oxford 817289 if you have any questions.

Yours sincerely

Dr. A. Johnson

Mrs. P. Yudkin

Note: We suggest that you keep this letter and show it to any doctor who may become involved in your care.

FOR ENCLOSURE WITH PARENTS' LETTER

Follow-up at age 4 to 5 years

CHILD'S NAME.....AGE.....

ADDRESS.....

.....

.....

PLACE FOR ASSESSMENT (Please indicate your choice. Print address if different from above).

Home.....

Hospital.....

TELEPHONE NUMBER

Home.....

Work.....

Please state any dates and times that are **NOT** convenient for the assessment. Remember that the assessment takes about 1½ hours.

We will telephone you (or write) to arrange your appointment.

APPENDIX 4

RECORD BOOK

for use with the

GRIFFITHS MENTAL DEVELOPMENT SCALES

for testing babies and young children

from birth to eight years of age

NAME .....

ADDRESS .....

.....

DATE OF BIRTH .....

SEX .....

WHERE SEEN .....

DATE OF EXAMINATION .....

C.A. .....

M.A. .....

GENERAL INTELLIGENCE QUOTIENT .....

EXAMINER .....

The Test Agency Ltd.
COURNSWOOD HOUSE
NORTH DEAN
HIGH WYCOMBE, BUCKS.
Tel. National (0924 024) 3384

By arrangement with the Association for Research in Infant and Child Development

Eden House
Clifton Lawns
Chesham Bois
Amersham, Buckinghamshire

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SUMMARY of TEST RESULTS (Date of Test)

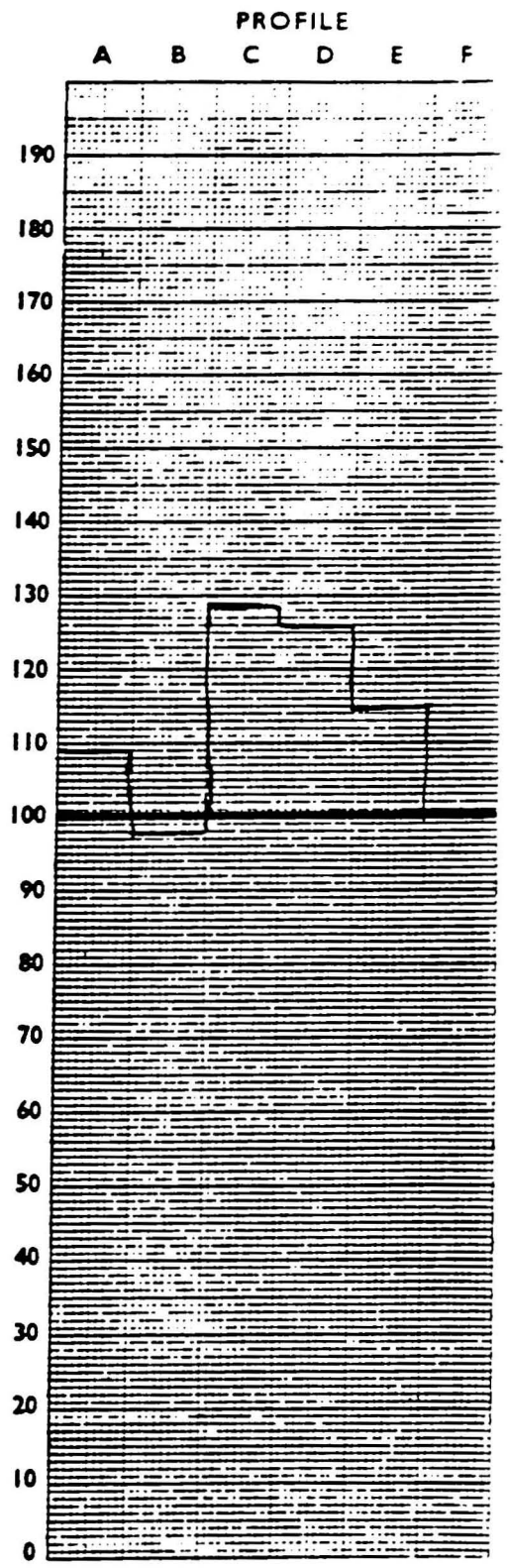
M.A. Credits in Months :

Scales :		A	B	C	D	E	F
YEARS	I	12	12	12	12	12	
	II						
	III						
	IV						
	V					10	
	VI	10	6			10	
	VII	4			10	6	
	VIII			4	4	4	
Extra Months							
Total M.A.'s (months)		74	66	88	86	78	
C.A. (months)		68					
Sub-Quotients	M.A.'s × 100 / C.A.	107	97	129	126	115	

Summary in Months

Scales A to F	Months
I ..... items passed / 10	=
II ..... items / 10	=
III ..... items / 3	=
IV ..... items / 3	=
V ..... items / 3	=
VI ..... items / 3	=
VII ..... items / 3	=
VIII ..... items / 3	=
Extras ..... items / 3	=
Total M.A. (months)	=
C.A. (months)	=
G.Q.	

Note : The General Quotient or G.Q. is obtained by taking the average of all the six sub-quotients.



Examiner's Report :

	A LOCOMOTOR		B PERSONAL—SOCIAL		C HEARING & SPEECH	
YEAR III	Jumps off one step,—both feet together.	1	Gives first name on request.	1	Names 12 of 18 objects in box.	1
	Can stand on one foot: for 6+ seconds.	2	At table, uses spoon and fork together without help.	2	Picture vocabulary (12).	2
	Rises from kneeling without using hands.	3	Puts away toys when encouraged to do so.	3	Defines by use (2+) cup, knife, chair, coat, car, house, pencil, watch, key. (See also C V, 1)	3
	Can cross both feet and both knees when seated.	4	Knows own sex.	4	**Repeats** one six-syllable sentence. (See page 10)	4
	Can **stand** and **walk** tip-toe (6+ steps).	5	Can undo buttons (buttoning test).	5	Uses 2 descriptive words. (See page 10)	5
	Walks **upstairs** : one foot on each step, adult manner.	6	Gives family name on request.	6	**Talks** well in sentences of 6— syllables (record). (See page 10)	6
	Months credit : YEAR III—A **items** = ... × 2 = ...		**Months credit : YEAR III—B** **items** = ... × 2 = ...		**Months credit : YEAR III—C** **items** = × 2 = ...	
YEAR IV	Can run fast (indoors).	1	Can do up buttons (buttoning test).	1	Names six or more objects in large picture. (See page 10)	1
	Can ride a tricycle or other pedal toy.	2	Can put on shoes and socks.	2	Names 17—18 objects in box.	2
	Marches in time to music.	3	Knows age—(years).	3	Uses 2+ personal pronouns. (See page 10)	3
	Walks a chalk line—4+ ft. long, good balance.	4	Plays well with other children.	4	Comprehension 2+ items. (See page 11)	4
	Can hop on one foot—3+ steps.	5	Helps to lay table—can place a few items.	5	Picture vocabulary (18+).	5
	Jumps off 2 steps.	6	Can undress self.	6	Knows 6+ colours. (Test) (See C VI, 6)	6
	Months credit : YEAR IV—A **items** = ... × 2 = ...		**Months credit : YEAR IV—B** **items** = ... × 2 = ...		**Months credit : YEAR IV—C** **items** = ... × 2 = ...	
YEAR V	Can run to kick a ball.	1	Washes own hands and face.	1	Defines by use : 6— (as for item C III, 3 above).	1
	Walks downstairs : one foot on each step, adult manner.	2	Gives address (2), — house and street.	2	Opposites—2. (See page 11)	2
	Touches toes with knees straight.	3	Uses knife and fork at table fairly well.	3	Materials (2+) "What is **a table** made of ? ..... **a window** ? ..... **a house** ? ....."	3
	Jumps a 6 in. high rope—both feet together.	4	Can dress and undress self—(not difficult fastenings).	4	Repeats sentences of 10— syllables (See page 10)	4
	Can climb on and off a bus unaided.	5	Can fasten shoe buckles.	5	Picture Description : 1— sentences. (See page 10)	5
	Can **run** upstairs.	6	Manages top coat unaided.	6	Names 12 objects in large picture.	6
	Months credit : YEAR V—A **items** = 6 × 2 = 12		**Months credit : YEAR V—B** **items** = 6 × 2 = 12		**Months credit : YEAR V—C** **items** = 6 × 2 = 12	

Notes and Comments :

& FIFTH YEARS

D		E		F		
EYE & HAND CO-ORDINATION		**PERFORMANCE**		**PRACTICAL REASONING**		**TOTALS A to F**
Draws a horizontal stroke in imitation. (See page 6)	1	Re-assembles screw toy.	✓	Repeats one digit—8; 2; 7.	1	
Threads 6 beads.	2	Returns 9 bricks to box and replaces lid within one minute. (Time taken 18)	✓	Knows "penny" or "money". (See F V, 1)	2	
Builds a tower of 8— bricks.	✓	Four-squares board completed within one minute—2 trials. (Time taken ....)	3	Repeats 2 digits—16; 53; 94.	3	
Handles scissors—tries to cut paper (4 in. square).	4	Six-hole board completed within one minute—2 trials. (Time taken 12)	✓4	Compares 2 insets for size: "Which one is bigger?" (See F III, 6)	4	
Copies a circle—primitive model. Stage I (page 7).	5	Four-squares board: (40 seconds). (See E III, 3)	✓5	Repeats 3 digits—982; 475; 136.	5	
Copies a cross (recognisable) Stage I (page 7).	6	Six-hole board (40 seconds). (See E III, 4)	✓6	Knows "big" and "little." (See F III, 4)	6	
Months credit: YEAR III—D		**Months credit: YEAR III—E**	10	**Months credit: YEAR III—F**		**YEAR III A to F**
items = ...		items = ...		items = ...		items / 3 = ...
× 2 = ...		× 2 = ...	20	× 2 = ...		
Folds a four-inch square of paper once (i.e., in half).	1	Returns 9 bricks to box and replaces lid within 40 seconds. (See E III, 2)	✓	Compares 2 towers: "Which one is higher?" (5; 3) bricks. (See F VI, 6)	1	
Threads 12— beads (not by pattern). (See D VI, 1)	2	Builds bridge with 3 boxes—inferior model, but stands.	✓2	Compares 2 lines for length. (See F VII, 6)	2	
Can cut square into two fairly equal pieces.	3	Assembles brick-boxes by colour—no error.	✓3	Preliminary counting to 4—.	3	
Folds a four-inch square twice.	4	Four-squares board (15 seconds). (See E III, 3)	✓4	Counts 4 bricks correctly.	4	
Copies a "ladder". Stage I.	5	Train under bridge successfully.	✓5	Repeats 4 digits—5816; 3729; 4952.	5	
Draws a "man," recognisable. Stage I (page 7).	6	Eleven-hole board (within 60 seconds). (Time taken 22)	✓6	Compares 2 weights. Which is heavier? (See also VIII, 4)	6	
Months credit: YEAR IV—D		**Months credit: YEAR IV—E**	10	**Months credit: YEAR IV—F**		**YEAR IV A to F**
items = ...		items = ...	12	items = ...		items / 3 = ...
× 2 = ...		× 2 = ...		× 2 = ...		
Copies a cross—good shape and well drawn. Stage II (page 7).	✓1	Six-hole board within (20 seconds). (See E III, 4)	✓1	Knows 2 coins (of 7 shown) N = ...	1	
Copies circle—good shape—neatly closed. Stage II (page 7).	✓2	Builds bridge—superior model.	✓2	Can count 10 bricks.	2	
Draws a square—recognisable. Stage I (page 14).	✓3	Pattern making No. 2 (60 seconds) (Time taken 25)	✓3	Knows morning and afternoon.	3	
Window—recognisable. Stage I (page 14).	✓4	Builds gate to model.	✓4	Knows 3 coins. (of 7 coins shown). (See F V, 1)	4	
House. Stage I (page 15). (See standards)	✓5	Pattern making No. 2 (40 seconds). (See E V, 3)	✓5	"Which goes faster?" 3— (See—below)	5	
Scissors: Can strip edge of paper neatly.	✓6	Pattern making No. 5 (60 seconds). (Time taken 24)	✓6	Can count 15 bricks.	6	
Months credit: YEAR V—D		**Months credit: YEAR V—E**	10	**Months credit: YEAR V—F**		**YEAR V A to F**
items = 6		items = ...		items = ...		items / 3 = ...
× 2 = 12		× 2 = 10		× 2 = ...		

Item F V, 5. "Which goes faster?"

1. A big boy running, or a little boy?
2. A bird flying or an aeroplane?
3. A car or a bicycle?

Item F IV, 2. "Which is the longer line?"

	A LOCOMOTOR		B PERSONAL—SOCIAL		C HEARING & SPEECH	
YEAR VI	Can bounce and catch a ball.	1	Has **one** special play-mate.	1	Talks in sentences of 10— syllables. (Record). (See page 10	1
	Can run fast out of doors.	2	Can tie single knot.	2	Comprehension 4—. (See page 11	2
	Can throw a ball up about 2 ft. and catch it.	3	Can go alone on errands to nearby shops, etc.	3	Uses 6— descriptive words.	3
	Can hopskip 4—.	4	(Credit as 2 items)	4	Knows 10— Capital letters. (Test	4
	Can jump off 3 steps.	5	Can brush and comb own hair.	5	Uses 6— personal pronouns.	5
	Hopscotch I (one successful hop)	6	Knows full address (3). [house, street, etc., and district]	6	Knows 10 colours. (Test.	6
	Months credit : YEAR VI—A items = 5 × 2 = 10		**Months credit : YEAR VI—B** items = 3 × 2 = 6		**Months credit : YEAR VI—C** items = ... × 2 = ...	
YEAR VII	Jumps a 10 in. high rope, both feet together.	1	Can tie a bow-knot: one loop.	1	Repeats sentence of 16 syllables. (See page 10)	1
	Hopskips more freely: 12—.	2	Uses knife and fork neatly: cuts own meat.	2	Picture Description — (3—), three sentences describing picture. (See page 10)	2
	Hopscotch II. (2 successful hops—second foot up).	3	Shoes: Can tie shoe-laces.	3	Know 20+ Capital letters. (Test)	3
	Can run, with steady trot, all round playground.	4	Efficient and competent at table, in all respects.	4	Similarities—**one**. (See page 11)	4
	Can skip a little with a rope, 3+ skips.	5	(credit as 2 items)	5	Differences—**two.** (See page 11)	5
	Hopscotch III. (3 hops—with second foot up).	6	Can tie a bow-knot: two loops.	6	Capital Letters—knows all 26.	6
	Months credit : YEAR VII—A items = ... × 2 = 4		**Months credit : YEAR VII—B** items = ... × 2 = ...		**Months credit : YEAR VII—C** items = ... × 2 = ...	
YEAR VIII	**Runs**—downstairs.	1	Can dress and undress without help completely.	1	Picture Description — (4—), four sentences describing picture.	1
	Can jump off 4+ steps.	2	Has **one** special **school** friend.	2	Similarities—**two.** (See page 11)	2
	Rides a bicycle (2-wheeler) in garden short distance.	3	Takes full responsibility for tidiness of hair.	3	Comprehension—**six.** (See list on page 11)	3
	Hopscotch IV. (4 hops — with second foot up).	4	(credit as 2 items)	4	Differences—**three.** (See page 11)	4
	Fast single skipping with rope.	5	Knows birthday—day and month. (2)	5	Similarities—**three.** (See page 11)	5
	Skips well 12+ ordinary double skipping.	6	Can lay a table — with some supervision.	6	Opposites—**three.** (See page 11)	6
Extra items	Hopskips some distance—out-of-doors.	7	Can lay a table without help or supervision.	7	Differences—**four.** (See page 11)	7
	Rides a 2-wheeler with competence.	8	Knows full date of birth (3), day, month and year.	8	(credit as 2 items)	8
	Months credit : YEAR VIII—A items = ... × 2 = ... **Extra items**:— × 2 **A** = ...		**Months credit : YEAR VIII—B** items = ... × 2 = ... **Extra items**:— × 2 **B** = ...		**Months credit : YEAR VIII—C** items = ... × 2 = ... **Extra items**:— × 2 **C** = ...	

Notes and Comments :

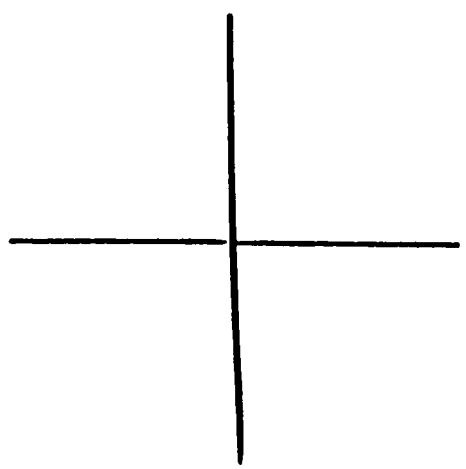
& EIGHTH YEARS

D		E		F		
EYE & HAND CO-ORDINATION		PERFORMANCE		PRACTICAL REASONING		TOTALS A to F
Threads 12 beads to colour pattern.	1 ✓	Eleven-hole board—within 40 seconds. (See E IV, 6)	1 ✓	Knows No. of fingers on **each** hand.	1	
Triangle—fairly good. (Stage A)	2 ✓	Pattern making No. 5—within 40 seconds. (See E V, 6)	2 ✓	Knows 4 coins. (See F V, 1)	2	
Draws man (Stage II). (See standards)	3 ✓	Ten-brick Memory Stairs. (imitation)	3 ✓	Knows 5 coins. (See F V, 1)	3	
Makes 3— letters. (See below)	4 ✓	Pattern-making No. 3—within 60 seconds. (Time 25)	4 ✓	Repeats 5 digits—61384; 59271; 92786.	4	
Can write or print own first name.	5 ✓	Returns 9 bricks to box and replaces lid in 20 seconds. (See E III, 2)	5 ✓	Knows fingers on both hands (5 − 5 = 10).	5	
Draws a house (Stage II). (See standards)	6 ✓	Pattern-making No. 4—within 60 seconds. (Time 21)	6 ✓	Knows "high" and "low." (See F IV, 1)	6	YEAR VI A to F items / 3 = ...
Months credit : YEAR VI—D items = ... × 2 = 12	6	**Months credit : YEAR VI—E** items = ... × 2 = 10	5	**Months credit : YEAR VI—F** items = ... × 2 = ...		
Copies a square (Stage II)—good shape and drawing.	1 ✓	Pattern-making No. 3—within 40 seconds. (See E VI, 4)	1 ✓	Counts to 30.	1	
Ladder (Stage II). (See standards)	2 ✓	Pattern-making No. 4—within 40 seconds. (See E VI, 6)	2 ✓	**Knows "right" and "left".** (8−) 1. right hand 5. left hand 2. left ear 6. right ear 3. right foot 7. left foot 4. right eye 8. left eye.	2	
Draws diamond (Stage A)—recognisable.	3 ✓	Four-squares board—within 7 seconds. (See E III, 3)	3 ✓	Can count backwards from 10.	3	
Draws triangle—good shape—neatly drawn. (Stage B)	4 ✓	Eleven-hole board—within 30 seconds. (See E IV, 6)	4 ✓	Can say the days of the week. (See F VIII, 1)	4	
Can write figures to 9—correctly.	5 ✓	Pattern-making No. 2—in 20 seconds. (See E V, 3)	5 ✓	Tells the time—hours only. (clock face test)	5	
Can write full name.	6 ✓	Pattern-making No. 3—in 30 seconds. (See E VI, 4)	6 ✓	Knows "long" and "short." (See IV, 2)	6	YEAR VII A to F items / 3 = ...
Months credit : YEAR VII—D items = ... × 2 = 10	5	**Months credit : YEAR VII—E** items = ... × 2 = 6	3	**Months credit : YEAR VII—F** items = ... × 2 = ...		
Makes 10+ letters.	1 ✓	Pattern-making No. 4—within 30 seconds. (See E VI, 6)	1 ✓	Days of the week: **questions** (2+) "What day comes after Tuesday?" "What day comes before Saturday?"	1	
Window. (Stage II) (See standards)	2 ✓	Six-hole board—within 10 seconds. (See E III, 4)	2 ✓	Knows 6 coins. (See F V, 1)	2	
Draws a man. (Stage III) (See standards)	3 ✓	Pattern-making No. 5—within 20 seconds. (See E V, 6)	3 ✓	Says 3 digits backwards: 186; 725; 493.	3	
Diamond—good shape—neatly drawn, etc. (Stage B)—(credit as 2 items)	4 ✓	Returns 9 bricks to box — lid—within 15 seconds. (See E III, 2)	4 ✓	Knows "heavy" and "light." (See IV, 6)	4	
	5 ✓	Pattern-making No. 2—within 15 seconds. (See E V, 3)	5 ✓	Can count backwards from 20.	5	
Makes 24+ letters.	6 ✓	Pattern-making No. 3—within 20 seconds. (See E VI, 4)	6 ✓	Knows 7 coins. (See F V. 1)	6	YEAR VIII A to F items / 3 = ...
House—very good. (Stage III) (See standards) (credit as 2 items)	7 ✓	Pattern-making No. 4—within 20 seconds. (See E VI, 6)	7	Tells the time—half hours (from clock face test).	7	
	8 ✓	Pattern-making No. 5—within 15 seconds. (See E V, 6)	8	Tells the time—quarter hours.	8	EXTRA items / 3 = ...
Months credit : YEAR VIII—D items = ... × 2 = 4	2	**Months credit : YEAR VIII—E** items = ... × 2 = 4	2	**Months credit : YEAR VIII—F** items = ... × 2 = ...		
Extra items:+ × 2 **D** = ...		**Extra items:+** × 2 **E** = ...		**Extra items:+** × 2 **F** = ...		

Child's writing :

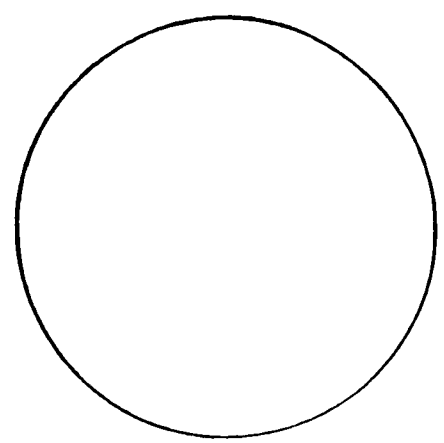
Makes Letters
D VI. 4 (3 — letters)
D VIII, 1 (10 — letters)
D VIII, 6 (24 + letters)
Can write (*a*) First name D VI. 5
(*b*) Full name D VII, 6
Can write figures to 9. D VII, 5

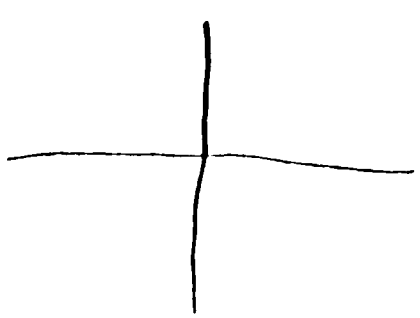
Drawing a Cross
(Items D III, 6; D V, 1)

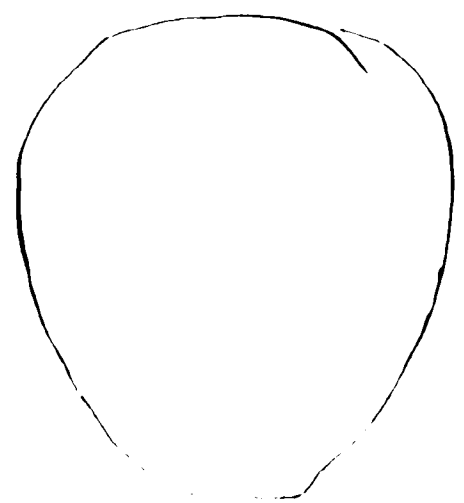


Drawing a Man
(Items D IV, 6; D VI, 3)

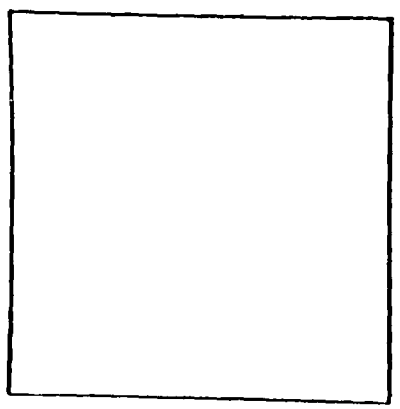
Drawing a Circle
(Items D III, 5; D V, 2)



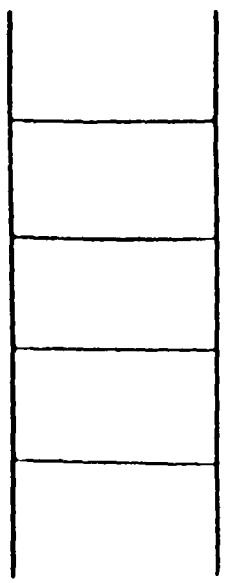




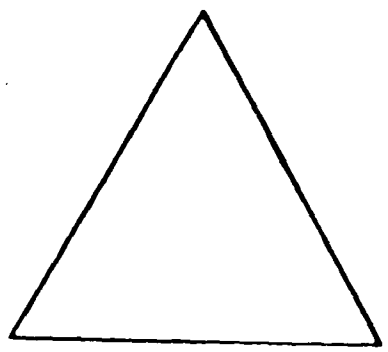
Drawing a Square
(Items D V, 3; D VII, 1)



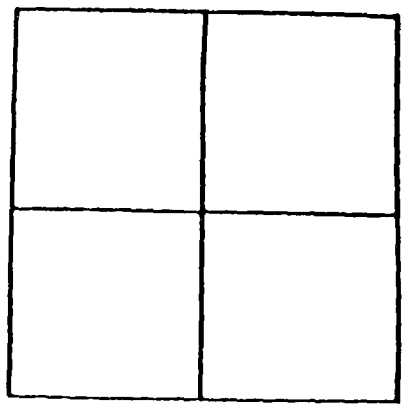
Ladder
(Items D IV, 5; D VII, 2)



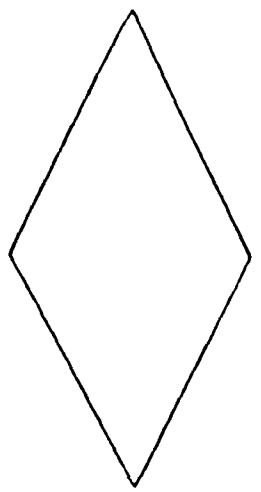
Triangle
(Items D VI, 2; D VII, 4)

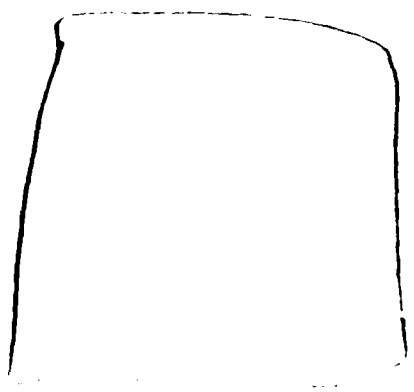


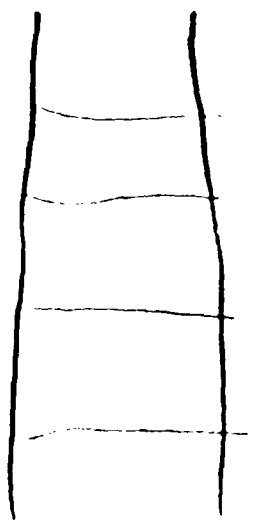
Window
(Items D V, 4; D VIII, 2)

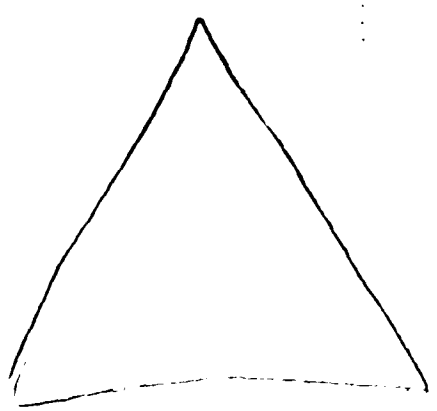


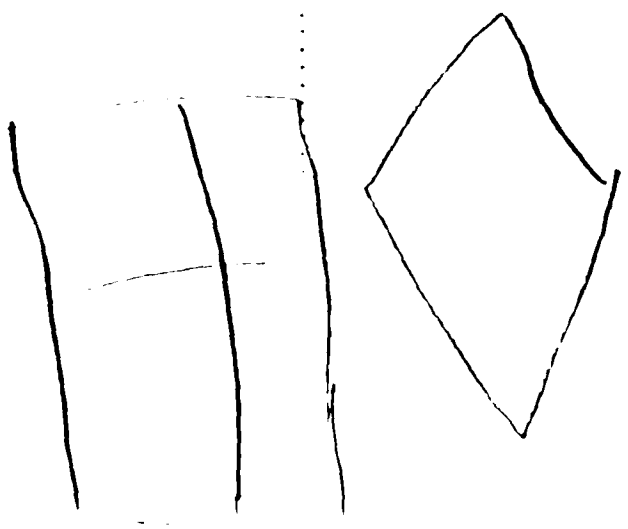
Diamond
(Items D VII, 3; D VIII, 4)



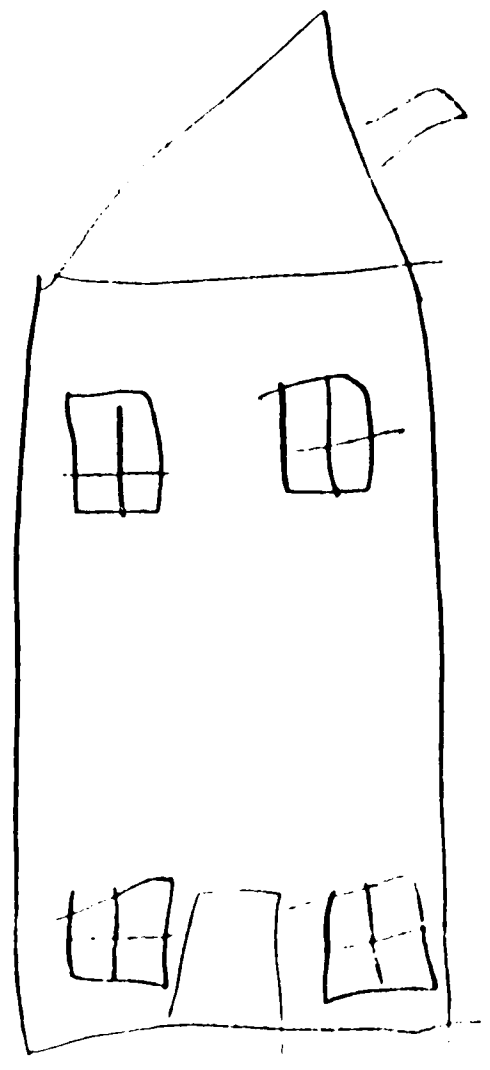








Drawing a House
(Items D V, 5; D VI, 6; D VIII, 7)



Gabriel
12345678910

Drawing People
(Items D IV, 6; D VI, 3; D VIII, 3)



Verbal details relevant to Scale C.—Older children

Child's Response to the Large Picture.

1. Full Verbatim Report : Record everything the child says.

   Some are going in a boat
   Two are long
   Four are long something else

2. **Objects** named (nouns) N =
   (Items C IV, 1; and C V, 6)

3. Descriptive words used (adjectives, adverbs) N =
   (Items C III, 5; C VI, 3)

   They are swimming in the water

4. Personal pronouns and possessives N =
   (Items C IV, 3; C VI, 5)

   Eleven trees
   are in all
   clouds.

5. Descriptive Sentences of 6 or more syllables N =
   (Items C V, 5; C VII, 2; and C VIII, 1)

   2 swans & three babies
   2 people going down to the
   water.
   Bridge.

Record also other sentences used spontaneously by the child during the examination.

1. Six or more syllables (Item C III, 6)

2. Ten or more syllables (Item C VI, 1)

Repetition of Sentences :

(*a*) Six syllable sentences (Item C III, 4) **one** correct scores plus.

(i) "I have a little cat." ✓

(ii) "My pussy caught a mouse."

(iii) "The mouse had a long tail."

(*b*) Repeats 10 syllables (Item C V, 4) **one** sentence scores plus.

(i) "My dog is a very good friend to me." ✓

(ii) "I take my dog when I go for a walk."

(*c*) Repeats a sentence of 16 syllables (Item C VII, 1)

"It will be my birthday next week, Mother will give me a party." ✓

Comprehension : (Items C IV, 4; C VI, 2 and C VIII, 3)

E 1. "What should you do if you feel tired ?"

2. "What should you do if you are cold ?"

3. "What is the thing to do if it is raining when you want to go out?"

4. "What should you do if you are going somewhere and you have missed the bus ?"

5. "What do you do if you feel lonely ?"

6. "What is the best thing to do if you are on your way to school, and you find it is getting late ?"

7. "What would you do if you were lost ?"

Opposites : (Items C V, 2; C VIII, 6)

E "A boy is big, a baby is ..... ?"

"Coal is black, snow is ..... ?"

"A lion is fierce, a lamb is ..... ?"

Similarities : (Items C VII, 4; C VIII, 2 and C VIII, 5)

E "How are a **carrot** and a **turnip** like one another ?"

"How are a **tiger** and a **cat** like one another ?"

"How are a **penny** and a **button** alike ?"

"How are a **tree** and a **daisy** alike ?"

Differences : (Items C VII, 5; C VIII, 4 and C VIII, 7 and 8)

"What is the difference between a **fly** and a **bee** ?"

"What is the difference between **ice** and **glass** ?"

"What is the difference between **string** and **rope** ?"

"What is the difference between **salt** and **sugar** ?"

APPENDIX 5

BEHAVIOUR CHECKLIST

These behaviours are often shown by young children. Please tick whether or not you think any of them apply to your child ***at present,*** *either definitely or only to some extent, or not at all.*

Would you say your child:	No	To some extent	Definite
1. Is very restless, often jumping up and down and hardly ever still	☐	☐	☐
2. Is a fidgety child	☐	☐	☐
3. Often destroys his own and other people's things	☐	☐	☐
4. Frequently fights with other children	☐	☐	☐
5. Tends to be disliked by other children	☐	☐	☐
6. Often worries about things	☐	☐	☐
7. Often has temper tantrums when frustrated	☐	☐	☐
8. Often appears miserable or unhappy	☐	☐	☐
9. Tends to be afraid of meeting new people	☐	☐	☐
10. Is often disobedient	☐	☐	☐
11. Cannot settle to anything for more than a few minutes	☐	☐	☐
12. Tends to be afraid of new situations	☐	☐	☐
13. Is a fussy child	☐	☐	☐
14. Often tells lies	☐	☐	☐
15. Often has tears on arrival at nursery or playgroup	☐	☐	☐

Is there anything else about his/her behaviour that worries you?

APPENDIX 6

PARENTS' QUESTIONNAIRE

Child's name _____ Date of birth _____

Your name _____ Your date of birth _____

Name of G.P. _____

Please circle your answers where appropriate:-

Are you: Married / single / widowed / divorced / separated?

Are you a single parent? Yes/No

What is your usual occupation? _____

_____

Are you currently employed? Yes/No

What is your partner's usual occupation?_____

_____

Is your partner currently employed? Yes/No

The following questions are about your child NOW

Does he/she go to nursery school/playgroup? Yes/No

If yes, how often does he/she go each week? _____

When do you expect him/her to start school? _____

Which school do you expect him/her to go to? _____

He/she will have routine hearing and vision tests done in school, probably in his/her second term.

May we contact the school medical officer for the result? Yes/No

The following questions are about the first 4 years of your child's life

Has your child had any serious illnesses or accidents? Yes/No

If yes please give details and approximate dates:

Is there a history of serious illness in your family? Yes/No

If yes please give details:

Has your child ever been admitted to hospital? Yes/No

If yes please give details, name of hospital and approximate dates:

Does your child currently attend a hospital outpatient clinic? Yes/No

If yes, please give details:

Does your child take any medicines regularly? Yes/No

If yes, what?

Is there anything which particularly worries you about your child? Yes/No

If yes, what?

APPENDIX 7

CODING FORM

(Unless stated otherwise, 0=no 1=yes 9=n.k.)

Baby Details

1.	Study number	1-3 ☐☐☐
2.	Date of birth (YYMMDD)	4-9 ☐☐☐☐☐☐
3.	Sex (1=male 2=female)	10 ☐
4.	Birthweight (g)	11-14 ☐☐☐☐
5.	Gestational age (completed weeks)	15-16 ☐☐
6.	Birthweight centile	17-18 ☐☐
7.	Head circumference (cm. to 1 dp)	19-21 ☐☐☐
8.	Head circumference centile	22-23 ☐☐
9.	Time to spontaneous respiration (mins) (98=never estab. 99=nk)	24-25 ☐☐
10.	Time to establish heartrate >100 (mins) (98=never estab. 99=nk)	26-27 ☐☐
11.	Apgar score 1 minute (n.k. = 99)	28-29 ☐☐
12.	Apgar score 5 minutes	30-31 ☐☐
13.	Apgar score 10 minutes	32-33 ☐☐
14.	Apgar score 20 minutes	34-35 ☐☐
15.	Intub. for meconium aspiration	36 ☐
16.	Resuscitation : intubation	37 ☐
17.	: bag and mask	38 ☐
18.	: THAM/bicarb.	39 ☐
19.	: cardiac massage	40 ☐
20.	Method of ventilatory support : IPPV	41 ☐
21.	: CPAP	42 ☐
22.	Reason for ventilatory support (0=none 1=resp. 2=neurol.)	43 ☐
23.	Duration of ventilatory support (days)	44-45 ☐☐
24.	Later management of acidosis : bicarb.	46 ☐
25.	: THAM	47 ☐
26.	Hypoglycaemia less than 1.5 mmol/1	48 ☐
27.	Transfusion of blood/plasma in first 24 hrs.	49 ☐
28.	Administration of dopamine	50 ☐

29. Cardiac arrest — 51 ☐

30. Definite necrotising enterocolitis — 52 ☐

31. Infection: evidence on blood culture — 53 ☐

32. CNS infection — 54 ☐

33. Clinical seizures — 55 ☐
(0=none 1=abn movements 2=clonic)

34. Onset of first clinical seizure (hrs) — 56-58 ☐☐☐

35. Duration of clinical seizures (days) — 59-60 ☐☐
(0=none 1=≤1 day 99=fitting at discharge)

36. Continuous EEG — 61 ☐
(0=none EEG 1=intermittent 2=continuous)

37. Seizure activity on EEG — 62 ☐
(0=none 1=definite 9=EEG not done)

38. Duration of EEG seizures (days) — 63-64 ☐☐
(0=none 1=≤1 day 99=fitting at discharge)

39. Anticonvulsant drugs — 65 ☐
(0=none 1=one 2=multiple drugs)

40. Encephalopathy — 66 ☐

41. Encephalopathy, worst stage — 67 ☐
(0=none 1=hyperalert 2=obtunded 3=stuporose)

42. Encephalopathy, status at 1 week — 68 ☐
(0=none 1=hyperalert 2=obtunded 3=stuporose)

43. Cranial ultrasound — 69 ☐
(0=normal 1=poss. abn. 2=def. abn. 9=not done)

44. CAT scan — 70 ☐
(0=normal/poss. abn. 1=def. abn. 9=not done)

45. Age on full sucking feeds (days) — 1-2 ☐☐

46. Admission to SCBU — 3 ☐

47. Length of inpatient stay (days) — 4-6 ☐☐☐

48. Congenital abnormalities: ICD Codes (1) — 7-10 ☐☐☐☐

49. ICD Codes (2) — 11-14 ☐☐☐☐

50. ICD Codes (3) — 15-18 ☐☐☐☐

51. ICD Codes (4) — 19-22 ☐☐☐☐

52. ICD Codes (5) — 23-26 ☐☐☐☐

53. ICD Codes (6) — 27-30 ☐☐☐☐

Maternal Details and Labour

54. Age at delivery (years) 1-2 ☐☐
55. Marital status 3 ☐
(1=married 2=single 3=divorced/sep/widowed)
56. One parent family 4 ☐
57. Social class (code) 5 ☐
58. Number of previous: deliveries 6-7 ☐☐
59. stillbirths 8 ☐
60. 1st mth. deaths 9 ☐
61. preterm deliveries 10 ☐
62. spont abortions 11 ☐
63. induced abortions 12 ☐
64. Existing disease (code) 13 ☐
65. Anti-hypertensive drugs 14 ☐
66. Pre-eclampsia diagnosed 15 ☐
67. Placental abruption 16 ☐
68. Onset of labour 17 ☐
(1=spont. 2=induced 3=c/s before lab.)
69. Fetal distress diagnosed before labour 18 ☐
70. Analgesia within 4 hrs of del. : general 19 ☐
71. : epi/spinal 20 ☐
72. : pethidine 21 ☐
73. : pethfan/meptaz. 22 ☐
74. CTG monitoring in labour 23 ☐
(0=none 1=admiss. only 2=other)
75. Duration of CTG (mins) 24-26 ☐☐☐
(0=no CTG)
76. Time missing before delivery (mins.) 27-29 ☐☐☐
(999=no CTG)

CTG Observations 1st. Stage

77. Overall grade 30 ☐
(0=no CTG 1=reassuring 2=grade 1 3=grade 2 4=grade 3)
78. Period of grade 2 changes (mins) 31-33 ☐☐☐
79. Period of grade 3 changes (mins) 34-36 ☐☐☐
80. Tachycardia 37 ☐
(0=none 1=mild 2=mod. 3=severe)

81. Bradycardia (0=none 1=mod. 2=severe 3=v.severe) 38 ☐

82. Non-accelerative FHR 39 ☐

83. Baseline variability (0=normal 1=reduced 2=inc. 3=v.inc. 4=absent) 40 ☐

84. Decelerations (0=none 1=mild 2=mod. 3=severe 4=v.severe) 41 ☐

85. Recovery (0=norm/NA 1=slow 2=overshoot) 42 ☐

86. Periodic accelerations 43 ☐

87. Late decelerations (0=none 1=severe 2=v.severe) 44 ☐

88. Uterine hyperstimulation 45 ☐

89. Sinusoidal patterns 46 ☐

90. Poor quality recording 47 ☐

CTG Observations 2nd. Stage

91. Overall grade (0=no CTG 1=reassuring 2=grade 1 3=grade 2 4=grade 3) 48 ☐

92. Period of grade 2 changes (mins) 49-51 ☐☐☐

93. Period of grade 3 changes (mins) 52-54 ☐☐☐

94. Tachycardia (0=none 1=mild 2=mod. 3=severe) 55 ☐

95. Bradycardia (0=none 1=mod. 2=severe 3=v.severe) 56 ☐

96. Non-accelerative FHR 57 ☐

97. Baseline variability (0=normal 1=reduced 2=inc. 3=v.inc. 4=absent) 58 ☐

98. Decelerations (0=none 1=mild 2=mod. 3=severe 4=v.severe) 59 ☐

99. Recovery (0=norm/NA 1=slow 2=overshoot) 60 ☐

100. Periodic accelerations 61 ☐

101. Late decelerations (0=none 1=severe 2=v.severe) 62 ☐

102. Uterine hyperstimulation 63 ☐

103. Sinusoidal patterns 64 ☐

104. Poor quality recording 65 ☐

105. Length of 1st stage (hrs. to dp.) 66-68 ☐☐•☐

106. Length of 2nd stage (minutes) 69-71 ☐☐☐
107. Mode of delivery (code) 72 ☐
108. Reason for operative delivery (code) 73-74 ☐☐
109. Paediatrician present at delivery 75 ☐

Child Assessment

110. Age at assessment (months) 1-3 ☐☐•☐
111. Weight (kg) 4-6 ☐☐•☐
112. Weight centile 7-8 ☐☐
113. Height (cm) 9-11 ☐☐☐
114. Height centile 12-13 ☐☐
115. Head circumference (cm) 14-16 ☐☐•☐
116. Head circumference centile 17-18 ☐☐
117. Attendance at Playgroup, Nursery, School (0=no 1=playgp. 2=nurs. 3=school) 19 ☐
118. Sessions attended per week 20-21 ☐☐
119. Serious illness or accident (0=no 1=yes) 22 ☐
120. Dysmorphic features (0=no 1=yes) 23 ☐
121. Central motor deficit (0=no 1=yes) 24 ☐
122. Sensory impairment (0=no 1=yes) 25 ☐
123. Squint (0=no 1=poss. 2=definite) 26 ☐
124. Griffiths scales : Motor 27-29 ☐☐☐
125. Personal/Social 30-32 ☐☐☐
126. Hearing/Speech 33-35 ☐☐☐
127. Eye/Hand 36-38 ☐☐☐
128. Performance 39-41 ☐☐☐

(777=no test 888=child refused 999=child unable)

129. Behaviour questionnaire : Conduct 42-43 ☐☐
130. Neurotic 44-45 ☐☐
131. Overall 46-47 ☐☐

Movement ABC assessments.

(7 or 77 = no test 8 or 88 = child refused 9 or 99 = child unable)

132.	Manual dexterity:	Coins: right (secs.)		48-50
133.		left (secs.)		51-53
134.		Beads (secs.)		54-56
135.		Trail (errors)		57-58
136.	Ball skills:	Bean bag		59-60
137.		Goals		61-62
138.	Static balance:	right (secs.)		63-64
139.		left (secs.)		65-66
140.	Dynamic balance:	Level 1: Jump over cord:	knee	67
141.			low	68
142.		Level 2: Steps on toes		69-70
143.	Pen hold (1=fist 2=distal 3=static 4=dynamic)			71
144.	Handedness (1=R 2=L 3=R+L)			72
145.	Overall level of impairment			73

Cord Blood Gas Values Etc.

148.	Time to analysis (minutes)		1-3
149.	Arterial pH		4-6
150.	Arterial pCO_2 (mm Hg)		7-8
151.	Arterial pO_2 (mm Hg)		9-10
152.	Arterial Bd (mmol/L)		11-12
153.	Vein pH		13-15
154.	Vein pCO_2 (mm Hg)		16-17
155.	Vein pO_2 (mm Hg)		18-19
156.	Vein Bd (mmol/L)		20-21
157.	Poor outcome predicted from CTG:	1st stage	22
		2nd stage	23
158.	Movement ABC score:	Manual dexterity	24-25
159.		Ball skills	26
160.		Static balance	27-28
161.		Dynamic balance	29
162.		Total	30-32
163.	English not first language at home		33
164.	Time reassuring on CTG (mins)		34-36

NUMERIC CODES TO BE USED ON CODING FORM

Social Class

Record social class of assumed head of household

1 = SC 1
2 = SC 2
3 = SC 3 non-manual
4 = SC 3 manual
5 = SC 4
6 = SC 5
7 = Armed Forces
8 = Single mother, not employed
9 = N.K.

Mother's existing disease

Code only if on medication for the disease

1 = Diabetes
2 = Hypertension
3 = Psychiatric illness
4 = Hypothyroidism

Mode of delivery

1 = Spontaneous
2 = Low forceps
3 = Mid/high forceps
4 = Ventouse
5 = Vaginal breech
6 = Caesarean section before labour
7 = Caesarean section in labour

Reason for operative delivery

1 = Delay/disproportion
2 = Fetal distress
3 = Previous caesarean section
4 = Breech presentation
5 = Pre-eclampsia
6 = Transverse lie
7 = Placenta praevia
8 = Deep transverse arrest
9 = Brow presentation
10 = POP
11 = Failed forceps