THE ASSESSMENT OF ASPHYXIATED TERM INFANTS BY SOMATOSENSORY EVOKED POTENTIALS

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This thesis is dedicated to Carol, Shona and Douglas, who resent the time and trouble taken to write it even more than does the author.

"My brain.....its my second favourite organ"

Woody Allen in 'Sleeper'

"If the cells and fibre in one human brain were all stretched out end to end, they would certainly reach to the moon and back. Yet the fact that they are not arranged end to end enabled man to go there himself. The astonishing tangle within our heads makes us what we are."

Colin Blakemore

Declaration

The work described in this thesis was carried out in the Department of Child Health, University of Leicester between March 1987 and January 1990. The study had received prior ethical approval from the local ethics committee. All of the writing of this thesis was done by myself. The reporting of evoked potential data was done in conjunction with Dr. Vlasta Brezinova and the follow-up data was collected by Dr. Margaret Graham.

All of the evoked potential recording, the analysis of results and the writing of this thesis was done by myself.

Three papers have been published from this work and these are presented with permission as Appendix 5 at the end of the thesis.

Neil Gibson

Abstract

The prognosis of asphyxiated term infants can be best related to the severity of their hypoxic ischaemic encephalopathy and therefore the findings on neurological examination, which is an index of brain function. This has a degree of subjectivity. Most of the useful objective techniques used to assess these infants have been imaging based studies. The measurement of somatosensory evoked potentials (SEP) is a relatively objective test which gives an index of function in the parts of brain most commonly affected in perinatal asphyxia. This study was therefore undertaken to investigate whether SEP could improve the prognostic information in affected infants.

Forty healthy term infants had SEP measured from surface electrodes over the cervical cord and cortex after median nerve stimulation at the wrist. A wide normal range of response was encountered. The cervical response was fairly stable and consisted of up to three negative peaks with the largest amplitude peak at a mean of 10.2 msec after the stimulus. The configuration was similar to that found in older children and adults. The cortical trace was found to vary markedly and consisted of a wave which was of increasing complexity with increasing postmenstrual age (PMA). The mean for the peak of the first negative wave (N1) being 30.0 msec. There was a negative correlation between increasing PMA and latency of N1.

Subsequent study was made of 30 term infants over the course of their asphyxial encephalopathy. The cervical response was normal in all but one infant but three types of cortical SEP were measured in these infants: a normal response; a immature/delayed response or an absent response. In general, over time, the SEP went from abnormality towards normality. The more asphyxiated infants had the more abnormal SEP results.

Ten of the infants died. The surviving infants were seen at a mean age of 12 months for a neurological examination and Griffiths developmental assessment. Thirteen were unequivocally normal, 4 had doubtful findings at follow-up and 3 had cerebral palsy. There was a good correlation between SEP results and outcome. All infants with normal SEP by 4 days of age were unequivocally normal at one year. All the others had abnormal SEP beyond four days.

The results suggest that SEP is a useful objective test in the evaluation of term infants who have suffered perinatal asphyxia and has additive weight to encephalopathy grade in prognostic assessment.

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Introduction

Perinatal asphyxia remains one of the most important identifiable causes of handicap in the term infant. This handicap is virtually always manifest as motor impairment, although cognitive and special sensory impairment may also occur. Much is known of the pathophysiology of hypoxic-ischaemic injury and the resultant neuropathology which gives rise to the neurodevelopmental sequelae. The neurodevelopmental outcome, the prognosis, of the infants affected by this condition is very variable. It is highly desirable to be able to monitor the effects of hypoxic-ischaemic injury especially for potential therapeutic reasons and also to assess prognosis. The currently available methods of prognostic assessment are all subject to a grey area of uncertainty. None are 100% sensitive or 100% specific. There is a need for better methods of assessment of these infants.

Perinatal asphyxia in the preterm infant is common and often has a major contribution from immediate postnatal factors due to the disease processes consequent upon preterm delivery. This thesis does not concern itself with this group of infants. In the term infant perinatal asphyxia is a more clearly definable entity. The term perinatal asphyxia describes the process by which the dual effects of hypoxia and ischaemia are experienced by the infant due to events surrounding birth. It is well recognised that the old idea that most of this insult occurred during labour itself is oversimplistic. Many infants suffer chronic adverse circumstances in utero due to a poorly functioning fetoplacental unit and this may be exacerbated by the labour process. In other infants it seems likely that they only suffered insult during the process of labour itself. In the term infant, asphyxial injury due to post natal factors is much less common. The common insults of hypoxic and ischaemic injury give rise to a neonatal encephalopathy from which there are three broad outcome groups. A group of infants make a full recovery with normal subsequent progress and no handicap. A further group have partial recovery with neurodevelopmental delay and motor impairment with possible special sensory problems and mental handicap. The other outcome is death, usually in the perinatal period, as a result of the asphyxial illness.

The most useful prognostic indicators in current practice are based mainly on clinical examination and investigation by imaging of neural tissue to give an index of damage present in the susceptible areas of the central nervous system. The other useful tests are those of function by recording the

electroencephalogram. Both imaging based techniques and examination have an important subjective element in their interpretation. A technique that gives an assessment of damage to function with a less subjective method might prove a useful addition to the prognostic armoury.

Somatosensory Evoked Potentials were first described by Dawson in 1947 but have taken several decades to find clinical uses in neurology. Their reliance on electrical signal processing techniques has meant that refinement has taken quite some time. They would appear to have potential for use in paediatric neurology, especially in the newborn at risk for neurodevelopmental handicap when treatment factors and immaturity make clinical assessment so difficult.

The principle of SEP involves the measurement of the electrical potentials generated at various levels of the somatosensory system in response to a given stimulus. Modern methods involve the use of cutaneous electrical stimuli, normally delivered over the median nerve at the wrist or the posterior tibial nerve at the ankle. The response to a large number of stimuli is computer averaged so that the low voltage evoked response which is time locked to the stimulus can be enhanced in relation to the randomly placed background electroencephalogram (EEG) and electrical "noise." This allows an assessment of the function and integrity of the somatosensory system from wrist (or ankle) to cortex. Abnormalities of response will reflect pathological processes occurring in the pathway. In general the motor pathways are in close proximity to the sensory ones and share a similar blood supply. It is therefore likely that both pathways will be affected by the same pathologies and that detectable damage in one pathway may reflect similar damage in the other.

Hypothesis

Better and more subjective methods of assessment of the asphyxiated term neonate are desirable. In these infants the neurological damage is normally sustained by the periventricular and immediate subcortical white matter and the cortex itself. The somatosensory system traverses these areas of neural tissue. This gives rise to the hypothesis that :

1. SEP will prove to be measurable in the term newborn.
2. A normal range of response can be established.
3. SEP will be measurable in the asphyxiated term neonate.
4. The result of SEP measurement in perinatal asphyxia will relate to the degree of encephalopathy.
5. SEP will give a guide to prognosis in these infants.
6. SEP will be a useful addition to the process of assessment of clinical condition and prognosis in asphyxial encephalopathy in the term newborn.

Firstly the subject of perinatal asphyxia is reviewed in terms of its pathophysiology, its clinical features and the tests currently helpful in predicting outcome. This sets the background to the subject of perinatal asphyxia and the question of improving prognostic information. Then the basic concepts of neuronal development and neural function relevant to this study are described followed by the theory, history and methods of SEP measurement. The current literature is reviewed with reference to studies in infants and children and relevant adult studies which gave rise to the hypothesis that SEP may be a useful means of assessment in perinatal asphyxia. The study design is then set out in light of the literature review. The next chapter will then detail methods and results of the study of SEP in neurologically normal newborns and the factors affecting their response, thus providing a normal range. Next, the clinical features and SEP results obtained on study of asphyxiated babies are detailed. The following chapter outlines the developmental assessment used in the follow-up examination of the infants and the results obtained. Then follows a discussion of the relevance of the SEP results to the clinical outcome and an assessment of the findings of the study. The thesis ends with a discussion of the findings of this study in relation to the existing literature and to the author's hypothesis.

Perinatal Asphyxia

The reasons for continuing experimental and clinical study of perinatal asphyxia is that it is a major cause of illness, death and handicap in the term infant and is an important contributor to the ranks of children with cerebral palsy. It remains a condition of which much is still to be learnt and in which determination of the prognosis of surviving infants is still an inexact science. There is also conflicting evidence as to possible changes in its incidence and prognosis.

In this chapter the biochemical pathophysiology and neuropathology will be described; then clinical features and prognosis are discussed before the tests and investigations that have previously been evaluated as to their prognostic ability are described. This sets the context of the work described in this thesis.

1.1 Biochemical Pathophysiology

Much of what is known of the biochemical and physiological events following an asphyxial insult is derived from the study of animals and is severely hampered by the difficulty of extrapolating from adult and fetal rodents and primates to the neonatal human; and the difficulty of simulating the same insult. However, the recent work done on cerebral blood flow and metabolism using Doppler ultrasound (Archer et al 1986, Levene et al 1989), positron emission tomography (Volpe et al 1985), nuclear magnetic resonance spectroscopy (Hope et al 1984) and near infra-red spectrophotometry (Edwards et al 1988, van Bel et al 1993) is allowing confirmation that much of the information gained from animal work is relevant to the human newborn.

The cerebral damage in perinatal asphyxia is due to the biochemical and physiological events which occur as a result of the combined effects of hypoxia, low oxygen tension in the blood, and ischaemia, diminished perfusion of blood, resulting from the cessation of exchange of respiratory gases due to perinatal compromise. Much of the experimental work on hypoxic-ischaemic cerebral damage has been done in animals and adults and has been exhaustively reviewed (Siesjo 1981, Siesjo 1984, Volpe 1987). oxygen tension drops, carbon dioxide levels rise and acidosis develops as metabolism is impaired leading to accumulation of toxic substances such as lactic acid and CO2, which, because of hypoperfusion or even cardiac arrest,

are not removed causing further damage. This may further affect the regulation of blood flow on reperfusion thereby exacerbating the damage. The immature brain is dependent on glucose as virtually its sole fuel for energy production and in anaerobic conditions can only harvest 2 of the 38 molecules of ATP it can normally produce from the full aerobic metabolism of a molecule of glucose. Despite this, the neonatal brain is less efficient at glucose uptake and contains little stored glycogen. Therefore, in the situation of both low oxygen tension and low perfusion there is a major disturbance of carbohydrate and energy metabolism. The additional poor removal of the harmful waste products of metabolism results in physiological changes, especially in cerebral blood flow and cellular function which worsen the situation and eventually cause cell death.

Animal work has shown that clinical and electrophysiological changes are apparent in minutes but that marked drops in energy status may not be measurable for hours (Vannucci and Duffy 1977). Work in the human newborn using Phosphorus Magnetic Resonance Spectroscopy has shown that depletion of energy stores is not measured until at least the second 24 hours after the asphyxial insult (Hope et al 1984). The loss of electrophysiological function could be due to changes in potassium levels but primate work (Astrup et al 1977) has demonstrated complete electrical failure with only small potassium changes. A more likely explanation could be that the profound early changes in neurotransmitters (Hedner and Lundborg 1980, Gibson and Duffy 1981) cause the marked functional disturbance before energy stores are exhausted. This may be a protective mechanism to conserve energy.

Hypoxia necessitates anaerobic glucose utilisation with a consequent build up of lactate, a decrease in phosphocreatine and eventually in ATP. There is resulting acidosis which, in turn, causes impairment of vascular autoregulation, inhibition of phosphofructokinase and thereby inhibition of glycolysis and a direct toxic effect on tissue. There is evidence (Cavazzutti and Duffy 1982) of differences between white and grey matter with respect to glucose influx in hypoxia suggesting that white matter is less able to maximise glycolysis in such situations.

Ischaemia is perhaps more damaging in that not only is there no glucose supply but there is no removal of toxic waste substances. There is, therefore, a build up of lactate and of cyclic AMP with a marked drop in cellular pH due to lactate, resulting in an additional loss of the normal buffering of CO_2. The

response to ischaemia may also include impaired reflow of blood in damaged tissue (Ames et al 1968) with a worsening imbalance between supply and tissue metabolic demand which hampers recovery and probably causes further damage. This finding is still the subject of debate and postnatal human data is discussed below.

Asphyxia is a more complex insult than just the coexistence of hypoxia and ischaemia in that there are also the deleterious effects of hypercapnia with its tendency to increase cerebral blood flow, decrease cerebral metabolic rate and decrease intracellular pH by an additive effect to that of lactate. Some of the best experimental work has been done in the dog (Vannuci and Duffy 1977). Survival was related to the length of insult. A dramatic early drop in oxygen tension and in pH was associated with a rise in CO2, fall in mean arterial pressure and bradycardia. Cerebral perfusion related to arterial blood flow, with the biggest drop in cortex and the least in brain stem. Biochemical changes were those of hypoxia and ischaemia.

The effects of glucose status before the asphyxial insult are also important, especially as the growth retarded chronically hypoxic fetus may have low glycogen stores and therefore impaired glucose homeostasis. Important studies of neonatal rats (Vannucci and Vannucci 1978) have shown that pre-existing hypoglycaemia worsens the response to an asphyxial insult. Hypoglycaemia seems to be deleterious due to changes in ability to mobilise glucose for an enhanced glycolytic rate necessary to minimise brain energy depletion. Studies on mature animals (Myers 1976) have suggested that pretreatment with glucose was harmful due to lactic acid effects. The reasons for these discrepant findings most probably relate to the fact that immature brain produces less lactic acid and has less good glucose uptake.

It has been known for over 50 years (Kabat 1940) that the neonatal brain is relatively more resistant to the effects of hypoxic/ischaemic injury. This may have a number mechanisms including a lower rate of cerebral metabolism possibly due to immaturity (Duffy et al 1975) and cardiac resistance to hypoxia because of increased glycogen stores (Dawes et al 1960). Animal work on the effects of anoxia on potassium concentrations in rat brain cortex (Hansen 1977) suggests that the more immature a brain is the longer it takes before the extracellular potassium concentration rises precipitously in anoxic conditions. It is postulated that immature cortex can maintain acceptable potassium gradients across cortical cells for longer than

mature tissue. There is evidence that the newborn suffers a mild state of ischaemic insult physiologically during the process of normal vaginal delivery (Vannucci and Duffy 1974). It is therefore possible that the relative resistance to hypoxic insult is a physiological defence mechanism. There is also the fact that the neural cells are less well developed in terms of their dendritic trees and synaptic complexity (see chapter 2) and therefore energy requirement for surviving function may be less and the effects of build up of toxic substances muted.

It would appear that in the clinical condition of perinatal asphyxia there are two phases of cerebral damage; firstly the initial hypoxic/ischaemic insult and secondly, when normoxia and perfusion are restored, a cascade of events leading to cell death occurs as a result of the initial damage. Neonatologists, powerless to do anything to modify the initial insult, are very keen to try to intervene in this second phase (Levene et al 1990, chapter 7.7).

Cell death occurs due to a complex set of events which are most probably interconnected (Siesjo 1981). Each of tissue lactic acidosis, extracellular potassium efflux and loss of calcium regulation can kill the cell but their combination is more potent. Energy failure is the end result of the events of initial hypoxic-ischaemic damage. Energy is required for the maintenance of cellular integrity by the synthesis of lipoprotein and the supply of membrane pumps, for cell function by transport processes and synthetic activities and for cell interaction by electrical excitability. Cell death ensues when all these functions fail to a greater or lesser extent. Structure is gradually disrupted and failure of membrane pumps results in membrane depolarisation with release of excitatory amino acids and failure of their re-uptake causing damage and further energy demand. Intracellular pumps also fail and potassium leaks out of the cell and sodium and calcium flood in.

Due to shortage of ATP, calcium accumulates in the cytosol as there is a lack of energy dependant calcium uptake by the endoplasmic reticulum and the cytosolic sodium is exchanged for calcium in the mitochondria. Further attempts by the cell to control the changes results in further ATP depletion. The high concentration of cytosolic calcium then acts to cause further damage by activating phospholipases and proteases thereby disturbing membrane stability. There is a release of arachidonic acid and free fatty acids which causes the creation of prostaglandins, thromboxanes and leukotrienes together with immensely damaging free radicals (McCord 1985). These compounds stimulate phospholipase activity setting up a vicious circle

and in themselves cause damage by peroxidation and break up of fatty acid in membranes leading to their destruction and the compromise of transport molecules and enzymes (Chan et al 1984). It is this stage of events that offers such an attraction in terms of therapeutic intervention with calcium channel blockers and oxygen free radical scavengers (Steen et al 1983, Steen et al 1984, Thiringer et al 1987, Levene et al 1990 and chapter 7.7). Excitatory amino acids are released from synapses by failing cell integrity and may also cause further cell damage (Rothman 1984). Increased levels of aspartate and glutamate have been shown in spinal CSF in asphyxiated human neonates (Hagberg et al 1993) giving support to this concept.

Fitting into this picture are the disturbances of cerebral blood flow which occur as a result of the initial insult and probably play an important part in the secondary damage. There is much that remains to be learnt about cerebral blood flow and its control in the human newborn but a little is now known about its behaviour from studies using Doppler ultrasound (Levene et al 1989), positron emission tomography (Volpe et al 1985), Xenon 133 clearance (Pryds et al 1990) and near infra-red spectroscopy (Edwards et al 1988, van Bel et al 1993). It is thought that the human newborn may autoregulate its cerebral blood flow over a narrow band of blood pressure, at least in "health" (Volpe 1987). There is also a degree of coupling of CBF to function and metabolism through such vasoactive substances as potassium ion, hydrogen ion, calcium ion and adenosine. Variations have been shown in regional CBF with higher flow in cerebral grey matter and brain stem and lower flow to the cortical white matter. Parallel studies with labelled glucose (Chugani and Phelps 1986) show more metabolic activity in these areas of higher flow giving evidence of coupling of supply and demand. There is also evidence that in situations of lower overall flow the areas with higher flow normally are preferentially perfused. It may be that the 'watershed' areas in the cortex (see below) are damaged in the initial hypoxic/ischaemic insult and that a breakdown in autoregulation (Milligan and Bryan 1979, Van Bel and Walther 1990) and uncoupling of flow/metabolism lead to further damage. There is evidence from animal studies of both inappropriately low cerebral perfusion soon after asphyxia the "no-reflow phenomenon" (Ames et al 1968) and of possibly later inappropriately high perfusion which cannot be utilised "luxury perfusion" (Lassen 1966). Van Bel and Walther (1990) have recently produced evidence using Doppler of pressure passive (low) cerebral blood flow in severely asphyxiated infants who have suffered myocardial

damage and have poor cardiac output in the first 2 days. Subsequent work with near infrared spectroscopy (van Bel et al 1993) has provided evidence of lower cerebral blood volume in the first 12 hours of life in severely asphyxiated infants.

There is evidence of high flow later after the asphyxial insult from other work in human newborns. Using Doppler ultrasound, high flow in the second 24 hours was seen after severe asphyxial insult (Levene et al 1989). This is supported by Xenon 133 studies (Pryds et al 1990) suggesting loss of autoregulation results in very high flow. Clearly much remains to be studied in this area particularly in relation to whether the prevention of these phenomena of abnormal blood flow may improve the outlook after asphyxial injury.

1.2 Neuropathology

The pathological changes associated with perinatal asphyxia are well documented (Norman 1978, Volpe 1987, Levene 1988). In the preterm infant the features are often blurred by the occurrence of periventricular haemorrhage. The term infant brain normally shows a combination of the following features.

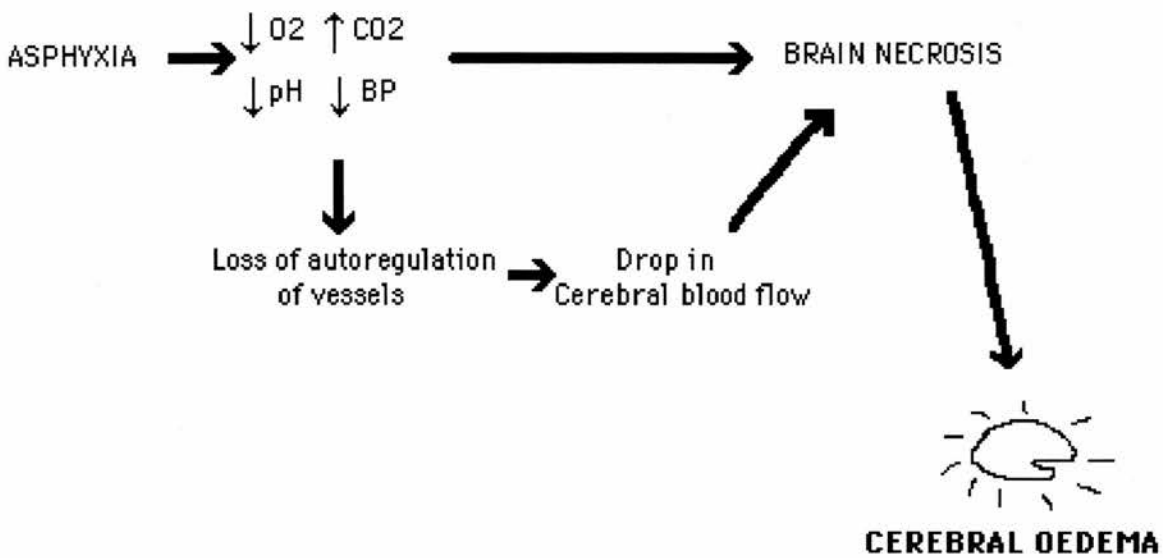
Selective ischaemic neuronal necrosis
Brain swelling - cerebral oedema
Damage to watershed zones
- periventricular leukomalacia
- subcortical leukomalacia
- parasagittal brain injury

Selective neuronal necrosis is commonly seen. The neuron appears to be the most vulnerable brain cell and first shows cytoplasmic vacuolation caused by mitochondrial swelling soon after the onset of the asphyxial insult. There follows loss of endoplasmic reticulum and fragmentation of the nuclei. Over the next few days cell necrosis occurs, microglia and hypertrophic astrocytes are seen and macrophages consume the necrotic debris. In severe asphyxial insults the cellular destruction may be extensive enough to lead to cavity formation. The damage may well be focal and its distribution may be partly but not wholly due to vascular factors (see below). These regional differences may relate to the metabolic function and needs of particular cell groups involving differences in energy consumption, anaerobic

glycolytic capacity, calcium homeostasis and defence against oxygen free radical attack. Another theory is that tissue most sensitive to hypoxic damage, such as cortical neurons, is contacted by synaptic terminals containing excitatory amino acids (Clark 1989) and that this may be an important determinant of the pattern of damage.

The role of brain swelling has been debated over the last 10-20 years. Much of the work has been done in fetal animals. It was formerly thought (Myers 1971) that cerebral oedema caused increased intracranial pressure leading to reduced cerebral blood flow and brain necrosis by these two mechanisms of pressure and further ischaemia. It is now thought more likely that brain swelling is a sign of severe tissue necrosis rather than its cause. Fetal lamb studies (Tweed et al 1981) have shown that vasogenic brain oedema is not quantitatively significant immediately after severe fetal asphyxia. An interesting study of 32 term human infants all of whom had serial intracranial pressure (ICP) measurements and most of whom had CT scans performed (Lupton et al 1988) showed that raised ICP was not common and seemed to coincide with worsening of the CT hypodensity. This suggests that cytotoxic oedema occurs in the presence of severe neuronal necrosis rather than as its cause.

Fig 1.1



The pattern of blood supply to cerebral tissue is thought to be vitally important in the genesis of cerebral injury. There are three particular patterns

of cerebral damage recognised which are listed above. Elegant and meticulous study of cerebral angioarchitecture (Takashima and Tanaka 1978, Takashima et al 1978) has shown that there is a vascular watershed zone at the boundary of the supplies from the major cerebral arteries. In the preterm infant this is in the region of the periventricular white matter and hypoxic-ischaemic damage to these infants may cause periventricular leukomalacia (Banker and Larroche 1962). In the term infant this boundary lies in the immediate subcortical tissue and in the deeper layers of the cortex itself and severe insult gives rise to subcortical leukomalacia (Takashima 1978, Trounce and Levene 1985) and widespread cortical damage. Recent work with Magnetic Resonance Spectroscopy (Moorcraft et al 1991) has shown that the energy impairment is most marked in subcortical areas.

The other lesion of presumed similar aetiology is 'parasagittal cerebral injury' (Volpe and Pasternak 1977, O'Brien et al 1979, Volpe et al 1985) which has been anatomically demonstrated with positron-emission scanning and radionuclide brain scanning. This is thought to be a boundary zone infarct in the cortex and subcortical zone between the territories of the anterior, middle and posterior cerebral arteries with a tendency to be more significant posteriorly than anteriorly. It may account for the clinical picture of grade 2 hypoxic/ischaemic encephalopathy (see below) with more marked disturbance of upper limb than lower limb.

1.3 Clinical Aspects

The incidence of perinatal asphyxia in a previous study population in Leicester in the years 1980 to 1983 inclusive was 6.0/1000 live births (Levene et al 1985) which is comparable to the figure of 5.9/1000 live births (Brown et al 1974) in an Edinburgh study of the late 1960s and early 1970s. Other authors suggest that the incidence is falling in their areas (Ergander et al 1983, Amiel-Tison and Ellison 1986). There is, however, evidence that the incidence of perinatal asphyxia in Leicester in the period 1982-4 was increased compared with another similar centre in the midlands of England (Field et al 1988). In the period of this current study (May 1987-December 1988 inclusive) there were 26 inborn infants who fitted the description from the earlier paper (Levene et al 1985) in a time when there were 10 182 live births giving an incidence of 2.6/1000 live births. This suggests there has been a large fall in the incidence. It is however interesting that the incidence of moderate and severe asphyxia (see definitions below) has not changed

markedly between 1980-83 and 1987-89. A possible explanation is that the author has used a much stricter definition of grade one (mild) asphyxial encephalopathy in this prospective study and this matter is further discussed in chapter 7.

How might a definition be reached of what is significant asphyxia? It is probably best described as a sufficiently large insult to the perinatal/neonatal brain to cause an increased risk of permanent damage resulting in handicap. In clinical practice this equates to the clinical patterns known as moderate and severe encephalopathy. These are described below.

The reported outcome of perinatal asphyxia in different centres reflects the criteria used to define it and the length of follow-up. In the Edinburgh study (Brown et al 1974) where all the infants (mostly but not all term) had adverse perinatal factors and abnormal neurology there was a 48% incidence of death or major handicap, 16% with 'minimal cerebral disorder' and only 36% with a normal outcome at a mean follow-up of 21 months. Similarly, Ergander et al (1983) had a poor outcome rate of 38% in the term members of a cohort whose asphyxia was defined as Apgar $\leq$ 3 at 5 minutes. The Edmonton cohort of 226 of whom only 28 had severe asphyxia had a death or major handicap rate of 25%. Two studies have quoted an adverse outcome rate per 1000 live births, which are 1.0 for term infants only (Levene et al 1985) and 0.9 for all births (Mulligan et al 1980).

It has increasingly been realised over the last 20 years that infants suffering significant perinatal asphyxia show abnormalities of neurological function and behaviour in the neonatal period. The extent of these features vary with the degree of asphyxia and are termed post-asphyxial encephalopathy (PAE) or hypoxic/ischaemic encephalopathy (HIE). There is a great variation in the definition used for asphyxia in the literature making comparison between studies very difficult. Many earlier authors defined asphyxia on the basis of depressed Apgar scores (Apgar 1953). It is quite clear from the original paper that Apgar did not intend her scoring system to indicate anything other than the condition of the infant immediately after birth. Measurement of biochemical parameters of asphyxia (lack of oxygen and poor perfusion) such as cord pH and gases have also been used as have the presence of adverse perinatal factors.

The evidence that significant damage due to asphyxia in the term infant only occurs in the presence of abnormal neurological findings in the neonatal period is strong. As part of the large National Institutes of Health (NIH) study

in the US covering over 40 000 deliveries (Nelson and Ellenberg 1987) an attempt was made to compare the incidence of cerebral palsy (CP) in infants of >2.5 kg birthweight between those infants with adverse perinatal factors such as abruptio placentae, prolapsed cord, breech delivery, etc... but no neonatal signs and those with no adverse perinatal factors. The incidence of CP was not increased. It was found that only when adverse perinatal factors were followed by abnormal neonatal neurological signs was the incidence of CP increased. Two study groups (Brown et al 1974, Levene et al 1985) searched local hospital records and each was unable to find any infant with handicap likely to be due to perinatal asphyxia born during their study period who had an adverse perinatal history but had exhibited no abnormal neurological signs in the newborn period.

The idea was originally credited to Little (1861) that most of cerebral palsy had its origins in the perinatal period as brain damage caused by asphyxia. This view is now refuted by modern epidemiological studies particularly those of the NIH in the US and the Western Australia cerebral palsy register. It is clear from the above that absence of neonatal signs makes perinatally acquired brain dysfunction most unlikely. From the Australian data (Blair and Stanley 1988, Blair et al 1992) it was shown that probably less than 8% of the 183 children on the CP register born between 1975 and 1980 had perinatal asphyxia as the likely cause. The NIH data (Nelson and Ellenberg 1987) are in broad agreement and state that at the beginning of the perinatal period one can already ascribe a high risk of CP to many infants from social, antenatal and other factors. Freeman and Nelson (1988) go further in suggesting that for a causal relationship between perinatal asphyxia and CP to be established there must be signs of intrapartum asphyxia (CTG abnormalities, low fetal pH, etc...), moderate to severe encephalopathy, a neurological condition consistent with perinatal insult and a work-up sufficiently thorough to have excluded any other reasonable cause of brain dysfunction.

A very interesting recent controlled study (Gaffney et al 1994) looked at term infants who had CP with regard to their intrapartum care and the response of obstetric staff to signs of fetal distress. Their data also suggest a figure of 7% of CP being likely to be due to intrapartum asphyxia. In addition they suggest an increased risk of CP and perinatal death in term infants if the response to signs of severe fetal distress was suboptimal. It is important to note that one third of their infants with subsequent CP and suboptimal

response to fetal distress did not have a neonatal encephalopathy. Two interpretations are possible: either the above assertions of Freeman and Nelson are incorrect or that these infants show fetal distress because they are already abnormal "damaged" infants but not that the fetal distress is a sign that damage is being done during labour.

There is no doubt that a proportion of infants who develop an asphyxial encephalopathy have had an important contribution to their problems from prenatal asphyxia or hypoxia. There is also literature evidence that this may affect the outcome (Scott 1976). It is certainly recognised (Scher et al 1991) that destructive brain lesions can occur in the antenatal period which may lead to cerebral palsy.

There has, therefore, been much work over the last 10-15 years to develop clinical methods of assessment of fetal wellbeing. This has been stimulated by a desire to better detect fetal compromise and facilitate decisions about delivery especially when there is a question of fetal hypoxia. One of the most striking signs of fetal compromise is that of growth retardation. Fetal heart rate monitoring has been extensively investigated in labour (Bissonnette 1975) and during the third trimester and patterns of lack of beat to beat variation, tachycardia and bradycardia give rise to concerns over fetal health. The development of fetal ultrasound has given further information and the concept has been advanced of a fetal biophysiological profile (Manning et al 1980) consisting of assessment of fetal breathing movements, general fetal movement, fetal tone, amniotic volume and fetal response. This technique is widely used, often in conjunction with fetal heart rate monitoring. A more recent development has been the use of Doppler ultrasound techniques. This aims to pick up markers of increased peripheral resistance from analysis of the bloodflow velocity in the fetal aorta. Several studies (Soothill et al 1986, Hackett et al 1987) have demonstrated a good correlation between these measurements and neonatal features suggestive of fetal compromise.

Clinical categorisation of neonatal hypoxic-ischaemic encephalopathy was first described in the german literature by Ewerbeck (1971) who recognised that the pattern of neurological abnormalities over the early days related to outcome. He described mild cases with hyperexcitability, hyperreflexia, clonic reflexes, frequent crying and insomnia with a good prognosis. A 'doubtful' prognosis was described for those with hypotonia, sluggish reflexes, weak suckling, whining and sleepiness whilst in those severe cases with coma,

extreme hypotonia or rigidity and hemiparesis accompanied by EEG findings of seizure potentials or isoelectricity the outlook was bad. Later a similar staging system was described in the English literature by Sarnat and Sarnat (1976), who gave a grading of severity related to both clinical and EEG features. Fenichel (1983) and Levene et al (1985) have slightly modified the Sarnat system so as to exclude the need to do routine EEG on asphyxiated babies.

Grade 1 HIE (mild) is characterised by the finding of a general increase in muscular tone associated with neurological irritability and poor feeding. Spontaneous startles occur and the infant handles poorly. The neurological abnormality persists for only one to two days and the baby returns rapidly to normal. In this study this category does not include any baby which had been admitted to the neonatal unit with irritability following resuscitation and settled within 12 hours, departing to the postnatal ward within 24 hours of birth (see chapter 7.1).

Grade 2 (moderate) babies have more persistent and marked abnormalities of tone. Characteristically they have differential neck tone (flexor > extensor) with decreased upper limb tone and increased lower limb tone. They virtually all have seizures which may be focal but are normally brought under control by a single anticonvulsant. The tonal abnormalities tend to become more marked over the first two to three days and then gradually resolve over the next week. Feeding difficulties are universal in this grade.

Grade 3 (severe) babies are at greatest risk of death or handicap. They often are profoundly hypotonic with loss of bulbar reflexes and require respiratory support. Seizures are multiple and poorly controlled, if at all, by anticonvulsants. Many die and survivors may gradually increase their tone over several weeks to a state of relative normality or to a hypertonic condition. These infants may require prolonged tube feeding. A small proportion may survive neurodevelopmentally intact.

Recent concern has been expressed (Nelson and Leviton 1991) about the use of the term HIE as the authors felt that an asphyxial cause may not be universal and that an unknown proportion of those with 'HIE' may have non-asphyxial causes. There is also pressure for precision in diagnosis and labelling arising from the explosion of litigation against Obstetricians over brain injured children and the growing knowledge of the relatively small proportion of children with cerebral palsy caused by perinatal asphyxial

insult. The use of the term Neonatal Encephalopathy avoids some of these problems and it has been suggested that it be used unless or until there is clear evidence that an asphyxial insult is responsible for the neonatal neurological findings.

In addition to their neurological problems the infants may show other clinical features of asphyxial damage to other organs such as pulmonary hypertension and meconium aspiration pneumonia (Yu 1985), myocardial failure (Lees 1980), necrotizing enterocolitis (Goldberg et al 1983), hepatocellular failure (Goldberg et al 1979), coagulation defects (Chadd et al 1971), renal impairment (Dauber et al 1976, Roberts et al 1990) and inappropriate secretion of ADH (Kaplan and Feigin 1978, Smith et al 1990).

1.4 Prediction of outcome

The principal aim of this study is to investigate infants with asphyxia by somatosensory evoked potentials with the hypothesis that SEP may give useful prognostic information. It is therefore now pertinent to consider what other tests and features have been investigated in the past as to their ability to predict outcome.

Neonatal neurological examination

One of the most important and extensive studies to clearly show the value of the neurological examination in perinatal asphyxia was conducted in Edinburgh (Brown et al 1974). The authors were able to demonstrate that certain patterns of neurological findings were associated with the adverse outcome of major handicap or death in over 60% of cases. These patterns were hypotonia and hypotonia progressing to extensor hypertonia. Confirmation of these findings came from a study of 53 term infants followed up to at least 2 years of age (DeSouza and Richards 1978) in whom the most ominous neurological pattern was initial apathy progressing to hyperexcitability and extensor hypertonia. Lipper et al (1986) described the use of a standardised neurological score and CT scanning (see below) for outcome prediction. They found that there was a uniformly poor outcome for those with the lowest scores i.e. most abnormal neurology. In each of these studies the infants with the most abnormal neurology would have fallen into the worst Sarnat grade. All authors that have applied the Sarnat scoring system (Sarnat and Sarnat 1976), or their own modification thereof, have found it a useful guide to outcome. Grade 1 encephalopathy results

universally in a good outcome (Sarnat and Sarnat 1976, Finer et al 1981, Robertson and Finer 1985, Levene et al 1986). Grade 3 results in a generally poor prognosis with no good outcome (Sarnat and Sarnat 1976, Robertson and Finer 1985) or 25% good quality survival (Levene et al 1986). The prognosis for grade 2 in all studies is very variable and this is the grade for which there is probably the most difference in categorisation. Like all the other tests so far used there results a grey area of uncertainty.

Apgar scores

The Apgar score (Apgar 1953) was formulated to give as objective as possible an indication of the infants condition one minute after birth, not as a sort of neurodevelopmental fortune telling exercise. It has recently been suggested that it has served its usefulness and should be "pensioned off" (Lancet 1989a). Other authors have suggested it retains a role in clearly delineating those infants in need of resuscitation (Marlow 1992) but not as a diagnostic pointer towards asphyxia or the prediction of outcome therefrom (American Academy of Pediatrics 1986).

In the NIH study (Nelson and Ellenberg 1981) it was found that low Apgar scores were a risk factor for adverse outcome. The authors took a number of values and looked at their predictive value. Ninety nine infants had a score of 3 or less at 10 minutes. Of these infants 11 had Cerebral Palsy and mental handicap and one infant CP alone. There were a further 8 infants with other disabilities. At school age 80% of those with an Apgar score of ≤3 at 10 mins were free of handicap. Levene and co-authors (1986) compared Apgar scores with encephalopathy grading in the prediction of outcome. They found the encephalopathy grading to be more sensitive than depressed Apgar scores.

Scott (1976) looked at a group of infants with an Apgar score of 0 at one minute and those with no spontaneous respiratory effort at 20 mins. Fifty per cent of the infants died but of the survivors three quarters were apparently normal. She postulated that those infants with a chronic asphyxial insult were more likely to have poor outcome than those with a relatively shortlived asphyxial insult. Another study of infants born in the late 1960s and early 1970s (Thomson et al 1977) looked at survivors of Apgar scores of zero at one minute or < 4 at 5 minutes. Ninety three per cent were free of serious handicap at review 5 to 10 years later. A more recent study (Jain et al 1991) has confirmed that the majority of the survivors of a one minute Apgar score

of zero are normal on long term follow-up but lack of response to resuscitation by 10 minutes made survival extremely unlikely.

The general consensus from the literature is that depressed Apgar scores particularly at 10 or 20 minutes are often associated with adverse outcome but that earlier scores are insensitive and nonspecific.

Intracranial Pressure

Raised intracranial pressure is associated with asphyxia and may affect the cerebral circulation. The concept of cerebral perfusion pressure (CPP), mean arterial blood pressure minus the intracranial pressure, has been established and is thought to be a possible index of cerebral blood flow. Raju et al (1983), using a Ladd tonometer technique, have shown 86% of term infants in their study with a CPP below 25 have an adverse outcome and 75% with normal CPP values are normal on follow-up. This is open to two interpretations from the above argument. Either that low CPP is the cause of poor outcome by the mechanism of raised ICP and/or hypotension reducing cerebral perfusion to such a depth that cell damage occurs or that the infant who allows the CPP to drop is the most severely damaged infant and is suffering cytotoxic oedema and/or severe myocardial damage and that low CPP is just a marker of the severity of the asphyxia.

Levene et al (1987), using a subarachnoid catheter, also studied ICP and CPP in 23 infants with grades 2 and 3 HIE. They found that no infant with CPP < 20mmHg for over an hour survived intact, nor did any infant with sustained rise in ICP above 15mmHg. Low CPP was most often due to low BP. They also demonstrated that some infants died without rises in ICP.

Seizures

It follows from the definition of HIE and its association with outcome that there be a reasonable correlation between seizures and outcome. Holden et al (1982) using data from the NIH study concluded that the association of seizures with other factors was important. They also showed that early onset of seizures and prolonged seizures carried a worse prognosis. The Edmonton study (Finer et al 1983) showed that seizures uncontrolled by phenobarbitone as a single agent anticonvulsant were significantly associated with adverse outcome. EEG data is discussed below.

Onset of respiration

In contrast to Scott's work (1976) other authors have found this index of asphyxia useful in prognostication. Steiner and Neligan (1975) in a paper strongly advocating vigorous attempts at resuscitation after perinatal cardiac arrest found that failure to establish spontaneous respiratory effort by 30 minutes was always associated with death or severe handicap. Ergander et al (1983) showed that in their study of 76 term infants absence of spontaneous respiratory effort by 20 minutes predicted severe handicap. However, another study (DeSouza and Richards 1978) showed no major handicap in 7 infants with no respiratory effort at 30 minutes.

Biochemical parameters

There have been 2 approaches to the biochemical assessment of the asphyxiated newborn. The first is to measure characteristics of the cord blood to assess the acid-base status as an indication of the response of the fetoplacental unit to the rigours of late pregnancy and labour. The second approach has been to measure, in the infants blood or CSF, metabolic products which may reflect the extent of abnormal metabolism due to hypoxic-ischaemic insult.

Sykes et al (1982) in their oft quoted paper detailing the features of 1210 consecutive deliveries showed a poor correlation between the Apgar score and cord arterial blood pH, a measure to which many Obstetricians have had an almost religious faith as a marker of asphyxia. They suggested that cord pH may be a better indicator. However, it has been shown (Josten et al 1987) that many vigorous babies have low cord pH and that this measure is insensitive and non-specific. This has been confirmed by further follow-up at 4.5 years of part of the cohort described by Sykes (Dennis et al 1989) in which no significant relationship was found between cord blood acidosis and outcome. Another study (Ruth and Raivio 1988) which looked at one year outcome found that cord pH and Apgar scores were equally insensitive and poorly predictive of neurodevelopmental outcome.

An exciting development in the assessment of the asphyxiated newborn is the study of cerebral energy metabolism by Phosphorus NMR spectroscopy. This allows spectra to be obtained from transcranial examination. These are then analysed in order to calculate the ratio of Phosphocreatine (stored energy) to inorganic phosphate (released on energy depletion). Hope and coworkers (1984) in a study of 10 infants showed that the measured ratio

was normal in the 6 infants studied on the first day but fell in the most asphyxiated infants. All infants with normal outcome had levels above 0.8 of the ratio found in normal term infants. Extension of this work to preterm and term infants suffering various hypoxic-ischaemic insults has confirmed the usefulness of this technique in the assessment of brain injury (Azzopardi 1989). Separate study solely of infants with perinatal asphyxia with follow-up at one year (Roth et al 1992, Peden et al 1993) has shown a strong correlation between the extent of abnormality of cerebral oxidative metabolism and the outcome. Refinement of the technique to look specifically at oxidative state in parts of cortex rather than globally has not improved the predictive value of this test (Moorcraft et al 1992).

Measurement of direct chemical markers of asphyxia has been investigated in many studies. It has been felt that due to disturbances in blood-brain barrier function both CSF and blood values may be useful. Hall et al (1980) showed that lactate dehydrogenase (LDH) in CSF was significantly elevated in those who died but not significantly different between those with normal and abnormal survival. Saugstad (1988) postulates that hypoxanthine may be a useful indicator as it is the product of degraded AMP from ATP when energy stores are depleted. Thiringer (1983) measured this variable in cord blood and showed higher levels in 'hypoxic' infants. She found a reasonable correlation with clinical features and two infants in the study with subsequent spastic paresis had very high hypoxanthine levels. Similarly, Laing and colleagues (1988) measured this metabolite in urine and showed raised levels in the more asphyxiated infants with some correlation with outcome. In addition they found raised levels in some infants in whom asphyxia was less severe and suggested that this metabolite may reflect the presence of other unidentified problems such as inherited metabolic disease in the infant giving rise to neurological dysfunction.

The so-called 'brain specific' creatine-kinase (CK-BB) is thought to be released from damaged astrocytes and has been investigated in asphyxia. A study of 33 term infants (Fernandez et al 1987) showed good correlation between raised levels of CK-BB in the first 12 hours and adverse outcome but the authors concluded that there was no benefit over prognostication on the basis of CT scanning or joint clinical/EEG criteria. They reasonably stated that as there was a good correlation between level of CK-BB and degree of asphyxia that it did provide an early indication of the severity of the insult. A similar conclusion was reached in an earlier study (Walsh et al

1982), who found that levels of CK-BB in cord blood and from the infant at 6-12 hours correlated with outcome.

Imaging

The results of imaging of the cerebral contents by computed tomography (CT), radionuclide brain scanning and ultrasound have been compared with outcome by a number of groups to assess their contribution to prognostication.

Using CT there are two main types of lesion which can be seen in the asphyxiated term neonate (Flodmark et al 1980). In this study a correlation was made between the results of CT scanning and autopsy findings in 90 asphyxiated neonates of whom 11 were term babies. In all cases CT had been obtained within 10 days of autopsy. Haemorrhagic lesions were well demonstrated in both position and extent, including subarachnoid haemorrhage, and showed up as increased density areas. Ischaemic brain on autopsy correlated well in the term infant with areas of hypodensity although not as well in the preterm infant when hypodensity could be present in the absence of ischaemic changes.

The same group of workers (Fitzhardinge et al 1981) then went on to a clinical study of 62 term survivors of HIE in whom 47% had bad outcome. These infants had CT performed in the first 2 weeks of life and again at 6 months of age. Follow-up extended to at least 18 months of age. Three patterns of decreased density of brain tissue were seen in neonatal scans; mild hypodensity in the periventricular area, extensive hypodensity with a mottled appearance of both white and grey matter and generalised low density appearance due to cerebral oedema. Eighteen of 20 with extensive hypodensity were abnormal on follow-up. This group also found parenchymal haemorrhage to be strongly associated with subsequent handicap. Adsett et al (1985) came to similar conclusions in a study of 56 term infants with HIE all studied within 2 weeks of birth whose CT scan was graded as normal or as showing hypodensity which was global, diffuse or patchy. Normal or patchy scans were associated with normal outcome or only minor difficulties on follow-up at a minimum of one year of age. However, of the 6 with global hypodensity 2 died and 4 were severely handicapped and of 23 with diffuse changes 2 were normal, one had minor problems, 15 major handicap and 5 died.

The other group from Lausanne studying CT in perinatal asphyxia have addressed themselves particularly to the timing of the scan. They have shown (Lipp-Zwahlen et al 1985b), in a group of 9 term infants scanned early (1 to 7 days), intermediate (2 to 7 weeks) and late (3 months or more) that appearances changed over time. Early scans showed slight to moderate periventricular low density especially around the frontal and occipital horns of the lateral ventricles. Intermediate scans revealed distinct well demarcated low density in 6 of the 8 scanned which was periventricular with extension into the subcortical and cortical areas. The late appearances were of ventricular dilatation with cerebral atrophy and parenchymal low density probably representing cysts. Intermediate scans best correlated with outcome as early low density which resolved was not associated with sequelae but low density on intermediate scan predicted adverse outcome. This confirmed their previous work (Lipp et al 1980) on 36 infants. A similar report (Lipp-Zwahlen et al 1985a) describes the results of 25 infants in whom the predictive ability of encephalopathy grade and early and late scans was investigated. A scoring system for the amount of hypodensity in brain slices was constructed. High scores (more extensive hypodensity) in later scans (9-23 days) were most predictive of bad outcome. This work probably explains why in one study in which CT scans were done in the first week (Finer et al 1983) CT was not found to be of any use in predicting outcome.

Radionuclide brain scanning involves generating images after injection of Technetium 99, the images relating to blood flow and distribution. The technique has fallen by the wayside owing to the development of CT but has been investigated in perinatal asphyxia (O'Brien et al 1979). Studies were done on 85 term infants of whom 38 had serial scans. Nine infants died and follow-up was to at least 6 months. Persistently abnormal scans predicted abnormal outcome but a single scan had poor prognostic power. The test was rather insensitive and non-specific as 72% of those with a normal scan had normal outcome and 76% of those with an abnormal scan had abnormal outcome. Interestingly, 5 of the 6 infants with a unilateral pattern of reduced signal in the territory of the middle cerebral artery developed hemiplegia on follow-up.

Ultrasound has also been investigated in perinatal asphyxia but is of limited use. It has been shown (Hill et al 1983) that ischaemic lesions seen on CT as hypodensity correspond to hyperechoic areas on ultrasound but unfortunately haemorrhage and ischaemia both show as increased

echogenicity (Martin et al 1983). A study of 27 infants (Babcock and Ball 1983) showed 8 with abnormal early ultrasound all of whom had abnormal outcome. The abnormal scans consisted of a compressed ventricular system and increased echogenicity in the brain. In addition 7 of those with a normal scan had abnormal outcome showing early ultrasound to be specific but insensitive. Late scan appearances of loss of brain tissue and cysts were also specific for abnormal outcome. Some of the infants had CT scans and the authors point out that ultrasound is better than CT for showing cysts. Another study (Siegel et al 1984) looked at 32 term infants with HIE concentrating on the appearances of ventricular size and parenchymal echodensities. Results were related to follow-up at a mean of 11 months (range 6 weeks to 24 months). Of the 20 infants with abnormal scans 10 died, 6 were severely handicapped, 2 mildly handicapped and 2 normal. Twelve infants had normal ultrasound scans of whom 8 were normal, one severely handicapped and 3 lost to follow-up. The authors concluded that ultrasound was useful in prognostication but suggested that from the autopsy data collected it appeared that ultrasound underestimated the extent of hypoxic/ischaemic damage.

A similar conclusion was reached in a recent paper (Gray et al 1993) comparing ultrasound imaging, CT scan and Doppler assessment of cerebral blood flow parameters. These authors found imaging ultrasound to be poorly predictive but CT evidence of reduced tissue density was predictive of poor outcome.

Doppler Ultrasound studies

From the unit in Leicester 2 papers have been published looking at the patterns of cerebral blood flow in asphyxiated term infants. The first paper (Archer et al 1986) dealt with the parameter of Pourcelot's resistance index (PRI) which is calculated from the ratio of systolic and diastolic flow (PRI = (s-d)/s) and is thought to relate to resistance to flow and is independent of the angle of insonation of the ultrasound beam. In studies of 49 normal controls the PRI was always > 0.55 and therefore abnormal PRI was defined as ≤ 0.55. Most infants were studied daily during the course of their illness. Eighteen asphyxiated infants out of 43 (16 grade 1, 15 grade 2, 12 grade 3) had abnormal PRI and on follow-up at a median of 18 months 12 of these children had adverse outcome of death or major handicap. No child with

persistently normal PRI had adverse outcome. PRI was shown to fall after 24 hours of age and remain low for some time.

A subsequent report (Levene et al 1989) includes only infants with grades 2 and 3 encephalopathy and looks at cerebral blood flow velocity (CBFV) measured daily from the anterior cerebral artery in 34 infants. Control data was collected from 126 healthy term infants to give a normal range for this parameter. Two types of abnormal CBFV were found. In 4 infants, at a mean of 21 hours, low CBFV (<-2 S.D.) was measured and 3 of these infants died. A more commonly encountered abnormality was high CBFV (>+2 S.D.) which was first recorded at a mean of 26 hours and often persisted. Of the 17 with abnormally high CBFV 13 died, 3 are severely handicapped and one is normal. If the high CBFV relates to actual flow then perhaps we are observing the concept of 'luxury perfusion' (Lassen 1966). In this study it was possible to have adverse outcome without low PRI as PRI was always >0.55 in the presence of abnormally low CBFV.

A further study from Australia (Gray et al 1993) also found that Doppler assessment of resistance index (RI) was useful. Measurement of RI from the anterior cerebral artery was 88% sensitive and 89% specific. These authors discuss at considerable length that this assessment allows the identification of bad prognosis infants who might benefit from biochemical intervention. However, their Doppler assessments were done at 2-5 days, by which time the damage is almost certainly already done.

Electroencephalography

EEG has been found by a number of groups to be a useful indicator of those infants destined for a poor outcome. Sarnat and Sarnat (1976) incorporated EEG in their grading system in that grade 1 had a normal EEG, grade 2 was characterised by voltage depression and high amplitude seizure discharges and grade 3 infants showed extreme voltage depression (isoelectric EEG) or burst-suppression pattern. They reported seizures as rare in grade 3. There is real consensus on the prognostic ability of EEG in that all groups have found that background EEG pattern and not paroxysmal activity is the best guide to outcome. Background suppression with burst-suppression pattern or even isoelectricity is strongly associated with poor outcome and normal EEG predicts normal survival (Watanabe et al 1980, Finer et al 1981, Holmes et al 1982, Fenichel et al 1985).

Doing a full EEG study in a neonatal intensive care situation is sometimes difficult and another technique which has been evaluated is cerebral function monitoring (CFM). This consists of measuring from only 3 scalp electrodes and summating and simplifying the EEG information to give a printed readout of the amplitude and frequency band of cerebral activity. It can therefore show in simplified form the background EEG and seizure activity. In a study of 39 asphyxiated infants of whom 13 were term infants with perinatal asphyxia (Bjerre et al 1983) it was found that the CFM trace correlated well with an EEG performed early in the illness. CFM findings of isoelectricity or burst suppression pattern were strongly associated with poor outcome whereas seizure activity correlated poorly with outcome. A study of 31 infants of whom 12 were born at term (Archbald et al 1984) described three patterns of CFM findings. Normal pattern was universally associated with a favourable outcome. A disorganised pattern was associated with death and a pattern of "reversal to a more immature gestational age" was associated with abnormal survival.

Evoked potentials

The four papers on SEP (Hrbek et al 1977, Willis et al 1987, DeVries et al 1991, Taylor et al 1992) in perinatal asphyxia will be discussed in chapter 4.7 along with the literature on other uses of SEP in the newborn.

Brainstem auditory evoked potentials or responses (BAEP, BAER, ABR) have been investigated by a number of groups but the papers are difficult to interpret as they include heterogeneous groups of infants both term and preterm with different diagnoses studied in non-uniform ways. Hecox and Cone (1981) performed BAER a few days to 3 months after a hypoxic insult in 126 infants. They looked at wave I and wave V and the amplitude ratio V/I. Follow-up was to a mean of 2 years. Twenty one infants were found to have an abnormal amplitude ratio of greater than 2.0 and all were dead or handicapped. However, normal amplitude ratio could also be associated with poor outcome. The authors postulated that loss or abnormality of wave V was associated with midbrain damage where this potential is said to be generated. Kileny et al (1980) studied 14 asphyxiated term infants with ABR at 3-17 days but report no long term follow-up data. Raised thresholds for response, increased wave I latency and increased wave I-wave V interpeak latencies were found and in some infants recovery in ABR was seen with clinical recovery.

There are four papers describing visual evoked potentials (VEP) in perinatal asphyxia. The first is that by Hrbek et al (1977) which described VEP abnormalities in 85% of asphyxiated term and preterm infants but contained no follow-up data. Three papers describe work in Toronto (Whyte et al 1986, Muttit et al 1991, Taylor et al 1992). In the first they describe 25 term asphyxiated infants followed up to 6 months. Severe VEP abnormality was associated with death or major neurodevelopmental difficulties whereas 8 of 9 with normal or only mildly abnormal VEP had normal follow-up. There was, however, an area of uncertainty with this test. The findings are confirmed in the two other studies.

1.5 Conclusions

There are, therefore, a number of ways of identifying those infants with a very high chance of a neurodevelopmentally normal outcome. In particular this is predicted by the presence of only grade 1 encephalopathy, a normal EEG or a normal late CT scan. It is almost as clear cut to pick out the doomed infant who may have an isoelectric EEG, extensive hypodensity on CT scanning, severe energy depletion shown by 31P NMR spectroscopy or profound and persistent clinical neurological abnormality. In most studies there is a grey area in the middle, in which, no matter which test is used, a particular test result may predict intact survival, relatively minor problems or major sequelae. The problem therefore remains of identifying a more sensitive and specific means of predicting survival status in perinatal asphyxia in the term infant. Subsequent chapters of this thesis will discuss why SEP were thought to merit further study in this clinical problem thereby giving support for the hypothesis.

The Somatosensory System

In order to understand the process of evoked potentials and the means by which they are generated it is necessary to have a feel for the elements which make up the nervous system, the development of the nervous system and its organisation and function. In particular, with relevance to this body of work, it is important to be aware of the changes taking place in the nervous system in late fetal life and early extrauterine life. This chapter gives an account of the physiology of nerve cells and their function before giving a description of the relevant features of the somatosensory system.

2.1 Cellular elements

The nervous system consists of two broad groups of cells: neurons (nerve cells), which possess the property of excitability which gives the nervous system its function, and neuroglia which are the supportive cells on which neurons depend.

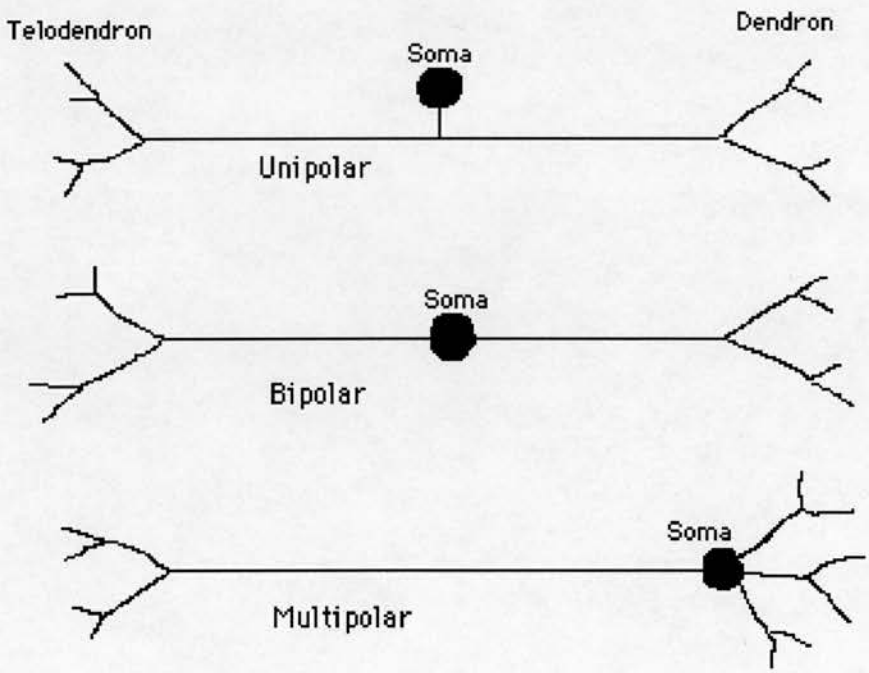


Fig 2.1 Types of neuron

Neurons are highly specialised cells capable of excitation and communication between each other. They comprise of a cell body with processes. The longest of these processes is called the axon and it has two

distinct ends: the dendron and the telodendron. Neurons can have three basic structures; they can be multipolar, bipolar or monopolar as shown above in figure 2.1.

There is highly complex organisation of neural cells to allow the grouping together of neurons for functional ends. Within the nervous system there are collections of cell bodies from neurons with similar function which are called nuclei. A group of similar axons from these nuclei are called tracts and are named by the site of origin and termination e.g. thalamocortical tract (between thalamus and cortex).

The cell membrane is thought to consist of a basic phospholipid bilayer with the hydrophilic protein elements at the external and internal interface and with the lipid elements buried within the membrane. The cell membrane contains pores or channels which allow or facilitate the passage of ions to create electrical changes on which the cell depends for its function.

The axon of a neuron is the cable down which information is passed. The peripheral nerves consist of bundles of axons passing towards (afferent) or away from (efferent) the central nervous system. The afferent nerves are the sensory nerves and the efferent nerves carry motor or secretory impulses. The dendron is the receptive pole of the neuron and is often branched into dendrites. These are a highly specialised region which can be part of the system of sensory receptors. The telodendron transmits information and is also known as the axon terminal. At its end is a swelling called the bouton terminal which facilitates cell-cell communications. Both the dendron and telodendron are metabolically active areas with plentiful organelles. A synapse is where the axon terminal contacts the cell membrane of another cell. Where information is chemically transmitted there is a gap known as the synaptic cleft. The largest vertebrate axons are 20μm and are myelinated. Amongst the largest known fibres are the unmyelinated Squid axon at 800μm. It is from study of this axon that much has been learnt of neuron function.

The neuroglia are the supportive cells and consist of three main types. One set of cells specifically support the neurons; in the central nervous system (CNS) these are called oligodendrocytes and in the peripheral nervous system, Schwann cells. The Schwann cells provide for the process of myelination in the peripheral nerves and in the CNS the oligodendrocytes may allow the neurons to lie in a groove in their wall unmyelinated. The process of myelination involves the Schwann cell wrapping itself around the

axon and protruding to allow the wrapping round the axon of a sheath of myelin, a laminated lipid structure, which facilitates nerve conduction. Between each individual Schwann cell there is a small gap which is named the node of Ranvier.

Astroglia (astrocytes) are the main structural element of the CNS. They are profusely branched and form a supporting matrix for neural elements. They particularly envelop the neuron in the region of synapses giving rise to speculation that they have a role in insulation. The remaining neuroglia are the microglia which are small phagocytic cells which may be in a state of flux with cells of the lymphoreticular system.

2.2 Electrical conduction in nerve cells

The process of conduction of information within the nervous system is dependent of the capacity of nerve cells to undergo electrical changes as a means of communication. The predominant extracellular ions in the body are those of sodium and chloride. The predominant intracellular species are salts containing the potassium ion. The axons of neurons are capable of generating an action potential, i.e. a change in electrical potential difference, by manipulation of these balances of ionic species across the axonal membrane. The resting state consists of a negative inside to the cell with a large potential difference across it. This is the resting potential, RP. There is a theoretical sodium equilibrium potential (ENa) which is a positivity due a balancing of the intracellular and extracellular sodium concentrations with a net influx of cations. There is also a theoretical potassium equilibrium potential (EK) (negative) due to a net efflux of potassium to balance intra- and extra-cellular concentrations.

The action potential

Much work has gone into the generation of the Ionic Theory of the Action Potential. Studies with the ubiquitous giant Squid axon have shown that changes in membrane potential are reliant on the sodium ion with the rate and extent of rise of the action potential determined by the concentration of extracellular sodium. When a sufficient stimulus is applied across the membrane there is a large increase in membrane permeability to sodium causing sodium influx and a rise in membrane potential to a positive value close to the equilibrium potential for sodium. The ENa is not reached due to a leak of other ions. Sodium permeability then stops and potassium

permeability rises rapidly resulting in a rapid repolarisation to internal negativity. As the potassium permeability remains high and the sodium permeability returns to normal there is an overshoot past the resting potential to near the EK before the axon returns to normal. This is demonstrated in figure 2.2. There is a period of refractoriness when the axon is unable to respond to another stimulus and this relates to the period until the membrane permeability has returned to normal. In a single axon the threshold is that stimulus necessary to create the degree of membrane depolarisation to initiate an action potential; a so-called all or nothing response. The intensity of the stimulus will dictate the amplitude of the response up to a point at which maximum response has occurred. In the case of a whole nerve containing several types and sizes of axons the threshold is the current needed to stimulate the most sensitive fibres. The maximal level is that at which all fibres are recruited and further increase in stimulus intensity brings no further changes. The compound action potential is the name given to the summation of response of a nerve with different axonal elements within it. In a long nerve or pathway with more than one fibre type within it then there may be more than one time for arrival of the electrical signal at the receptor area due to conduction of the impulse along fast and slow fibre types.

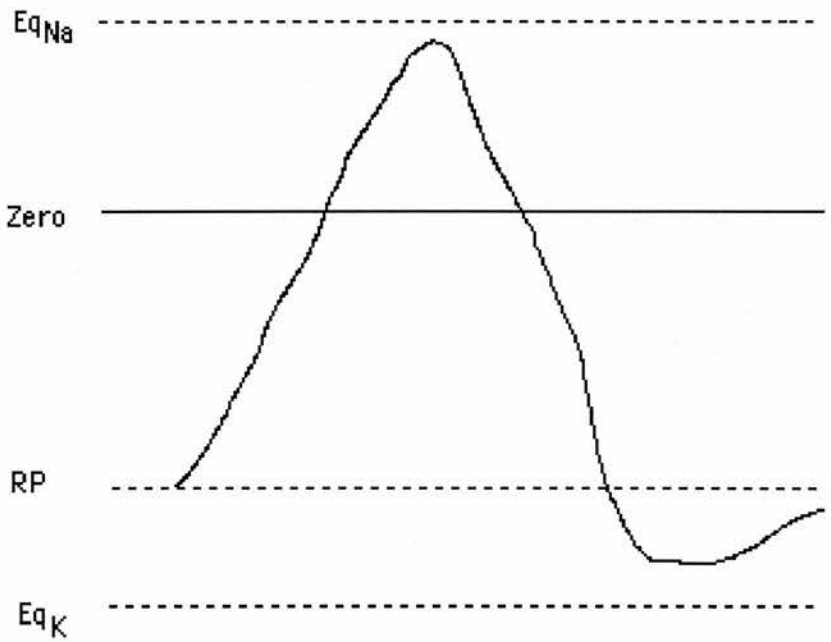


Fig 2.2 Permeability changes during an action potential

Conduction along a nerve is simply the process of generating an action potential at successive locations along the nerve axon. In an unmyelinated nerve a voltage gradient is created at one end when it is stimulated and this causes current flow resulting in the propagation of a wave front of action potential along the nerve. A different situation occurs in the myelinated nerve because the layer of myelin prevents the membrane changes occurring except at the nodes of Ranvier. Therefore, an action potential can only occur at nodes and the conduction jumps from node to node resulting in most of the conduction being as a result of direct current flow which is faster than progression of an action potential. Myelinated fibres have faster conduction time than unmyelinated fibres and the rate of conduction for a given type of myelinated fibre is determined by the distance between nodes. It has also been shown that larger fibres conduct faster and have lower thresholds for stimulation.

There are therefore a number of factors which may affect nerve conduction in a peripheral or central nerve. As has been discussed above, larger fibres conduct faster as do those that are myelinated. Temperature also has an effect on both threshold and conduction (Jack et al 1975). At lower temperatures there is a higher threshold for initiating an impulse and slower conduction along nerves. There is a curve which flattens out so that the effects of temperature are not marked in the range of 33^{o}C to 38^{o}C which would be encountered in normal human physiology. Above this range repolarisation begins to occur sooner and sooner eventually making the conduction of an impulse impossible.

Other factors affecting nerve conduction with particular relevance to this study of evoked potentials in immature subjects are discussed in chapter 2.5 and 2.7.

Types of fibres

There are a number of types of fibre contained within the nervous system. Each has its differing characteristics which make it particularly suitable for specific tasks. The fibres are divided up into A, B and C; and the type A fibres are further subdivided into types alpha, beta, gamma and delta. Their characteristics are listed in table 2.1.

Types A and B are both myelinated fibres and are therefore faster conducting with the speed proportional to size. The larger type A fibres are found typically in spinal nerves. There is little difference between small type

A and type B fibres. Type C fibres constitute many of the sensory fibres of peripheral nerves in the adult human and all of the postganglionic autonomic fibres. Peripheral nerves contain groups of fibres of differing types and differing functions.

Table 2.1 Types of nerve fibre.

Type of fibre	Diameter (μm)	Conduction velocity(m/sec)	Duration of spike (msec)	Function
A alpha	1.3-2.2	70-120	0.4-0.5	Motor, muscle proprioception
A beta	8-13	40-70	0.4-0.6	Touch, pressure, movement
A gamma	4-8	15-40	0.5-0.7	Touch, motor to muscle spindles
A delta	1-4	5-15	0.6-1.0	Pain, temperature, pressure
B	1-3	3-14	1.2	Preganglionic autonomic
C	0.2-1.0	0.2-2.0	2.0	Pain, itch, smell. Postganglionic autonomic

2.3 The somatosensory system

The somatosensory system is that specialised part of the sensory nervous system that deals with the transfer of information relating to the modalities of touch, pain, joint and position sense. It consists of peripheral sense organs located in the skin, muscles, joints and viscera which relay impulses along peripheral nerves and distinct neural pathways in the cord, medulla and brain stem to the primary somatosensory cortex which is situated in the post-central gyrus. Each of these elements of the pathway undergo profound growth and development both in size and functional complexity during the major period of neural development that occurs during the antenatal period and in infancy.

Firstly the mature pathway is described before a discussion of its development along with that of the nervous system as a whole.

The pathway

In response to stimulation the sensory system conducts an electrical impulse to the cortex through the somatosensory system. Conduction is mainly, but not all, through large well myelinated 'A' fibres which are rapidly conducting and mainly carry sensory modalities of touch, pressure and proprioception. 'A' fibres also take part in the conduction of pain and thermal sensations although these modalities are primarily carried by relatively slowly conducting unmyelinated 'C' fibres. The impulses therefore travel along peripheral mixed sensory nerves towards the spinal cord. As they enter the cord the various fibres from a particular peripheral nerve tend to regroup according to their function. They make synaptic connections with cells in the spinal grey matter. Some of the touch fibre pathways, with most of those relating to proprioception, position and joint sense, then travel from positions medial to the ipsilateral posterior grey matter in the dorsal columns as long tracts to the nucleus gracilis or cuneatus in the medulla where they cross the midline to the contralateral medial lemniscus. A second group of fibres mainly concerned with touch also enter the most lateral part of the posterior columns but only ascend for a few segments before entering the posterior horn of the grey matter and synapsing. These axons then cross the midline near the central canal and run upwards in the ventral spinothalamic tract and in the spinoreticular tract. The fibres in the tracts lie nearest the grey matter on first entering that tract. Still further collateral fibres from the peripheral sensory nerve will synapse on entering the cord and connect with neighbouring segments or with motor neurons or neurons of the autonomic nervous system to take part in spinal reflex activity.

The pain and temperature fibres run a similar course to those of the touch modality except that when crossing the midline they travel to the lateral spinothalamic tracts. These sets of fibres then come to traverse the brain stem on the contralateral side to their origin and travel as the medial lemniscus to the thalamus. Within the thalamus they synapse in the venteroposterolateral (VPL) nucleus. Thus the spinothalamic, trigeminothalamic and quintothalamic tracts synapse in the VPL nucleus of the thalamus. Fibres are also dispersed from the long tracts to the reticular formation and the superior colliculus to take part in higher reflex activity.

By the time sensory fibres have ascended to the thalamus they are grouped functionally. The axons arising from neurons situated within the venteroposterolateral nucleus of the thalamus then sweep round the lateral

ventricle within the periventricular white matter as the thalamocortical radiation and up to connect with neurons of the primary somatosensory cortex in the post-central gyrus. There are also fibre pathways carrying the same information to areas of the precentral gyrus as will be discussed below. The thalamocortical radiation therefore provides sensory input to Brodmann's areas 3, 1 and 2 in the postcentral gyrus. Within the primary somatosensory cortex there are then interneurons to other associated areas and to other cortical areas. The sensory messages are thereby relayed to other relevant cortical structures.

2.4 Development of the nervous system

This process starts in very early embryological life and continues well into childhood. However, much of the post-natal change consists of maturation and most of the formation of structures and interconnections occurs pre-natally. The development of the system involves a number of processes with different ones prominent in certain areas at certain times (Altman and Bayers 1988). There is cell proliferation, cell migration, cell growth and differentiation and also the processes of cell degeneration and cell death. These constantly shape the nervous system as it grows and develops its intricate structure and function.

The nervous system starts to develop in the first 20 days of gestation by forming the neural plate as a structure developing from ectoderm in the midsagittal line (Lemire et al 1975). This is essentially a single layer of neuroepithelial germinal cells on the dorsal surface of the embryo. The neural plate proliferates to become the neural groove whose sides are the neural folds and the most dorsal part is called the neural crest. Fusion of the folds begins in the upper cervical/hindbrain region towards the end of the third gestational week and proceeds rostrally and caudally to be complete in 7-10 days. The neural crest cells will subsequently migrate to form such structures as the sensory root ganglia, postganglionic neurons of the autonomic nervous system and Schwann cells.

The early identification of which are sensory nerves is difficult in the embryo. However, the first spinal ganglia fibres to connect with the developing cord do so at around 30 days (Lemire et al 1975). Over the next 10 days or so they mix with the motor root fibres and then from 8 to 14 postmenstrual weeks they extend distally within the developing fetus. Firstly there is sensory connection to the face, then to the extremities of the

upperlimb and finally the extremities of the lower limb are reached by about 2.5 fetal months. The fibres initially form plexuses in mesochyme but fibre endings are not found within ectoderm until 2.5 months. The nerve endings and sensory organs then develop over the next few months with the sensory endings being complete by term. The initial mixed bundles of axons become true peripheral sensory nerves and myelinate in the second half of gestation.

Each individual area of central nervous system (CNS) has its own timing and sequence of events and processes; with an early general caudal to rostral trend. The brainstem sets up its circuitry vital to basic existence in relatively early prenatal life whereas higher function 'wiring' may not fully differentiate until postnatal life.

The spinal cord has a ventral to dorsal sequence of proliferation. Cells cluster initially and then begin to subdivide into defined groupings. Posterior and anterior horn cells connect by around 50 days and at 65 days the dorsal spinocerebellar tract can be identified. Around this time apparently isolated unipolar and bipolar sensory ganglion type cells can be seen. These cells appear to be transitory and may assume functional organisation or may undergo degeneration and death (see below). The first synapses are seen at 77-91 days and the cord pathways develop along with the long tracts and the cord assumes mature organisation by 140 days.

Neuroblasts tend to be formed before glioblasts (Sidman and Rakic 1973) and most neuroblasts are formed by 24 weeks gestation, although neurogenesis does continue beyond this point. The cerebellar neurons, in particular, develop mainly in postnatal life but the Purkinje cells and deep cerebellar nuclei do begin to form prenatally. The important periventricular area of the cortex has major gliogenesis from term to two years of extrauterine life (Dobbing 1970).

The neuroepithelium lining the primitive neural tube is very active with frequent mitoses occurring predominately at the lumen. The 'offspring' of this ventricular germinal matrix move outwards to form an intermediate zone where they differentiate into neuroblasts and a subventricular area of proliferation (Sidman and Rakic 1973, Altman and Bayers 1988). Once they leave their germinal matrix, cells migrate and begin to differentiate losing their proliferative capacity. Some cells travel short distances but others undergo considerable migration. There are a number of patterns with some cells moving en masse from one germinal matrix to a common destination, so called accretion, as in layers II to IV of the cerebral cortex (Berry and

Rogers 1965). Other patterns are convergent when neurons converge on an area from a number of different origins as in the cerebellum (Altman 1982); and divergent when cells migrate from a common source to different sites.

At their site of function neurons then undergo differentiation and maturation to prepare them for that function. There is often a period of rapid manyfold growth of the soma but also growth of the processes with increase in size and complexity of the dendritic tree and dendritic spines (Marin-Padilla 1970). Dendritic differentiation is then the major and vital process which lasts many months and is strongly influenced by patterns of afferent connection and their degree of activity (Greenough and Chang 1988). The dendritic connections established will dictate future interneuron communication and therefore nervous system function.

Axonal projection is vigorously pursued by neurons and there is a theory initially put forward over 60 years ago by Cajal (Translated into English in 1959) that marked overproduction of axons and axonal connections takes place. Many axons then undergo degeneration and cell death with those retained being those with appropriate neural activity. There is evidence compatible with an overproduction of synapses in the primate (Rakic et al 1986). Retained axons increase in diameter markedly and myelination occurs proportional to the growth in diameter.

2.5 Myelination of the newborn brain

One of the most important determinants of the electrical potentials generated in the somatosensory system is the speed of conduction of the somatosensory pathway. The speed of conduction is determined principally by two interconnected factors, the size of the fibres and the degree of myelination. It has been shown by nerve conduction studies (Wagner and Buchthal 1972) that the degree of myelination in early life is related to the post-conceptual age (gestational age + postnatal age) rather than just to postnatal age. This is because the incident of birth appears to have no effect on the progress of myelination unless this incident leads to pathology which affects myelination. Studies of SEP provide further evidence for this (Klimach and Cooke 1988a).

The pattern and occurrence of myelination is fascinating in that it starts when a nerve fibre reaches around 1 μm diameter and continues as the fibre increases in diameter as the thickness of myelin relates to the fibre diameter. The process of myelination is described in cycles within a set of neurons.

The length of the myelination cycle will be determined by the rate at which the individual neurons in a tract or set of fibres reach the critical diameter of 1 μm and the length of time they continue to grow. Short cycles will occur in tracts which all reach 1 μm at the same time and do not get much larger and long cycles occur when the cells reach the critical size over a longer period or grow considerably. Examples of fibres with short cycles are motor roots, visual and acoustic pathways and those with longer cycles include the reticular formation and the great cerebral commissures (Yakolev and Lecours 1967).

The process of myelination partly follows the organisation of the CNS by function (Larroche 1977) probably because this reflects the maturation of fibre size and development. Yakolev and Lecours (1967) have shown from post-mortem study of 200 brains that, in general, myelination proceeds in a rostral direction. Their view of the direction of myelination is supported by work reported by Rowe (1982). Sensory root fibres begin to show myelin at the end of the fifth fetal month but do not complete the process until about 5-6 months after term. The medial lemniscus commences myelination in the sixth fetal month and this process takes until over one year in age to be completed. By the eighth fetal month myelin is beginning to appear in the thalamus and in the lemniscal connections but that part of the somatosensory pathway is not completely myelinated until eight months of postnatal life. These authors further showed that the thalamocortical radiations have the widest differences in myelin development, normally beginning at around one month after term, often virtually complete by one year but possibly continuing up to about four years of age. Growth in diameter and full myelination of the peripheral nerves is completed by 5 years of age. In the CNS, although myelination begins at 18 gestational weeks and is at its most active phase in infancy, final axonal size and myelination may not be achieved until adult life.

The work of Rorke and Riggs (1969) in their study of 107 brains of term and preterm infants largely confirms the above. In the 23 term specimens the spinal cord pathways were all well myelinated as were the fasciculus cuneatus, nuclei gracilis and cuneatus and their tracts through the medulla. The projection to the medial lemniscus was also heavily stained for myelin but the myelin fibres terminated in the VPL nucleus of the thalamus. Virtually no myelin was found rostral to the thalamus.

It can therefore be deduced that over the late stages of pregnancy and early post-natal life cycles of myelination are in progress in the somatosensory system from the sensory organs up to the thalamus but that in some more caudal parts all fibres are still not myelinated. The thalamocortical radiations reach the size for myelination in post-natal life.

2.6 Development of the cerebral cortex

The cortex begins its development on day 33 of gestation when the walls of the prosencephalon evaginate. Then begins the process by which the undifferentiated neuroepithelium becomes the cortex. On day 35 cerebral vesicles are formed and primitive fibres, perhaps from the thalamus or mesencephalic tegmentum, pass into them. There is no recognisable structure to the cortical tissue before the arrival of these fibres (Marin-Padilla 1970). The subpial marginal zone neurons begin to differentiate to provide a basic cortical organisation with synapses, receptors and neuropeptide activity (Marin-Padilla 1988). It is not known whether this primitive neural network is a temporary arrangement to allow the process of interconnection to be established or whether it acts as a framework for the eventual complexity of the maturing cortex.

The cortical plate grows within this primitive neural network from 54 days. It will eventually produce the cells of all six layers of mature cortex. It splits into a superficial lamina from which cortical layer I will develop and a deep lamina which will eventually produce subcortical white matter. There is a proliferative zone in the periventricular area (Sidman and Rakic 1973, Marin-Padilla 1988) from which cortical neuroblasts migrate to form the lower borders of the cortex. The cortex is laid down from inside to out so that cells have to migrate past ones already laid down on their way to their destination. New afferent fibres arrive at 15 weeks and appear to stimulate differentiation of cortical layers VI, V and IV. Further arrivals have a similar effect on subsequent cortical development with layer III apparently related to the arrival of interhemispheric fibres and layer II with intracortical connections.

Rapid development of dendritic trees and synapse formation within the cortical plate appear to be associated with the arrival of the afferent input, the earliest synapses within the human fetal cortical plate being recognised at 23 weeks gestation (Molliver et al 1973). These processes then continue throughout late fetal life and into the postnatal period.

2.7 Effects of developmental changes on electrical activity

The changes described above in terms of neuronal size, soma size, the dendritic tree and synaptic connections and axonal size and myelination have important effects in neurophysiological function which are likely to affect the recording of evoked potentials in the immature subject. There is a relationship between soma size and axon size such that neurons with a large body have large axons and small bodied cells have small axons (Cajal 1909). In general the susceptibility of neurons to discharge varies as a function of their size (Henneman 1957).

Studies with cat neurons (Henneman et al 1965) have shown that the threshold for excitation of the soma will increase with increasing soma size. This is because the resistance is chiefly determined by the membrane. The smaller the membrane surface area the greater the resistance and therefore a smaller threshold current is needed to cause a sufficient voltage to open the Na channels and cause an action potential. Thus smaller neurons have low thresholds for stimulation and large neurons have large thresholds. This allows the sequential recruitment of larger and larger neurons as the stimulus is increased. The axon functions simply as an electrical conduit with its resistance inversely related to its diameter. Therefore a larger axon has a lower threshold to conduction of an externally applied current (Kernell 1966). Other studies, also with cat neurons (Rall et al 1967), show important changes in conductance with change in the ratio of dendritic tree to soma. Immature neurons have slower rise time, longer duration and lower peak amplitude excitatory and inhibitory postsynaptic potentials than do more mature cells (Purpura and Shofer 1972). This may be accounted for by the temporal dispersion of impulses and the predominance of axodendritic synapses with the relative paucity of axosomatic synapses characteristic of the developing neuron (Rall et al 1967). Spike potentials are also longer in duration in immature cells probably reflecting differences in the ionic processes occurring in the action potential. The other major factors affecting nerve conduction are obviously the previously described changes in axon diameter and progressive myelination with consequent changes in threshold for activation and increase in conduction velocity.

The progressive development of different cortical layers is likely to be a factor that accounts for changes observed in evoked activity, as it is thought that excitatory postsynaptic potentials of pyramidal cells are the most significant events in generating the electrical activity which contributes to

cortical evoked potentials (Mitzdorf 1985). From around term to three postnatal months a tremendous proliferation occurs in the size and complexity of dendritic trees in cortical layers.

Animal studies (Bernhard and Meyerson 1972, Persson 1973) have demonstrated that changes in cortical evoked potentials occur in parallel with the cortical morphological changes. The first sheep fetal SEP occur midway through fetal life and consist of a positive deflection, possibly from afferents still short of their destination with no sign of intracortical activity. The development of positive-negative voltage swing in the SEP correlated with the appearance of cortical layers IV to IV and increasing differentiation of the potentials mirrored cortical differentiation. Cortical neurons also have slower rise time and longer duration of excitatory postsynaptic potentials (Purpura and Shofer 1972) and this would explain the longer duration of the voltage swings seen in EPs in immature subjects. Development of cortical interconnections will theoretically allow the elaboration of the response and increase in wave complexity. As the cortical pathways mature so their neurons will myelinate and an increase in speed of conduction will also effect the response seen.

2.8 Conclusions

It can therefore be seen that there is an ongoing process of cortical, brain stem and spinal cord development in structure, organisation and function throughout fetal and postnatal life. This has profound implications for the study of evoked potentials in such subjects. Further detail relevant to the measurement of evoked potentials in immature subjects is discussed in chapter 6 along with the results in this study of EP recording in the term newborn.

Technical aspects of Somatosensory evoked potential recording

Having described the somatosensory system and its components which are assessed by the technique of SEP this chapter deals with the theory underpinning the technique of collecting evoked potentials. The author will describe the electrical events being assessed, then the method by which SEP are collected and the technical aspects of signal processing and data analysis. There follows an explanation of the equipment used and basis for decisions regarding the methods employed in the study described by this thesis.

3.1 Principles of recording electrical activity

The aim in measuring SEP is to record faithfully the electrical events occurring in the somatosensory system and process the signal such that it can be interpreted.

The evoked potentials to be measured are due to current shifts occurring within the pathway and its surrounding structures. In chapter 2.2 the ionic changes associated with that neuron activity were described. The depolarisation of axonal membranes manifests as a positive potential field in advance of the direction of propagation with the recorded amplitude inversely proportional to the square of the distance from the generator to the sensor and directly proportional to the solid angle subtended by a cross section through the nerve trunk. A more intense but less clearly directed negative potential can be recorded at a perpendicular plane to the depolarised region of the nerve. This gives rise to the concept of a volley of electrical charge coursing along a group of similar fibres within a nerve or a pathway. This will give rise to swings in electrical polarity at a measuring electrode as the volley approaches and passes the 'point of view' of the electrode. This explains the concept of a dipole, or swing of positive-negative or negative-positive charge, due to neuronal activity and the passage of an electrical 'message' across a synapse. It is these volleys of electrical activity that are to be measured.

The collection of EP data involves the recording of the electrical activity between pairs of electrodes. As described, the events being measured are electrical signals which are not just discrete pinpoint happenings but swings of electrical polarity occurring at several points within the cortical layers or at synapses or nuclei. The principle is that one electrode is theoretically a reference electrode and is usually chosen to lie at a point at which no

significant relevant electrical events should occur. The other, the 'active' electrode is normally chosen to lie in a position so as to collect information from a certain part of the pathway. In this fashion the signal collected is that of a difference in electrical potential (voltage) between active and reference electrodes. In order to be able to discriminate the EP signal from the unwanted electroencephalogram and electrical "noise" some form of signal processing is necessary. The theoretical basis for positioning of electrodes as used in this study is discussed below in chapter 3.3 and the actual work done on position is described in chapter 6.3.

3.2 Signal Processing

The signal is collected by the electrode pair and fed to an amplifier. It is then amplified and filtered before being processed to a form that can then be analysed. These steps are now discussed.

Collection

An evoked potential recording system for SEP is a means of collecting information from a number of electrodes at the same time so as to give the maximum desired information at different levels of the pathway on potentials generated in response to the somatosensory stimulus. The system is set up to organise the collected information for subsequent analysis. The information is collected from the sited electrodes and fed into a 'headbox' as pairs of signals. Each pair of signals consists of an 'active' and 'reference' signal as described above. Each pair serves as a separate channel for processing and analysis. If a common reference electrode is being used then its signal is fed to each channel. The number of channels is dictated by the number of different levels of the pathway from which EP data are required. The information is collected for a set period of time (epoch, sweeptime) and this sweeptime is set so as to include the potentials to be studied. In addition, most systems allow the epoch to begin either at the time of the given stimulus or at a set number of msec before or after the stimulus. The use of an epoch beginning before or after the stimulus allows elucidation of any stimulus artefact or its eradication. There is an important limitation on the length of the sweeptime which relates to the way in which information is collected. In practice, an EP system collects a set number of points of electrical potential, bin widths, within each sweep e.g. 1024. If, for instance, a sweeptime of 100 msec is chosen then the bin width is c.0.1 msec but if the

sweeptime is increased to 400msec the resolution is less good as the bin width is now 0.4 msec. Therefore the sweeptime needs also to be decided in view of the resolution of signal required in the recording of EP data.

Each channel has its electrical sensitivity set so as to display a certain value of microV/division. In practice the channel sensitivity is set so that the maximum expected signals fall at 50% of the sensitivity to allow for variation in the signal without distortion.

The input board of the system therefore serves as a set of separate channels each set up on the basis of the arrangement of epochs and electrode pairs best to demonstrate the desired information. The input board then has 3 functions.

(a) To discriminate potential changes that appear at the electrodes

(b) To reject artefact

(c) To increase the amplitude of the potentials

Function (a) is achieved by subtracting the voltage at one electrode from that at the other and thereby obtaining the potentials which have a different voltage and timing at one electrode than the other. As theoretically the active electrode should be closer to the desired potentials than the reference electrode but each should be equally affected by unwanted signals this should contribute to the rejection of artefact, function (b). This function is also served by the subsequent signal processing and averaging, described below. The resultant voltage is then processed, amplified and displayed on the oscilloscope screen of the EP system. The system can also be programmed to reject information when the input voltage exceeds a certain value normally contributed by muscle action potentials and thereby further reduce unwanted information.

Averaging and filtering

Perhaps the major difficulty in measuring evoked potentials is that despite the manoeuvres mentioned above there is the fundamental problem that a small signal still has to be extracted from a larger volume of ongoing EEG activity and spurious electrical "noise". The signal of perhaps 1 or 2 microvolts is buried within a mass of electroencephalogram, electrocardiogram, myogenic action potentials and environmental interference such as 150 Hz emitting strip lights. This is one of the difficulties which has hindered progress in assessing their usefulness in neurology.

Previously large equipment and poor electronics made measurement in electrically hostile areas such as a neonatal intensive care units very difficult but the techniques of filtering and signal processing can at least partly alleviate these difficulties. Use can be made of a specialised evoked potential system dedicated to this purpose or a general computer can be specifically programmed for these functions.

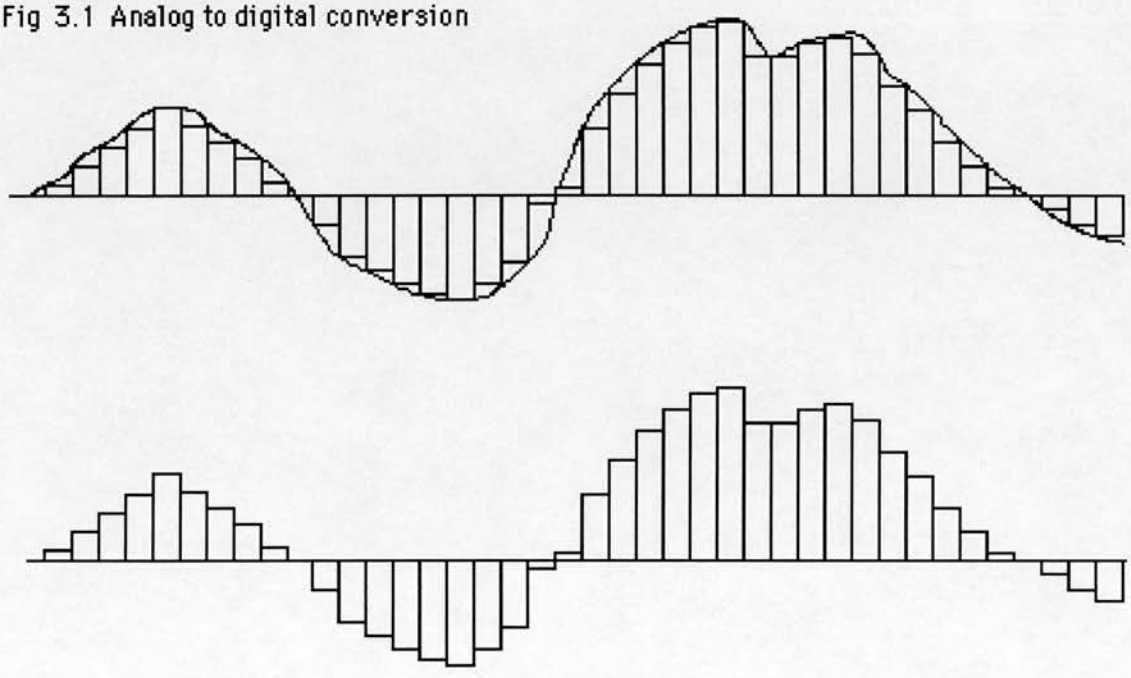
Every evoked potential system has a filtering arrangement in order to discard spurious "noise" which lies outwith a defined frequency range. This creates a 'bandpass' or 'bandwidth' of frequencies within which electrical information is collected and further allows the clarification of the signal and the suppression of noise. The bandpass has to be set so as not to affect the frequencies of the evoked potentials themselves. Short duration fast rise and fall waves which may last only 5 msec or so would be filtered out if the upper filter was set to a frequency of 200 Hz or less. This would make the measurement of cervical potentials quite impossible. It has been shown (Desmedt et al 1974) that major distortion of waveforms can occur if the bandpass is too narrow. It is necessary for the valid collection of SEP data that the bandwidth extends up to at least 1500 Hz. There is a great temptation to lower this frequency to help reduce noise but marked distortion may occur which will cause corruption of the SEP masking faster components of the waveform and causing the loss of potentially useful information. Each filter is designed to attenuate the information at one end of the frequency range. It begins its action well before its given value by reducing the signal by an ever increasing amount as the frequency rises. Therefore a filter designated 1500Hz(-6dB) will already have attenuated the signal by 6dB at 1500Hz. This is equivalent to a 50% drop in amplitude with a doubling of frequency. For this reason it is important to have the bandwidth extending as far beyond the EP data as possible. Use can be made of a 50Hz 'notch' filter to alleviate possible problems with mains interference. This functions by reducing the amplitude of a very narrow band of frequencies around 50Hz. This can, however, include important parts of the electrical evoked potentials of interest and is best not used. Analog filters can also induce a phase shift effect on EP data. Low frequency filters can make slow waveforms appear earlier and high frequency filters placed too low can lengthen latencies of faster deflections. Digital filters can be employed on the digitised signal before or after averaging and can give a very sharp cut-off and avoid phase shift.

The earliest work on SEP relied on superimposition of several response traces for the extraction of the signal (Dawson 1950) from the noise but modern averaging allows greater refinement. The technique of averaging, as the name implies, consists of taking a large number of epochs of electrical signal, adding them all together and then dividing by the number of epochs to get an average result.

Firstly the system has to be programmed to collect the epochs. They can be programmed to begin before the stimulus, with the stimulus or after it, but always in the same relationship. With this arrangement, because the signal should be in a constant relationship to the stimulus i.e. time-locked, it should always occupy the same position within the epoch. The unwanted signals, however, should be randomly distributed within each epoch and so their average over a large number of epochs will tend towards zero. Conversely with the evoked potentials, because their position within each epoch is fixed they are enhanced and so averaging allows one to improve the signal to noise ratio.

The evoked potential system actually achieves this process by firstly recording the electric activity during each epoch. The epoch is then separated into discrete time portions (binwidths) and the signal is converted from an analog electrical signal into a digital one (Fig 3.1).

Fig 3.1 Analog to digital conversion



When this is done for each epoch then simple arithmetic can be carried out to arrive at the average which can be converted back to an analog form for display. The individual analysis periods are called bins or points. As described above, the analysis dwells on each of these short periods for a dwell time or binwidth amounting to a fraction of a second per point. The rate of sampling of points is the reciprocal of the number of points sampled each second. The amplitude of the signal within the bin is converted to a number (digitised) thereby giving a string of numbers each representing a bin as a digital representation of the electrical trace. These are stored as a series of discrete locations or addresses in the computer memory and can be displayed on an oscilloscope or subjected to analysis. Averaging is therefore done arithmetically within each bin. During EP recording using commercially available systems the 'running average' can be viewed on the screen as the data is collected.

Most averaging computers have a set number of channels of electrical activity which can be recorded at a time. In most the number of addresses per channel is constant but in others, if more channels are required the number of addresses per channel may be decreased accordingly.

The number of stimuli needed to adequately separate signal and noise depends on the voltage of the signal and the voltage and character of the noise encountered. There are a number of important theoretical and practical determinants of this parameter.

The number of responses collected need to be enough that successively averaged EPs differ minimally from each other. This can be checked by comparing successive traces. In SEP measurement the cervical potentials, which are relatively 'far field,' are of low voltage and have to contend with much noise in the form of cervical muscle action potentials, may need 1000 or more stimuli whereas in measurement of 'near field' cortical potentials where noise is less of a problem only 200-300 stimuli may be required.

Theoretically the ratio of amplitude of time-locked components, signal, to unrelated components, noise, should determine the number of epochs required. The relationship of S/N ratio to number of epochs is not linear. The number of responses increases with the square of the ratio. Averaging therefore improves the S/N ratio by a factor equal to the square root of the number of epochs. If the signal varies or the noise is not random then this relationship is distorted. However, this rule gives a rough estimate for clinical purposes. Therefore a 5μV signal in 20μV of noise has an S/N of 1/4 and

with 256 epochs will have an improvement of 16 times giving an S/N of 4. In many cases in EP work the S/N starts off less favourable than 1/4. The number of epochs that can reasonably collected place practical limitations as a two fold increase in S/N means double as long to collect the epochs. This shows the great importance of avoidance of interference and the correct use of filtering to reduce the noise as much as possible and therefore to present the EP apparatus with the most favourable initial S/N ratio. It is also important to avoid long acquisition times as this may cause variation in signal and also deviations in the random nature of the noise.

The sweeptime is decided by the likely latency of desired information but must make provision for delayed response. Because most computer averagers work on a binary system the actual sweeptime is normally 1.024 times the stated time on a decimal system. The analysis period is normally chosen and this dictates the dwell time as the number of points available is usually fixed. However it is possible to dictate the dwell time and number of points and therefore derive the sweeptime from them. If an evoked potential system had a fixed number of 512 points per sweep then in a nominal sweeptime of 100 msec (actually 102.4 msec) each point is 0.2 msec and for a sweeptime of 200 msec the point is 0.4 msec. This has important implications for the resolution of data.

It follows that two requirement are necessary when determining the time characteristics of EP recording. The analysis period has to be sufficient to include the important peaks and the sampling rate or dwell time has to be sufficient to allow representation of the EP peaks and their discrimination from each other. To depict a sine wave digitally a minimum of two points are required per cycle. As a minimum therefore, the sampling rate has to be twice as fast as the fastest sinusoidal component to be resolved in the signal. This critical sampling rate is known as the Nyquist frequency. It only specifies the minimum to identify the fastest sine wave. To accurately delineate any fluctuation within the basic sine wave pattern will require a much higher sampling rate and a greater number of averaged sweeps. If a sampling rate less than the Nyquist frequency is used the sine waves will be falsely represented and this is given the term aliasing.

The amplitude of the recorded wave within a bin is recorded digitally with a set number of digits per address. This string of bits is called a word. The word length is normally 8 bit. This allows 2^8 or 256 discrete steps of amplitude within each address. This necessitates setting the gain within each

channel of recording to allow the potentials to sit comfortably within the range of amplitude response set on the averager unit. Many averagers include the manoeuvre of an artefact rejection option. This most commonly refers to the rejection of sweeps that include voltages outwith the range of amplitude set by the gain setting of the channel.

Other 'tricks' that can be applied to EP traces by an averager unit include smoothing, electronic cursors and addition, subtraction and inversion of traces. Smoothing is a technique whereby high frequency noise components superimposed on the EP can be reduced. The method involves digital filtering such that each point is replaced by a moving mean of the 3 or 5 neighbouring points. This technique may change waveform by reducing the amplitude of short waves compared with long ones. The measurement of latencies can be performed by using electronic cursors that can be run along the trace and give measures of the amplitude and latency of individual points or interpeak latencies if two cursors are available. Finally, the assessment of waveforms can be facilitated by comparisons of channels or runs of averaged traces by adding, subtracting or inverting traces. This is done digitally within the averager and can, for instance, help the assessment of waveform repeatability.

It therefore can be seen that a number of manipulations of the collected electrical information are necessary before it reaches a form suitable for analysis. These are set out below.

1. The correct length of epoch
2. A reasonable number of stimuli
3. Rejection of artefact
4. Filtering which leaves a sufficiently wide bandwidth
5. Averaging

The other factors that might affect the measured response and its assessment are most reasonably discussed as factors affected by the type of subject and situation of actual EP recording and are dealt with in chapter 6.

3.3 System used in this study

The following section describes the basis for the establishment of some of the methods employed in this study. There is also a brief description of the

technical aspects of the actual equipment used with reference to the above theoretical considerations.

Electrode placement

As described above, the collection of EP data involves the recording of the electrical activity between pairs of electrodes. It follows that the placement of the electrode pairs has to be decided carefully in order to measure the desired electrical events. During neurosurgery or in experimental animals it is possible to place recording electrodes in the relevant part of the pathway directly using clips or needles. With surface recording it is only possible to record at some distance i.e. the thickness of meninges, CSF, skull and skin, from the generators of the potentials. It is therefore inevitable that the signal collected at any one time will be influenced by all the electrical activity around it and is likely to contain more than one electrical event and so the overall nature of the signal will be a summation of several events. The positioning of the "active" electrode as near as possible to the part of the pathway from which you want to record is therefore paramount as in that position the desired electrical event will be in such close proximity to the recording electrode that it is most likely to predominate. The position of the "reference" electrode is influenced by the type of study undertaken. It can either be cephalic i.e. near to the position of the 'active' electrode, on the scalp, or non-cephalic and placed at a distance e.g. on the hand contralateral to the stimulated median nerve. The main concern in using a cephalic reference electrode is that it may not be sufficiently far from the evoked potentials to be a truly indifferent electrode. There is no such worry with a non-cephalic reference. The major difficulty however with the non-cephalic reference is a practical one which makes it relatively unsuitable for use in the newborn. Movement is a major cause of artefact and extra 'noise' is encountered due to limb movement in an uncooperative subject. A cephalic reference in a midline frontal scalp position is preferable in the newborn because it is not significantly likely to be contaminated by muscle action potentials. In general most clinical studies utilise cephalic reference electrodes for ease of data collection. It is also necessary for the safety of the subject to place an earth or ground electrode and this helps reduce interference when it is placed fairly near to the recording electrodes.

Another technique that is mainly used in experimental situations is that of 'far-field' recording. This consists of siting both electrodes at some distance to the generators and looking at the electrical events 'from a different angle' and thereby giving a different waveform and allowing for the separation of individual potentials in a different way from usual. This technique has been used mostly in adults in work on the elucidation of the generators of different components of the SEP waveform.

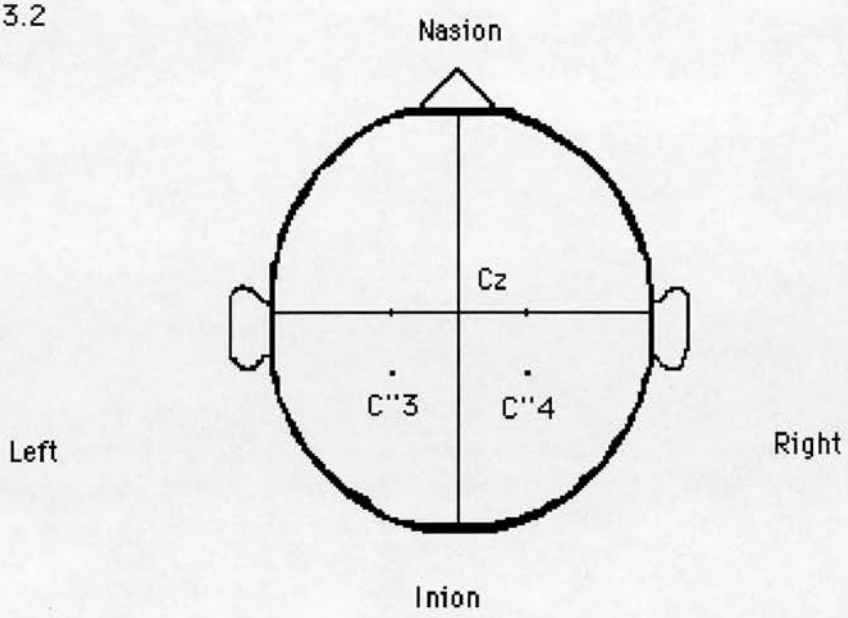
In this study the electrodes used were all silver/silver chloride and fixed on the skin surface. Alternatives include gold electrodes and stainless steel needle electrodes inserted through the skin. It is important to ensure that the impedance is fairly low but more important to ensure that it is fairly equal between electrodes as large differences in impedance may in themselves produce a potential difference between the electrodes.

In order to decide the positioning of active electrodes a decision has to be made as to which parts of the ascending pathway potentials are to be measured from. This may involve the placement of electrodes over Erb's point and over the cervical vertebrae at various levels, of which the second (Cv2) and seventh (Cv7) are most commonly used. This will allow an assessment of peripheral nerve conduction to Erb's point and an assessment of the speed of conduction across synapses into the cord and up the cervical cord. This is not a difficult decision and is affected by the information required and the number of channels available for recording. However, the placement of the surface electrodes to record activity in the primary somatosensory cortex is less obvious.

The position of EEG electrodes is normally described by determination of their relationship to the defined points of the International 10-20 system (Jasper 1957). This system relies on positioning electrodes in defined relationships to fixed points on the head, namely, the nasion, inion and pre-auricular points. The point Cz is located by the intersection of the line between the nasion and the inion and the line between the two pre-auricular points as shown in Fig 3.2 overleaf.

The points C3 and C4 are located 20% of the distance between the pre-auricular points on either side of Cz. C"3 and C"4 denote points 2cm behind C3 and C4 respectively. It is normally from electrodes in these positions that cortical SEP are measured. There is evidence from both adult and paediatric studies that these points do lie over the post-central gyrus and therefore the somatosensory cortex.

Fig 3.2



In a study of 12 adult volunteers (Homan et al 1987), scalp markers were placed at the positions of the International 10-20 system and CT scanning used to correlate their position with underlying brain structures. It was found that C3 and C4 lay over the precentral gyrus in most subjects and in the area serving the territory of shoulder to wrist. Therefore, several centimetres behind C3 and C4 would lie over the somatosensory cortex serving the median nerve. The authors did comment that heads may be very asymmetrical particularly in that pre-auricular points may not be 50% of the way from nasion to inion and this confirmed earlier work by Binnie et al (1982).

Hellstrom et al (1963) looked at the 10-20 system in 28 infants of one week to 13 months of age. They placed disc electrodes on the scalp and took a skull X-ray. From knowledge of the relationship between skull markings and sutures and the underlying brain features they were able to estimate the electrode positions. They found the C electrodes to lie over or just in front of the central sulcus. A different approach by Blume et al (1974) involved the placement of pins through cadaver skulls of six infants of 4 months or less and one 2 year old. C3 and C4 were located over the central sulcus or on the post-central gyrus in the area of lips, face or tongue.

The idea has already been introduced that the events being recorded in measurement of SEP are not pinpoint electrical events. Work by Desmedt et al (1987) with bit-mapped colour imaging (see chapter 4.1) has shown that

the potentials generated in the somatosensory cortex do indeed have a fairly wide distribution and therefore the exact positioning of electrodes is perhaps not absolutely crucial. There is therefore good evidence that the points C"3 and C"4 are appropriate positions for the active electrodes when measuring SEP in infants. Further discussion of this point is undertaken in chapter 6.

Interference

One of the primary methods by which interference is excluded is the ability of the amplifier unit employed to differentially amplify the electrical information received from the electrodes. If the same polarity and intensity of electrical charge is picked up by both the electrodes of a pair they are said to be in common mode and are rejected by the amplifier which only magnifies signals that are applied to the electrodes differentially. This ability to reject signals applied in common mode is the common mode rejection ratio. It is the ratio of the amplifier output produced when a signal is applied differentially to that when it is applied in common mode. It should be at least 10000:1 i.e. 80dB or more in recording of EP.

The ideal situation would be to record EP data in a specially designed environment free from extraneous electrical interference but this is not suitable for study of sick individuals. There are a number of manoeuvres that can be used to minimise the intrusion of spurious electrostatic and magnetic signals during EP recording. Extreme problems can be countered by the placing of an earthed metal shield between the source of interference and the immediate recording area. The electrodes can act as a conducting loop if in the vicinity of a changing magnetic field such as mains electricity and thereby induce interference potentials at 50Hz and its multiples which will then be amplified along with the desired information. This can be minimised by twisting the electrodes closely together or having them in a screened sleeve. Simple changes such as rotating the headbox amplifier in relation to sources of interference are also often remarkably successful.

During the course of this study infants were studied in a side room off the neonatal unit whenever possible to minimise the electrical interference in the electrically hostile intensive care area. A custom cable was designed which bundled the electrode cables together in a screened sleeve and allowed only the 20cm of cable nearest to the infant to be relatively exposed to interference.

The other potent cause of unwanted electrical activity is that of muscle activity with the production of muscle artefact. This is minimised by the study of a relaxed subject.

Averaging and Filtering

Many of the theoretical aspects have already been covered. The Medelec system employed collects the EP data in a "headbox" and amplifies it before employing analog filters applied to the signal before averaging. A notch filter to deal with 50Hz interference was not used. The sweeptime can be selected and there is a fixed sampling rate of 500 points per sweep. The word length is 8 bit, as is common in EP recording, allowing 256 discrete amplitude steps.

The subsequent parameters used (see chapter 6) included a 100 msec sweep beginning at the point of the stimulus, which with the 500 points per sweep gives a sampling frequency of 5000Hz. This should allow good discrimination of data and clarity of wave detail. A bandwidth of 10-3000 Hz was used which would result in the recorded EEG having an amplitude of around 10μV. The anticipated amplitude of the EP waves is around 1μV giving a S/N ratio of 1/10. Averaging 1024 sweeps will improve the S/N by 32 (square root of 1024) and therefore allow good discrimination of the responses from ongoing EEG and 'noise'.

The Medelec unit is capable of displaying the input or the updated average and is equipped with electronic cursors allowing the analysis of waveform and defined latencies to be done electronically on the screen before printing a hard copy of the data.

In chapter 6, which describes the collection of data on the normal SEP in newborn infants, some of the decisions regarding the technical parameters used are discussed.

The uses of Somatosensory evoked potentials

Although somatosensory evoked potentials (SEP) were first described by Dawson in 1947, it has taken some time for them to be used in the investigation of neurological problems in the paediatric population. Most of the early paediatric reports in the 1960s concentrated on normative data, the possible factors affecting the response and the use of the technique for examination of the functional integrity of the sensory system, for example, in spina bifida (Duckworth et al 1976).

In this chapter the normal mature (adult) response and its postulated generators will be described and the uses in adults with particular attention to some of the studies relevant to the current project. Having reviewed the factors which affect the response, discussion will then focus on the work done on SEP in children before reviewing the literature on SEP in the newborn infant.

4.1 The normal adult response

In the description of evoked potentials there are two main features that can be assessed, firstly, the waveform of the response which is of different shape in various structures of the somatosensory pathway and secondly the latency, i.e. the time taken from the stimulus to a defined point in the response waveform. In general, components of an SEP waveform are described (Donchin et al 1977) in terms of their electrical polarity, (in Europe the convention is that the EP recording system is arranged so that negative is an upward deflection on the waveform and positive is a downward deflection) and the latency of a defined point e.g. N20 is the negative wave 20 msec after the stimulus.

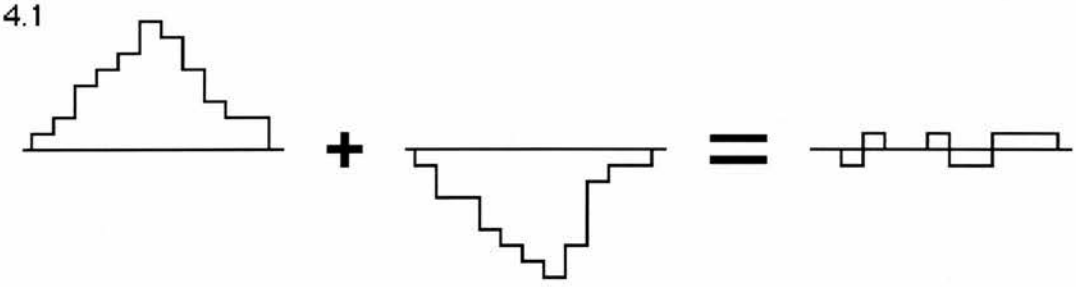
In recent years there has been much work and debate on the subject of the possible neural generators of the adult response. Much of this work has been done using the techniques of non-cephalic reference electrodes (described in chapter 3.1), intracranial monitoring during neurosurgery and the use of bit-mapped colour imaging (described below).

The evoked potentials measured are due to current shifts occurring within the pathway and surrounding structures. As described in chapter 3.1 the depolarisation of axonal membranes manifests as a positive potential field in advance of the direction of propagation with a more intense but less clearly directed negative potential recorded at a perpendicular plane to the

depolarised region of the nerve. These swings in electrical polarity give rise to a dipole, or swing of positive-negative or negative-positive charge, which is recorded by the EP system as a wave of changing voltage.

It might be presumed that the electrical events to be measured are defined electrical polarity changes occurring in discrete areas of neural tissue at exact times after the stimulus given. Unfortunately this is too simplistic a view. The electrical polarity changes in the final measured evoked potential traces are the summation of all electrical events recorded during the sweep time. It follows from the description of signal processing in chapter 3.2 that the digitally recorded value in each binwidth is the electrical potential measured at that point during the epoch. Therefore a large electronegative event relatively far from the recording electrodes may be cancelled out by a nearer electropositive event with exactly the same time course. This occurrence is represented In terms of a digital waveform in Fig 4.1.

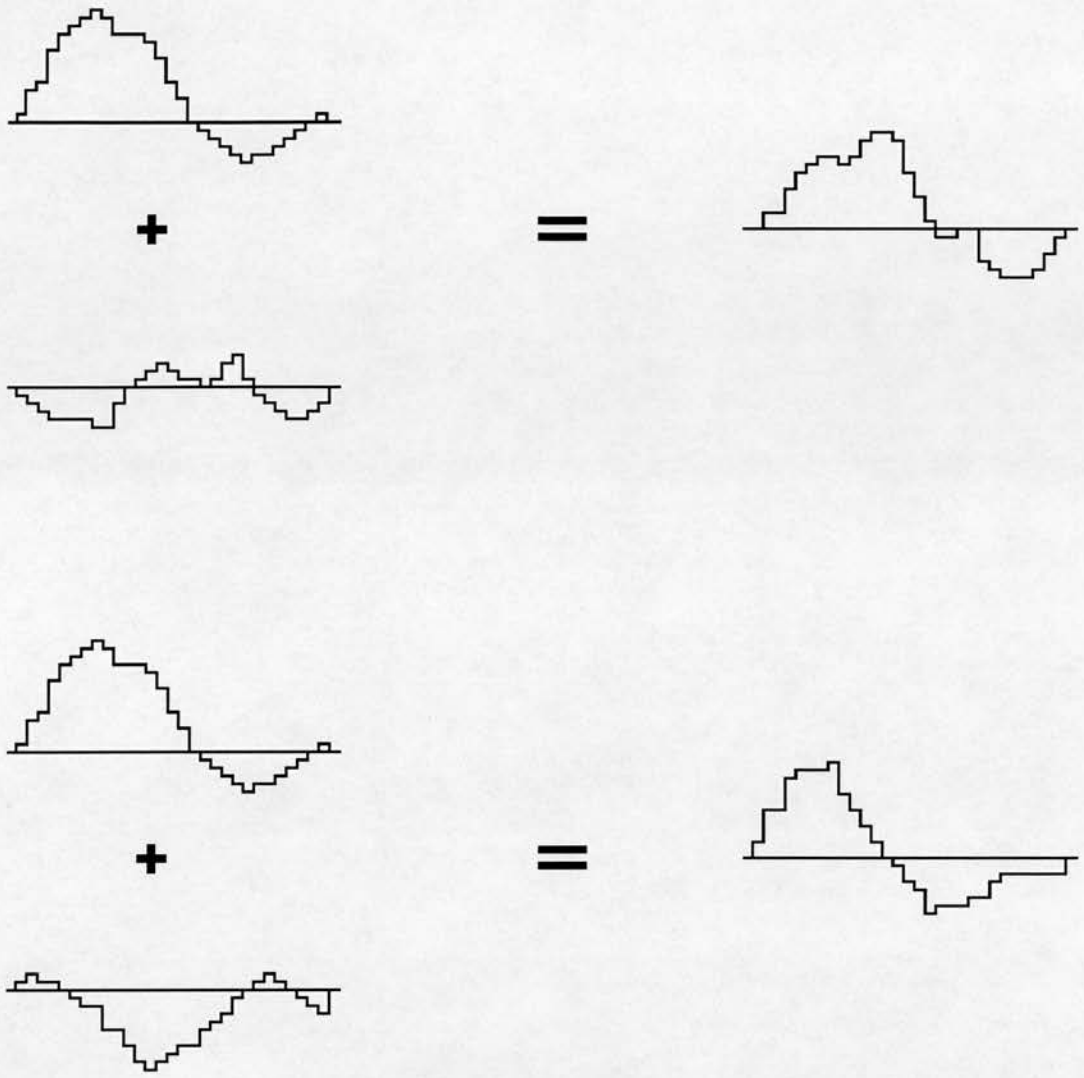
Fig 4.1



If, however, a large negative event close to the electrode overlaps with positive events at different time relationships this will alter the basic form of the electronegative event and the latency value of the peak of that electrical event may be altered as shown digitally in Fig 4.2.

This explains why, despite presumably measuring the same thing (the adult human SEP), different authors may differ slightly in the exact latency and polarity characteristics for SEP waveforms depending on the electrode positions and (as explained in chapter 3.2) different acquisition parameters.

Fig 4.2



The relatively new technique of bit-mapped colour imaging of EP data has added much to the appreciation of the many different events which contribute to the outline of a measured EP trace, especially with regard to the cortical generation of SEP. The technique uses many electrodes over the scalp and gives a printout map whose pattern of colour and intensity are related to the polarity and intensity of the electrical signals received by each electrode. A series of coloured maps are produced for distinct time epochs and can therefore show areas of strong negativity and positivity, their time distribution of occurrence and the evolution and demise of activity in specific cortical areas. These areas presumably correspond to the sites of generation of the different EP components.

As discussed below, there are a number of ways of providing a stimulus to the somatosensory system. Mechanical tapping and direct digital stimulation by touch or electrical means can be employed. Most clinical and research studies employ electrical stimulation of the skin over the median nerve. This allows direct delivery of the impulse to a nerve trunk and avoids any potential difficulty with peripheral receptors. A further advantage is that most of the larger diameter fibres can be simultaneously activated resulting in a stronger and more coherent electrical volley being passed up the pathway and that mainly these faster types of fibre will be involved minimising effects from a 'stuttering' impulse should several different fibre types be recruited.

Stimulation of the mixed median nerve at the wrist results in both motor and sensory fibres being activated. The motor action is expressed by contraction of the thenar eminence muscles giving a thumb twitch which helps to show that the nerve has received adequate stimulation. It has been shown (Ellingson and Ellis 1970) that the sensory threshold lies below that of the motor threshold. It is customary to stimulate just above motor threshold to try to ensure the most uniform recruitment of fibre types. It is possible that if peripheral nerve damage has occurred then the more peripheral the stimulus the more variable the waveform may be due to an increase in temporal dispersion in damaged and undamaged peripheral fibres (Jones 1982c).

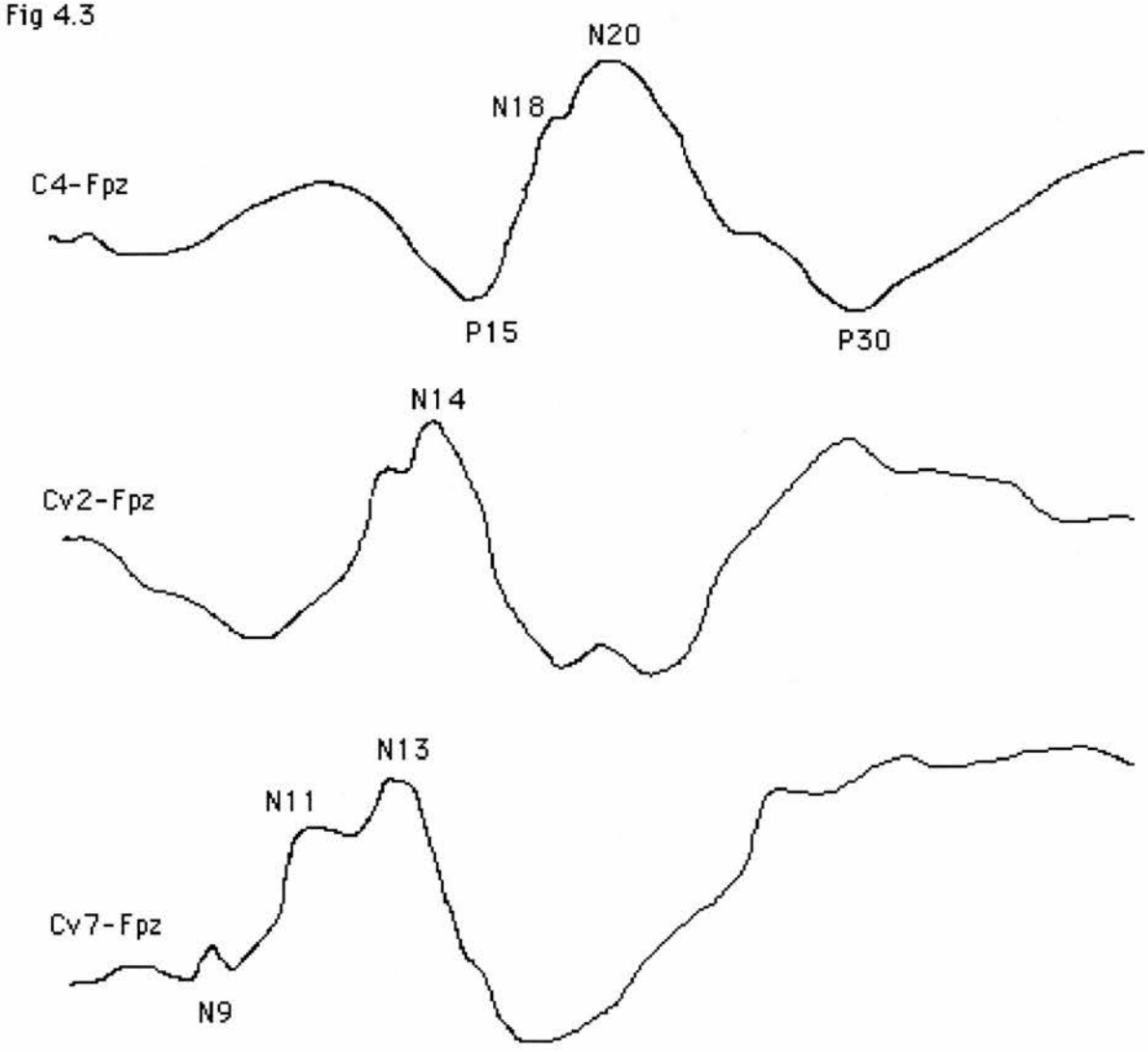
Origins of subcortical components

Fig 4.3 below shows a schematic representation of the normal adult SEP to median nerve electrical stimulation measured at low and high cervical electrodes and the parietal area with a cephalic reference electrode at Fpz (midline frontal). It can be seen that some peaks are present in more than one channel. For instance, the cervical components can be picked up as far-field potentials in 'cortical' traces.

The first EP, which is best recorded from an electrode over Erb's point, is the N9 which is thought to be generated by a travelling wave of current between the axilla and the dorsal roots in the spinal cord, i.e. the brachial plexus potential (Jones 1977, Drechsler 1985, Desmedt and Cheron 1981a). Next is the N11, recorded at the neck, which is probably at the entry of the signal into the spinal cord at the rootlets or posterior column (Jones 1982b, Desmedt and Cheron 1981a), followed by the N13 which is the most prominent of the lower cervical potentials and is possibly a summation of a

number of events post-synaptically in the dorsal horn and cuneate nucleus (Jones 1977, Desmedt and Cheron 1981a). Some authors describe both an N14 and P15 (Jones 1982a) and others only a N14 or P14 (Desmedt and Cheron 1981a) but it would appear that this potential is generated in the medial lemniscus. The N18 potential which can be recorded from cortical electrodes often appears as a notch on the rise to N20. It is thought to be generated in the thalamus or thalamocortical radiation (Desmedt and Cheron 1981b, Drechsler 1985). This is supported by reports of direct recording from thalamic electrodes (Hume and Cant 1978, Fukushima et al 1976) showing potentials around 16 to 18 msec with clear thalamic potentials before N20.

Fig 4.3



Origins of cortical components

In the past there has been dispute about the origin of N20 (Chiappa 1979) but consensus opinion now seems to be that N20 and subsequent potentials described by various authors as P25, P30 and P45 are all cortically generated. However, agreement does not exist as to precisely where in the cortex they are generated. They may be representative of individual electrical events but are much more likely to be the result of the negative and positive electrical swings occurring in various dipolar sources which overlap in time.

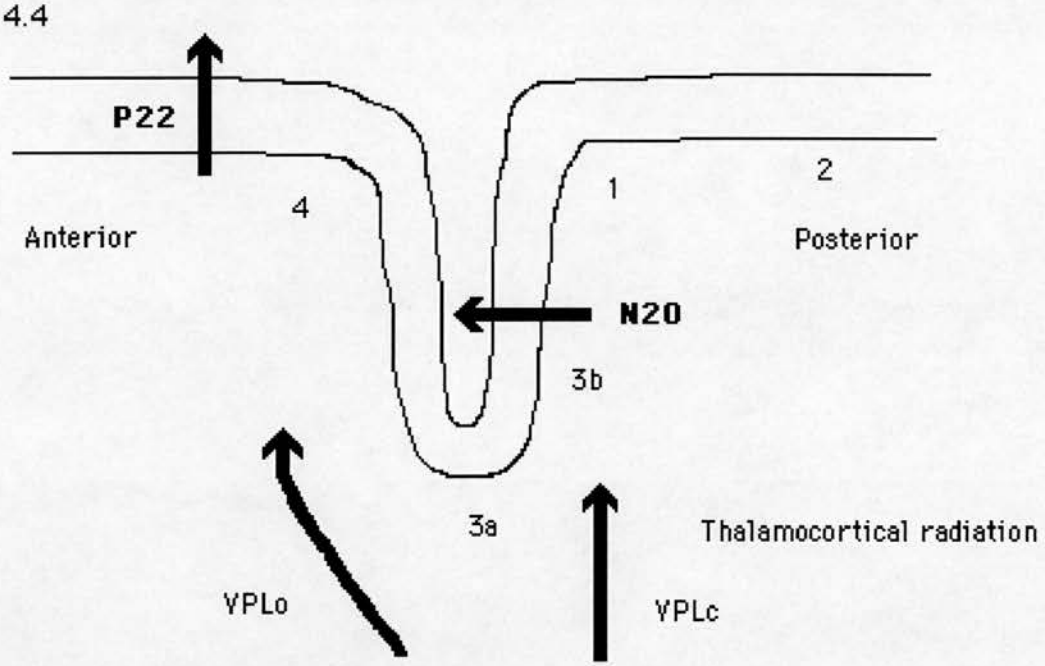
One of the most detailed descriptions (Goff et al 1977) of scalp topography describes 19 components to the SEP beyond the P15 potential. These authors used multiple electrodes to build up isopotential maps of the electrical events following median nerve stimulation. The first negative wave N20 is widely distributed over the posterior quadrant of the scalp contralateral to the stimulated median nerve. A P20 can sometimes be recorded from the anterior quadrant. Broughton has postulated (see Jones 1982) that an N20/P30 dipole is the 'primary' response of the somatosensory cortex. If the volley was firing directly at the electrodes a positive/negative swing would be seen. It has therefore been postulated that the primary receiving area for the first arriving thalamocortical radiation volley is buried within the posterior wall of the central sulcus. This theory is consistent with findings from pial recording during neurosurgery (Allison et al 1980). The N20 and P30 are therefore the primary positive and negative waves respectively with polarity 'inverted' due to the horizontal orientation of the dipole. Some authors (Allison et al 1980) also describe a P25/N35 complex which is said to be a dipole orientated vertically on the crown of the postcentral gyrus.

The fibres recruited by electrical stimulation at the wrist are mainly concerned with tactile sensation with some joint proprioception. A clinical study (Crespi et al 1982) showed that patients with cortical SEP abnormality had disturbance of proprioception. Other authors (Halliday and Wakefield 1963, Noel and Desmedt 1975) have shown abnormal SEPs in patients with impairment of joint/position sense but not in those with disturbance of pain and temperature sensation. This supports the view that type A fibres are recruited in the recording of SEP.

The schematic waveform shown above in Fig 4.3 is that likely to be recorded from a C3 or C4 electrode (over the postcentral gyrus) but with more anteriorly placed electrodes other potentials can be measured such as

a P22 and P25. As has already been stated there is debate as to how and exactly where these are generated and Fig. 4.4 shows the anatomy of the cortex in the region of the central sulcus with one of the theories of cortical EP generation shown. This idea (Desmedt et al 1987, Deiber et al 1986) suggests that N20 and P22 are separate generators providing electrical charge swings from the arrival of volleys from different parts of the thalamocortical radiation. They agree that N20 is generated in area 3b of the post-central gyrus and suggest that P22 is due to electrical events in the pre-central area or in the upper part of the post-central gyrus, area 1.

Fig 4.4



(Redrawn from Desmedt et al 1987)

Study of patients with chronically implanted electrodes for treatment of intractable seizures (Dinner et al 1987) gives support to the theory of separate post-rolandic (which are earlier and larger in amplitude) and prerolandic generators. The finding that there could be isolated loss of some but not all cortical components in patients with cortical lesions (Stohr et al 1983) also adds weight to this argument.

4.2 Uses in adults

The uses of SEP in adult neurology are many and include the diagnosis and monitoring of demyelinating disease, assessment of spinal cord injury, monitoring during neurosurgery of the spinal cord, surgery on intracranial aneurisms (Momma et al 1987), monitoring during cardiac surgery of the extent of ischaemia (Kopf et al 1984) and the assessment of patients in coma.

Symon's group have done extensive work on the effect of ischaemia on the SEP of experimental animals (Branston et al 1974) and concluded that the central conduction time (CCT) was the best method of assessment of the ischaemic threshold. The CCT, which reflects the speed of conduction through the central part of the pathway, is the difference between the latency of the most prominent cervical potential and the first cortical response, these being the N13 and N20 components of the adult human SEP. They extended their animal work to a study of CCT in 16 human patients admitted with subarachnoid haemorrhage (Symon et al 1979). They found that prolongation of CCT was a good indication of ischaemia due to bleeding and further in one patient demonstrated fluctuation in CCT with changes in blood pressure. They also noted that the CCT could lengthen before there was clinical evidence of ischaemia.

A number of studies have looked at SEP in adult coma. Brunko and Zegers de Beyl (1987) examined 50 patients who had suffered hypoxic/ischaemic injury due to cardiorespiratory arrest and were in coma for at least 4 hours. All had their first SEP recording within 8 hours and serial studies were performed. In 30 no cortical potentials were elicited and all these patients died without recovering cognition. The remaining 20 showed an N20 with varying abnormalities of the other cortical waves. The authors do not comment on prolongation of latencies but it is obvious from the EP shown in the paper that this did occur. Recovery of the later cortical potentials did occur in some patients. Of this group with initial cortical response 4 survived relatively intact. No patient without initial cortical SEP survived.

Walser et al (1985) studied 26 patients with anoxic coma with particular attention to the CCT and the amplitude ratio of N20 to P25. They suggest that P15-N20 represents the thalamocortical radiation and that N20-P25 is generated in the 'receptor' cortical neurones. Persistently normal SEP indicated a good chance of recovery but if the N20 was normal but the P25

distorted the prognosis was variable. All patients with absent N20 died or entered a persistently vegetative state.

A more recent study (Rothstein et al 1991) gives similar results. Forty patients with coma of at least 6 hours following hypoxic-ischaemic insult by cardiac arrest were studied with EEG and median nerve SEP. Bilateral absence of cortical SEP correctly predicted death in 73%. Delayed CCT was associated with a variable prognosis.

DeWeerd et al (1985) looked at 20 patients with less severe injury studied twice at a mean of 4 and 14 days post-insult. Most had ischaemia in the territory of the middle cerebral artery manifesting as transient ischaemic attack (TIA), reversible ischaemic neurological deficit (RIND) or stroke and in 13 there was evidence on computerised tomography scanning of hypodense areas. The most severe persistent abnormalities were found in the 2 patients with completed stroke. In contrast, those with TIA or RIND always had normal SEP. No correlation was found between changes over time in the SEP and clinical improvement. There was always good correlation between the side of neurological deficit and the abnormal SEP.

Two studies have looked at SEP in brain death in adults. Buchner et al (1988), whose paper analysed the evolution of brain stem death, could not evoke any cortical potentials in their patients and so looked at the cervical recorded potentials. They found that N9 was always normal but that N11 and N13 were variably absent or abnormal. N14 was recorded initially in all subjects using a Cv2-Fz channel. N14 was lost up to 3 hours after brain death was established and subsequent changes then took place in more rostral potentials. The authors concluded that loss of N14 was diagnostic of brain stem death. Ganes and Lundar (1988) investigated 76 deeply comatose patients with EEG and SEP and found SEP to be superior in the prediction of outcome. Forty four had flat or very abnormal initial EEG and no cortical SEP and all died. Thirty two had initial EEG waves of whom 20 had no cortical SEP and 10 had very abnormal SEP and these patients died. The two survivors were those with initial EEG and normal SEP.

Yamada et al (1983) studied 43 adults with localised neurological disorders. They found that N18 was affected in thalamic or hemispherical disease, cervical cord lesions affected N13 and that it was likely that N14 was of brain stem origin which agrees with the findings of Buchner et al (1988).

4.3 Factors affecting the response

The means and characteristics of the somatosensory stimulus have little effect on the recorded SEP. The use in the newborn of ring finger stimulation (Desmedt and Manil 1970) rather than median nerve stimulation makes little difference (see below). In the adult the stimulus frequency makes no difference except that lower rates have to be used when long latency potentials are being investigated. The stimulus intensity above the sensory threshold has no effect on short latency potentials' latencies but it has been found that increasing the intensity from the sensory threshold to the motor threshold increased the amplitude of the responses, although further increases in intensity had little further effect (Hume and Cant 1978). In subjects unable to communicate the sensory threshold it is conventional to stimulate at the motor threshold as done in this study.

The major factors affecting latency is the speed of conduction of the pathway which is related to myelination and the length of the pathway. These are dealt with below in the section on the response in children. The speed of conduction along any nerve fibre is also dependent on the temperature and so hypothermia is a potent affecter of the SEP. Taylor et al (1985) studied 30 children during hypothermia for cardiac surgery. They collected SEP from Erb's point, high and low cervical electrodes and from the cortex over the course of cooling and reheating. In some cases the temperature reached was as low as 9^{o}C and associated with (deliberate) cardiac arrest. It was found that N9 was progressively delayed and increased in amplitude and duration with increasing hypothermia but disappeared about 20 minutes after arrest. N12 and N13 separated as both increased in amplitude and duration with cooling. N13 was abolished below 18^{o}C whereas N12 remained until 10^{o}C. As moderate cooling affects synaptic transmission these results suggest that N12 and N13 are pre- and post-synaptic in origin and are not both travelling waves.

With especial relevance to the current study, the possible effects of drugs and, in particular, barbiturate anti-epileptic drugs, on the somatosensory system have to be considered. Borah and Matheshwari (1985) undertook a study of 45 patients of 11 to 54 years who were compared to controls. The patients were started on monotherapy with phenytoin, carbamazepine or phenobarbitone and had SEP measured before and after commencement of therapy. No differences were found in short latency SEP between the controls and the patients either before or after treatment. Similarly a study of

7 patients in coma (Ganes and Lundar 1983) looked at the effect of increasing the rate of infusion of thiopentone on SEP. They found that a large increase in serum level sufficient to flatten the EEG had no effect on the SEP, whether it was normal (2 patients) or abnormal (5 patients).

Also fundamental to any study of neurophysiological function in the newborn are the effects of changes in sleep state. Desmedt and Manil (1970) used finger stimulation in 34 term babies with very different method to the current study and using full polygraphic recording techniques. They described big changes in latencies for the long latency potentials between different sleep states. With respect to short latency potentials they described no differences in the onset latency of the first cortical response but suggested that its peak latency was prolonged in slow wave sleep (SWS) compared with rapid eye movement sleep (REMS). Similarly, Willis (1986) reported the effects of state in 15 infants. He found 2 different patterns: in neonates there was no difference in cerebral potentials between active and quiet sleep but in older infants cortical waves could be slowed or even lost in stage II sleep as compared with the awake state. Interestingly, he also found that lower stimulus rates produced SEP of higher amplitude but changed latencies very little. Hrbek et al (1969) studied 37 neonates in the first 9 days of life using a mechanical stimulus for SEP and polygraphic recording for the assessment of sleep state. Their conclusion was that the major components of the cortical SEP were more pronounced in irregular (active) sleep and wakefulness than in regular (quiet) sleep and that only long latency waves were changed with changes in sleep state.

A study of different EP types including SEP at different blood glucose levels was reported by Koh et al (1988). Their study arose from a desire to investigate the relationship between neural function and blood glucose levels in order to throw light on the controversial subject of what constitutes 'hypoglycaemia.' They studied children undergoing investigation of 'hypoglycaemia' and measured BAEP in 12 children and SEP in 5, the youngest of whom was 0.3 years. EP were always normal in children whose blood glucose remained > 2.6 mmol/l. In 10 out of 11 whose blood glucose fell below 2.6 mmol/l there were changes in the latencies of EP components and in 4 of the children these were sustained for up to 2 days. They found no differences between those who had or did not have symptoms at the time of their low blood glucose levels. Unfortunately it is not possible to decide the critical level of blood glucose for SEP measurement as only one of the SEP

patients (aged 0.3 years) had changes at a level of 2.3 mmol/l and one of those without any significant change (aged 6 years) had a level as low as 1.9 mmol/l. Clearly hypoglycaemia does have important effects and this parameter must be controlled for as much as possible in any study of infants especially when ill.

There is one study of the effects of hyperbilirubinaemia on SEP in the newborn (Bongers-Schokking et al 1990). This study compares SEP in three groups: those with maximum levels ≥250 μmol/l, those with levels of 125-250 μmol/l and those with no jaundice. The only group whose SEP were significantly different from the no-jaundice group were those with levels ≥250 μmol/l. This research group uses a very questionable SEP method with a very narrow bandpass and claim that responses disappear if too many stimuli (>100) are used and so their results need viewing in this light.

The effects of ischaemia and hypoxia on SEP are perhaps the most relevant to the current study. These have been studied in experimental animals by Branston et al (1974 and 1984). In their earlier study they examined the relationship between cerebral blood flow (CBF) measured by the hydrogen clearance method and SEP measured direct from the post-central gyrus in 9 ventilated baboons. Alterations in CBF were achieved by occlusion of the middle cerebral artery (MCA). A threshold effect was seen in that SEP were unaffected until the CBF fell below 16 ml/100g/min (from a mean of 47.7 ml/100g/min pre-occlusion) when amplitude diminished and on dropping below 12 ml/100g/min the SEP was abolished. The later study of 14 baboons included measurements of SEP from the medial lemniscus, the venteroposterolateral nucleus (VPL) of the thalamus and the cortex. These measurements were related to alterations in regional CBF evaluated by hydrogen clearance. Alterations in blood flow were achieved by occlusion of the MCA and controlled reductions in mean blood pressure. Their results showed that the different structures have different ischaemic thresholds with sensitivity to change of SEP with ischaemia increasing as signals ascend the pathway. The cortical threshold was 15-20 ml/100g/min whereas the VPL had a threshold of 10-15 ml/100g/min and the medial lemniscus lower still at < 10 ml/100g/min. This provides experimental evidence for the clinical observation of brain stem survival when the cortex has been irretrievably damaged by an hypoxic/ischaemic insult, the so called chronic vegetative state (Jennett and Plum 1972, Gillies and Seshia 1980).

4.4 The normal response in children

Much work has been done by many authors on the upper limb response (Desmedt et al 1976, Hashimoto et al 1983, Allison et al 1984, Nishimura et al 1986, Sitzglou and Fotiou 1985, Egerhazi et al 1986, Tomita et al 1986, Bartel et al 1987, Taylor and Fagan 1988) and that from the lower limb (Gilmore et al 1985). Most have come to roughly the same conclusions despite using rather different methods.

Perhaps the most extensive data is provided by the work of Taylor and Fagan (1988). These authors justifiably criticised other authors for lumping together data from quite large age ranges, e.g. 10 days to 2 years and 2-12 years (Sitzglou and Fotiou 1985), which is bound to obscure the profound developmental changes occurring, especially, in the first year of life. They studied 136 children from 4 months to 18 years of age. Different patterns of maturation were seen in spinal and central parts of the somatosensory pathway which are related to changes in the speed of conduction with myelination and the length of the pathway. Two channels were used (Cv7-Fpz and C'3 or C'4-Fpz) for recording and 256 0.2msec stimuli at 4.1Hz were averaged. The cervical generated potentials, N12 and N13, both changed little in latency until 2-3 years when they lengthened, approaching adult values at 14-18 years. The pattern of change in the brain stem and thalamic responses, P14, P16 and N18, was of shortening latencies until 2-3 years then a gradual lengthening until adulthood. The cortical potentials, N20 and P22, both speeded up until 6-8 years then lengthened towards adult values. It was of note that the CCT and the N20-P22 interpeak latencies fell sharply over the first 6-8 years when they reached adult values thus suggesting that it is mainly the lengthening of the peripheral pathway with growth that determines changes in latency thereafter. This fits in with what is known of sensory nerve conduction velocity (Wagner and Buchthal 1972).

4.5 Studies in children

SEP has been used in the diagnosis of brachial plexus traction lesions (Jones 1979), to monitor the spinal cord for ischaemia during neurosurgery, in correction of scoliosis (Jones et al 1983) and during the period of profoundly hypothermic circulatory arrest and its recovery in surgery for congenital heart disease (Coles et al 1984).

Demyelination has a marked effect on nerve conduction and function and SEP can been used in children as in adults to diagnose and monitor multiple

sclerosis (Trojaborg and Peterson 1979). A number of groups have assessed different EP modalities in the leukodystrophies of childhood. In one study (Markand et al 1982) SEP were measured in 15 children and 2 adults with either Pelizaeus-Merzbacher disease, adrenoleukodystophy (ALD) or metachromatic leukodystrophy. Twelve had no early cortical potentials but some had long latency potentials. The degree of loss of SEP was related to the severity of disease and the only subject with a normal N20/P22 complex had very early ALD. A slightly larger study (De Meirleir et al 1988) tested Auditory brainstem responses (ABR), Visual evoked potentials (VEP), Electroretinograms (ERG) and SEP in 22 children with different leukodystophies of whom 14 had SEP measured. The severity of SEP abnormality was shown to correlate with the severity of disease and serial study showed that SEP changes mirrored progression of disease. These authors concluded that ABR were of most use as their pattern of abnormality was a guide to the type of leukodystrophy and also demonstrated that abnormalities of ABR were present in 3 children with presymptomatic metachromatic leukodystrophy. It has also been shown that EP can detect carriers of leukodystrophies (Moloney and Masterson 1982, Tobimatsu et al 1985). Similarly, Cracco et al (1980) in a study of 17 children with severe metabolic neurodegenerative disease found that all had slowed spinal cord conduction and in all but the 3 least severely affected children, there was associated loss of cortical potentials.

Laget et al (1976) found that SEP abnormality correlated better than EEG with loss of function in 43 children with hemiplegia. All had EEG and median nerve SEP and whereas EEG abnormalities showed asymmetry in only 45% of the children the SEP was always decreased in amplitude or lost on the side contralateral to the hemiplegia.

Laureau et al (1987) investigated SEP in children with congenital hypothyroidism with the intention of using SEP as an index of neurological maturity (which is so dependent on thyroid hormone) and therefore of treatment. They looked particularly at N13, the N20/P22 complex and at CCT. In general, latency values were normal but in some cases there was an increase in CCT. They found a partial correlation between CCT and both T4 at time of diagnosis and TSH at time of study. In addition there was also a significant partial correlation of the N20-P22 interpeak latency at diagnosis and the practical reasoning scale of the Griffiths developmental test at 18 months or more. The authors concluded that SEP may be a useful guide in

detecting those with congenital hypothyroidism at risk of developmental delay. Similar findings were reported by a study comparing the use of bone age assessment and SEP in primary congenital hypothyroidism (Bongers-Schokking et al 1991). These authors concluded from their study of 27 infants that SEP were a superior method of assessment of degree of damage from hypothyroidism than is bone age.

Gorke (1986) also used SEP to look for indications of poor developmental progress. He studied 120 children of whom he denoted 47 with only minor risk of handicap and who were neurodevelopmentally normal at 1 year as a control group. SEP, done at 1 to 10 months, on the other 73 children were compared with those of the control group. In 28 there were abnormal SEP ranging from minor prolongation of latencies to absence of potentials. Of the 9 with minor abnormalities of SEP, 4 developed normally but the remaining 19 children had major SEP abnormalities and all had abnormal development. There were 19 children with abnormal developmental and normal SEP of whom 3 had cerebral palsy, 13 had psychomotor retardation and 3 developmental speech delay. The major criticisms of this study are that the control group is not well chosen and that it is perhaps not surprising that SEP could not predict developmental delay due to a large variety of causes such as speech problems. The same author in another paper reporting 28 of the same children (Gorke 1987) suggested that abnormal SEP could lend weight to the likelihood of abnormal outcome when other tests such as CT scanning or EEG gave an equivocal prognosis.

Four papers discuss the use of SEP in childhood coma. Goff et al (1983) confined themselves to consideration of 12 children with Reye's syndrome. They found that the one patient that died had only subcortical potentials and handicapped survivors had abnormalities of the long latency potentials. Good quality survival was associated with early abnormalities of SEP which improved but unfortunately some of their patients did not have serial studies from early in their illness and so loss and recovery of potentials may have been missed. Another study (DeMeirleir and Taylor 1987) showed that in Reye's syndrome cortical SEP could disappear after craniotomy for control of intracranial pressure but that its reappearance was indicative of good outcome.

Lutschg et al (1983) studied BAEP and SEP in 43 children in coma due to trauma in 26 and hypoxic/ischaemic insults in 17. N20 was lost in 13 of the 15 that died and in half of those with subsequent handicap and no patient

that died had normal BAEP and SEP. All the normal survivors had normal or only transiently abnormal EP results. Frank et al (1985) showed that in 5 comatose children who developed a chronic vegetative state the cortical SEP was absent in the presence of preserved BAEP.

The most extensive paper demonstrating the usefulness of SEP in predicting the outcome of childhood coma is that by DeMeirleir and Taylor (1987) in which they studied 73 comatose children on admission to intensive care. Twenty seven died of whom 19 had bilaterally absent cortical SEP, 7 had unilateral absence or asymmetry and 1 delayed latencies. Of the 14 normal survivors 13 had initially normal or delayed SEP but were normal by the second day and one had initially asymmetrical SEP which were normal by one week. In general there was correlation between the degree of SEP abnormality and the degree of subsequent handicap. Repeat testing gave valuable information, in that deterioration in SEP was associated with death or severe handicap, improvement but persistently abnormal responses led to neurological sequelae but improvement to normality of response was associated with a good outcome.

4.6 The neonatal and infant response

There have been quite a number of studies in the newborn but sadly no consensus exists mainly because no two authors have used exactly the same method. Early attempts were aimed at using SEP simply as a means of obtaining information on sensory function rather than as an index of brain compromise. Confusingly, the nomenclature used by authors is often different to that employed in adult work. The potentials are often denoted by their polarity and order of occurrence because average latencies are difficult to state. Therefore the N1 is the first cortical negativity, P0 the positivity preceding it, P1 the first cortical positivity and so on.

Normal data has been reported by a number of authors (Hrbek et al 1968, Hrbek et al 1969, Desmedt and Manil 1970, Blair 1971, Hrbek et al 1973, Cullity et al 1976, Desmedt et al 1976, Pratt et al 1981, Laget 1982, Willis et al 1984, Gorke 1986, Laureau et al 1988, Klimach and Cooke 1988a, Bongers-Schokking et al 1989, George and Taylor 1991). Methods of stimulation have varied from the use of tendon reflexes or mechanical stimuli (Hrbek et al 1968, Pratt et al 1981) to electrical finger stimulation (Desmedt and Manil 1970) and the most widely used method of electrical stimulation over a peripheral nerve such as the median (Willis et al 1984) or posterior

tibial (Gilmore et al 1985). Stimulus rates have varied between 0.5Hz (Cullity et al 1976) and 5.1Hz (Willis et al 1984). Some authors have averaged very small numbers of stimuli such as 100 (Klimach and Cooke 1988a), although they did not record from cervical electrodes (see chapter 3.2). Early workers were sceptical about the possible uses of the technique as they could only recognise reproducible potentials in 50% (Blair 1971) and 80% (Cullity et al 1976) of newborns and Willis (1984) reported that in 1/3 of newborns no replicable potentials could be measured at Erb's point (for technical reasons - see chapter 6.3) or over the cortex (for reasons of immaturity). The response is immature at term and even more so in preterm infants (Hrbek et al 1973, Klimach and Cooke 1988a).

Only three studies have reported significant data from preterm infants. Hrbek et al (1973) studied 48 newborns from 24 to 42 weeks gestation with a median nerve stimulus and the summation of only about 20 responses. They describe a very slow long negative wave with an ill-defined peak in infants less than 29 weeks and the appearance of a distinct N1 from this gestational age onwards. The N1 then becomes more distinct and of faster latency, increasing with a linear relationship to gestational age. At term they give an N1 latency of 35 msec and P1 of 63 msec. Klimach and Cooke (1988a) studied 94 preterm and 8 term infants and found their results related in a linear fashion to post-menstrual age (PMA = gestation in weeks + post-natal age in weeks) rather than to gestation alone. Their range was 27.7 to 41.4 weeks PMA and the group consisted only of those at low risk of subsequent neurodevelopmental problems. A clear response was obtained in 90% of patients with the mean for N1 decreasing from around 77 msec at 28 weeks to 37 msec at term. There are a number of problems in this study in that only traces from one cortex were recorded in most of the infants, no cervical recording was done and most seriously the bandpass was very narrow, almost certainly causing lengthening of the latencies and accounting for the relatively long value for mean N1 at term (see chapter 3.2 and Desmedt et al 1974). Likewise a Dutch study (Bongers-Schokking et al 1989) used a small number of stimuli and a narrow bandpass, their justification being that potentials were fading away to nothing if too many stimuli were used. This calls into question their method as the technique of averaging (see chapter 3.2) should not have that result if the potentials being measured are true. A possible explanation would be fatiguability of response but this has not been noted by other authors with similar numbers of stimuli.

Gilmore and colleagues (1987) have focussed their attention on the response to posterior tibial nerve stimulation giving data on that part of the neural pathways particularly affected by spastic diplegia in preterm infants (Powell et al 1988). Study of 29 newborns of 26-38 weeks PMA revealed no identifiable scalp potentials in infants of less than 31 weeks. All infants had an N16 recorded over the sixth thoracic vertebra but half had no potentials recorded over the seventh cervical vertebra (N27) and in only 65% was a cortical P55 recorded. N16 and N27 varied inversely with PMA but the cortical P55 and N65 were very variable.

Work on the normal response in the term infant has concentrated on upper limb SEP, however, Cullity et al (1976) did not report latencies, Hrbek et al (1968, 1969) concentrated on long latency potentials and Pratt et al (1981) were unable to record cortical potentials in 9 out of 10 newborns after mechanical stimulation of the fingers. Some authors did not record subcortical components but 2 studies (Willis et al 1984, Laureau et al 1988) found that an Erb's point potential can be recorded at around 6 msec with the cervical electrodes picking up a complex wave with a peak at around 9-10 msec. The values for cortical waves found by different authors are contained in the following table.

Fig 4.5 A schematic representation of the neonatal response

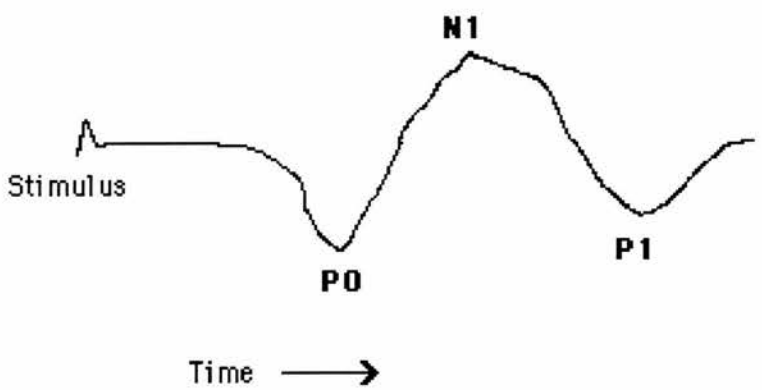


Table 4.1

Author	P0 msec	P0 msec	N1 msec	No. of infants
Desmedt et al (1970)	23	31.4	-	34
Desmedt et al (1976)	22	31	46	29
Laget (1982)	21.5	34.1	97.6	45
George and Taylor (1991)	24.0	31.0	39.4	16
Willis et al (1984)	15.3	24.3	37.0	9
Gorke (1986)	16.3	26.1	40.1	6
Laureau et al (1988)	-	25.0	34.8	18

It can be seen that the first 4 groups measured similar latencies to each other but generally longer than the other 3 groups. Desmedt and Laget's groups used stimuli at 0.5 Hz, whereas Gorke used 1Hz and George and Taylor 1.1 Hz. Laureau's group employed stimuli at 4 Hz and Willis at 5.1 Hz. Laureau et al (1988) did longitudinal studies on 13 of their 18 infants and found major maturational changes over infancy. They noted that there were more marked changes in the cortical response than in the Erb's point and cervical potentials.

It is quite obvious from these data that it is necessary to study a large group of control infants with a defined method for any clinical investigation using SEP and this is described in chapter 6.

4.7 Uses in the newborn

At the time this present study was undertaken there had been little work done on the use of SEP in neonatal neurology. The literature studies mainly report the use of SEP in determining the prognosis in cohorts of infants at risk of neurodevelopmental delay but there is also an interesting case report (Bell and Dykstra 1985). This describes the finding of no measurable potentials above the 6th thoracic vertebra on posterior tibial stimulation associated with a normal median nerve response giving support for the diagnosis of lower cervical/upper thoracic neonatal spinal cord injury.

Klimach and Cooke (1988b) studied 30 preterm infants with cranial ultrasound abnormalities who were therefore at risk of subsequent neurodevelopmental handicap. They found that normal SEP predicted normal outcome at a median follow-up of 10 months. Twenty one had

abnormal initial SEP at a PMA of 30-44 weeks with absence in 2 and gross prolongation of latencies in 6. Thirteen had repeat testing and in 7 the responses had reverted to normal. Infants with a unilateral scan abnormality and abnormal SEP developed hemiplegia but those with normal SEP and a unilateral scan abnormality had a normal outcome. Of the 9 infants with bilateral SEP abnormalities 1 was too young for follow-up, 1 died and 7 had developmental delay of whom 6 also had abnormal neurological findings. Their findings suggest that SEP may prove to have a use in predicting which of the 'high risk' neonatal survivors is going to develop neurodevelopmental delay.

Willis's group in New Orleans (1989) have done a study of SEP performed later in infancy on 39 ex-VLBW (very low birthweight) babies who had SEP studies planned for 2 months, 4 months and 6 months of corrected age, relating the results to neurodevelopmental function at 18 months. Twenty-two had all 3 studies, 9 had 2 studies and 8 had only one. Significant neurological disability always followed in the twelve infants who had unilateral absence of SEP or an N1 latency greater than 3 S.D. from the mean. However, normal SEP were not always associated with normal outcome especially if only one study (at 2 months corrected) was performed. Three normal studies did give a 86% chance of normal outcome. Interestingly the authors found no correlation between the side of periventricular haemorrhage (PVH), side of SEP abnormality and lateralisation of neurodevelopmental difficulties. This may be because of the absence of data on periventricular leukomalacia (PVL) in their study. The authors suggest that SEP may provide an ancillary to prediction of outcome in infants that have suffered PVH.

The specific use of SEP in evaluation of cystic PVL has been reported (Pierret et al 1993) but the study design failed to allow sequential study in all infants. As study of median nerve potentials at discharge from hospital were reported as normal in 14 of 27 infants who developed severe neurological abnormalities the authors concluded that SEP are of no value. However, the early SEP measured in 9 infants within two weeks of birth were all abnormal. Not surprisingly those infants with mainly posterior cysts tended not to show SEP abnormalities. A proper sequential study in this condition would seem warranted to assess the time course of SEP properly before concluding that they are of no use. The authors do suggest that study of posterior tibial responses may be more instructive.

There have been 5 studies of SEP in perinatal asphyxia. Hrbek et al (1977) describe the use of SEP and VEP in 57 infants. Their study is very difficult to assess as they do not state the gestational age of their patients, the EP method is not described and there is no follow-up. However, they developed a scoring system of SEP abnormality and reported that those with the highest score (most abnormal SEP) had the worse asphyxia. A rather better study looked at 10 term asphyxiated infants followed up to a mean age of 20 months (Willis et al 1987). They aimed to perform SEP at 2, 4 and 6 months and defined abnormality as N1 absent or more than 3 standard deviations above the mean. Persistently normal SEP predicted normal outcome and persistently abnormal SEP predicted severe disability at follow-up. Those with abnormal SEP at 2 months which improved had only moderate or mild disability at follow-up.

In addition to the publication of the work of this present study (Gibson et al 1992) there have been two other recently published studies of SEP in perinatal asphyxia. The group at Toronto (Taylor et al 1992) studied 57 term babies all of whom were outborn but admitted to their unit within 24 hours of birth. SEP and VEP were recorded and scored at the end of the first three days and at the end of the first week. The scoring was based on the best trace found on either side within that period of time. The overall mortality rate was 19% and the morbidity rate 21%. All infants had cranial ultrasound and these authors confirmed others' findings (see chapter 1.4) that this is a poor prognostic indicator. The SEP and VEP findings were found to be strongly predictive of outcome. They found that SEP at the end of the first week was most accurate in that 30 out of 31 with normal SEP at this stage had normal outcome and 22 had adverse outcome out of the 26 whose SEP were abnormal after 7 days.

The Dutch group (de Vries et al 1991) looked at 34 term infants with SEP, planning to perform studies in the first and second weeks of life. Unfortunately 11 did not have first week results. Infants with normal SEP results by the second week had normal outcome. Those with absent N1 in the second week all had abnormal outcome. The group with delayed N1 had a variable prognosis.

From this it can be seen that at the time that this study commenced more extensive study of SEP in perinatal asphyxia was required to assess prognostic ability of this test. It is also important that results of research can be replicated in other centres and the results of the Dutch and Canadian

studies, performed over the same time course as the present study, will be discussed further in the discussion of the results of this study in chapter 9.

Study design

5.1 Background

From the preceding chapters it has been seen that there is room for improvement in the assignment of prognosis to the asphyxiated newborn. A test which would give highly sensitive and specific information in the early stages of the encephalopathy would help guide decisions on the appropriateness of continuing intensive care. It would also help assign risk of subsequent sequelae and perhaps indicate infants who may benefit from pharmacological intervention, should such techniques become available. The best early indicators currently available relate to assessment of neural function by clinical examination and EEG.

The most important form of injury caused by an hypoxic-ischaemic insult affects the areas at the boundaries of the territory supplied by the cerebral vessels, the so-called watershed zones. In the less mature infant the area most often affected in those with subsequent handicap is the periventricular white matter giving rise to periventricular leukomalacia (Graham et al 1987). In the term infant the vascular watershed zone is different and the area at greater risk is the immediate subcortical area giving rise to the lesion subcortical leukomalacia (Takashima et al 1978). It can be seen from chapter 2.3 that the somatosensory pathway traverses those areas of brain most susceptible to significant injury in the sick term infant.

The attraction of SEP is firstly that the somatosensory system runs through these vulnerable areas and secondly that most infants handicapped after neonatal illness have motor dysfunction and the motor and sensory pathways are closely aligned. It is therefore reasonable to postulate that damage to the motor system may be reflected by abnormalities in sensory system function. It is also thought that many children with, for instance, hemiplegia have a sensory component to their problems. It therefore seemed reasonable to investigate the use of SEP in neonatal hypoxic-ischaemic cerebral injury associated with perinatal asphyxia.

5.2 Study design

The information in chapter 3 on the technical aspects of SEP recording outline the importance of having a specific method incorporating the various parameters which can be set in EP recording. This dictates that the first part of this study would be study of the acquisition parameters and familiarisation

with the techniques involved. This part of the study would be performed in normal term infants. After the author has settled on a technique then a group of normal term infants must be studied to provide a sample of the population to build up a normal range of response with the technique to be employed.

Subsequent study using the established technique would then be made of asphyxiated term infants. It would have been ideal to complete the study of the normal infants and analyse all those data before embarking on study of the asphyxiated infants but this was impractical as funding for the study only existed for two years. The incidence of perinatal asphyxia is thankfully low. This dictates that to realise a reasonable large sample of study infants would require enrolment to the study to begin as soon as practicable. It was decided to study the infants frequently at first then less frequently thereafter as clinical features change less rapidly as the encephalopathy progresses. This led to a plan to study infants as soon as possible after stabilisation in the neonatal intensive care unit and every two days thereafter during the first week. Further study was planned twice weekly until discharge.

Follow-up at one year of age was arranged by an observer blind to the neonatal course and to the SEP results.

Discussion of the details of the study design are included in the relevant parts of the next three chapters. A discussion of its appropriateness is included in chapter 9.

Recording SEP in normal term infants

The normal range of response to stimulation of the somatosensory system in the newborn human is a subject of debate as outlined in the previous chapter. In view of the previously discussed aspects of acquisition parameters it is considered good practice in evoked potential work of any kind to have internal departmental standards. In research work of this nature it was felt to be vital to investigate the range of normal response using a method developed with the operator and equipment to be used in the subsequent study of asphyxiated neonates. This process and the results obtained are described in this chapter.

6.1 Subjects

Term newborn infants were recruited from the postnatal wards of Leicester Royal Infirmary after a full explanation of the procedure to the parents and the obtaining of signed consent. Only infants whose mothers were completely happy to proceed were recruited. Despite careful selection by experienced midwifery staff of suitable mothers to approach a considerable number did not consent to their infant being studied and the success rate of recruitment was approximately 30% of mothers approached. It should be noted that no infants of non-caucasian origin were studied as normal controls as all Asian mothers approached refused permission to study their infants. As non-Caucasian infants constitute 19% (5 Asian, 1 African infant) of the cohort of asphyxiated infants and 30-40% of births in Leicester Royal Infirmary this was most unfortunate. However, the author is unaware of data suggesting that race is an important determinant of neurophysiological function. The permission of the local Leicestershire ethical committee had been granted for this study.

Infants were selected on the basis of delivery near term i.e 36-42 weeks with a fairly certain gestational age, normally determined by measurement of the biparietal diameter during ultrasound scanning at booking at around 10-12 weeks. Mode of delivery was not considered important as all those with signs of "fetal distress" were excluded as were those with congenital abnormalities, need for resuscitation or any neonatal illness. A neurological examination was done based on the Dubowitz examination (Dubowitz and Dubowitz 1981) and any infant showing abnormalities of tone or reflexes was excluded.

The study of normal infants was done in two stages. In the initial stage approximately 15 infants were studied in order to allow the investigator to become skilled at the procedures involved in measurement of SEP and the establishment of a set of recording parameters. In retrospect, this stage of the study was not as thorough as it might have been. In the second stage a group of 41 infants were studied to allow the establishment of a normal range of median nerve SEP for the conduct of the clinical study of asphyxiated newborns. The data obtained from study of these infants is described in detail below.

Follow-up of the "normal" infants was considered but rejected for a number of reasons. Firstly, it seemed a little difficult to ask a mother to allow study of her infant because it was 'normal' and then request to follow up the child's developmental progress to see if all went well. In view of the difficulties already alluded to in recruitment it was felt this might prove a further concern to mothers. One of the 'normal' infants developed seizures in the late neonatal period, closely followed by the development of cafe au lait patches and the diagnosis of neurofibromatosis with a cerebral abnormality demonstrated on CT scan. This child had assymetrical SEP with no cortical wave present on the affected cortical side. Understandably this infant was withdrawn from the cohort of normal infants leaving 40 sets of SEP for analysis. One of these control infants suffered a 'cot death' at the age of four months.

6.2 Equipment

A Medelec evoked potential system was used throughout the study consisting of an ST10 stimulator unit with attached hand held stimulator device, an ER94a 4 channel averager and an ER94a amplifier which acted as the "headbox" for patient connection. A custom made screened cable was used to lead from the headbox to the baby so that only 20cm of unscreened cable led to the individual silver/silver chloride surface electrodes. The stimulator unit had current controlled by a dial and readout on the face with a maximum current of 100mA. The maximum voltage was 270 V d.c. The duration of the stimulus delivered could be 0.1, 0.3 or 1 msec. The amplifier has analog filters with a large variety of settings and has a common mode rejection ratio of 50000:1 at 50 Hz. The analog to digital converter is 8 bit i.e. 256 discrete amplitude steps in each binwidth. The averager has 4 channels each with 500 points and a large range of programmable analysis times, pre-

stimulus delays and repetition rates. The sweep limits available were 1 to 4096 sweeps in binary sequence. There were available a number of preset programs for EP recording and the facility to customise acquisition programs.

The averager unit was interfaced to an Apple IIe microcomputer with twin 5.25 inch floppy disc drives. The software was Medelec's own programs for storage and retrieval of data from the ER94 system. Traces were stored on disc during each recording session and subsequently analysed and a hard copy was made onto paper using a Hewlett Packard 7040 graphics plotter. The unit had two electronic cursors which could be used for on screen analysis as each cursor gave a readout of its position on the trace with respect to its charge, polarity and latency. This allowed a cursor or cursors to be run along a trace and for the points at which polarity was changing to be clearly defined and therefore give a precise latency for a particular peak or trough on the waveform. It was by this method that latencies for defined points were defined and measured.

6.3 Methods

First stage

As there was no consensus in the literature as to the best method of measuring SEP in the newborn, work was required to establish a reliable reproducible method. There were three groups of variables: those concerned with recording parameters, those of the optimal electrode placement to gain maximum information and once these were established infant dependent variables were addressed in the second stage. The following parameters could have been examined in relation to recording.

Table 6.1

Main recording parameters to be decided

Stimulus rate	1Hz	3Hz	5Hz
Number of stimuli	256	512	1024
High pass filter	5Hz	10Hz	30Hz
Low pass filter	100Hz	1500Hz	3000Hz
Sweep time	50msec	100msec	200msec

It is clear from the discussion in chapter 4 that a crisp stimulus to give a well defined volley is highly desirable and therefore a stimulus duration of 0.1

msec was chosen without investigation. The stimulus rate and number of stimuli are interconnected as the time taken to collect a trace is obviously dependent on both. Observation of the traces obtained in stage one led to the subjective opinion that 1024 stimuli gave smoother traces without any loss of components. A stimulus rate of 5 Hz was chosen empirically. Cortical waveforms were encountered during stage one and so this combination gave a reasonable acquisition time of between 3 and 5 minutes. A slower rate of stimulation would make the collection of 1024 sweeps a lengthy process if repeated several times in a newborn baby. It was realised later in the study that this parameter needed assessment and this was addressed in stage 2 as detailed in Appendix 1 and discussed below. There did appear to be SEP changes associated with changes in rate subsequently demonstrated (see below) but for a good clear reproducible trace 1024 stimuli at 5Hz was chosen as the basic stimulus arrangement.

The filtering system is dependent on the amount and nature of unwanted interference and preferably the bandpass should be as wide as possible (see chapter 3.2). High pass filter settings at 30Hz and at 10Hz were investigated and a low pass filter at 1500Hz and at 3000Hz. It was objectively decided that 10Hz to 3000Hz bandwidth allowed the best compromise between allowing the maximum possible information on the traces and acceptable interference. Low pass filters below 1500Hz were tried in recording of two study infants but the traces were not stored or retained. A note was made that quite remarkable changes in the traces occurred with smoothing causing distortion of detail, change of waveform and lengthening of cortical latencies. In view of the technical considerations discussed in chapter 3.2, a 50Hz notch filter was not used.

The optimal sweep time was chosen easily as it was clear that short latency cortical response was longer than in adult work and that 100msec was required to allow visualisation of the rise and fall of the cortical wave and to allow for longer latency waves which were thought likely to occur in the less mature infants based on the known characteristics of nerve conduction discussed in Chapter 2. The channel sensitivity chosen for display reflected the amplification needed to clearly show the evoked potentials. In recording channels from the neck with relatively high amplitude waves 20μV per division was needed but for lower amplitude cortical waveforms 10μV per division was required.

Electrode placement was determined by trial and error and eventually governed by the desire to collect information on response in cervical/subcortical parts of the pathway as well as the cortex and the need to suppress interference from muscle action potentials in infants. A distant reference electrode on a lower limb or the contralateral arm proved impractical because of muscle artefact. It was therefore decided that a cephalic reference electrode was preferable and this was chosen as midline frontal i.e. Fpz on the International 10-20 system.

The position of the active electrodes involved the evaluation of Erb's point, an electrode over the low cervical region (Cv7 seventh cervical vertebra) and the high cervical region, Cv2. An attempt was made to pick up widespread subcortical components of the SEP with an Fz to left mastoid electrode pairing.

The Erb's point electrode was difficult to secure and easily contaminated by muscle artefact and was therefore discarded. Cv2 and Cv7 were both easy to fix and it was found that both were informative. However, Cv7 gave less clear information as its potentials were less clearly separated and normally also recorded by Cv2 which in addition had later potentials evident. The Fz to left mastoid pairing characteristically gave a sawtooth pattern of trace with no reproducible interpretable traces or peaks. It was abandoned.

For measurement of the cortical waves it was theoretically established (see chapter 3.3) that the electrodes should lie behind C3 and C4 and the positions C3, C'3 and C''3 were investigated. It was found in the study of three infants that the waveform and response latencies were not affected by the position of the electrodes within this anteroposterior axis. It appeared that the 2 cm behind position (C''3) measured the clearest highest amplitude response and this was the electrode position employed in the subsequent study. A more detailed montage of electrodes was not studied.

Although it is clear in retrospect that not enough work was done on systematically evaluating each parameter in a rigorous scientific manner the author proceeded to the second stage of the work on normal infants using the recording parameters which subjectively and theoretically gave recordable SEP in the term newborn. This is discussed further below after description of stage 2.

Second stage

Infants were studied in a sideroom nursery of the postnatal ward which was kept between 20 and 25 degrees Celsius. They were lying in a basinette cot lightly dressed and covered in a blanket. The infant's skin temperature was not routinely measured but it is unlikely that the peripheral temperature could have fallen sufficiently to significantly slow nerve conduction. The infants were studied within two hours of a feed thereby making hypoglycaemia extremely unlikely (Aynsley Green and Soltesz 1985) and giving rise to a study on a contented subject. Having chosen this period of likely normoglycaemia it was not considered ethical to take heal prick blood samples for blood glucose estimation by BMStix and this was also considered a further possible bar to gaining of parental permission.

The infants head was measured and silver/silver chloride 'active' electrodes placed on the skin over the second cervical vertebra and on C"3 and C"4 (i.e. 2cm behind C3 and C4 on the International 10-20 system). Each of these was referred to an electrode over Fpz i.e. midline frontal. An earth electrode was fixed on the upper arm. The scalp electrodes were fixed with collodion and those on the neck and arm with adhesive tape. The skin was gently scarified as each electrode cup was filled with conductive jelly and the impedance was adjusted to lie below 2kOhms. The impedance was checked periodically during the recording session

The 'normal' set-up consisted of giving an electrical stimulus of 0.1msec duration to the median nerve at the wrist at 5Hz with the stimulus intensity set to produce a thumb twitch (motor threshold). If no response was obtained a higher stimulus intensity was tried. A hand held stimulator device was used throughout with saline soaked felt pads over the electrodes. This was held such that the cathode lay distal and 5-15 mV was usually required to achieve the motor threshold. It was of note that with the more mature infants, especially in a few tested at 6 months or so of age in a separate study, smaller voltage was required to reach the motor threshold. This is most unlikely to be a feature of skin as it is thinner and less well keratinised in less mature infants and relates to the decreased threshold for stimulation in larger peripheral nerves with age.

The Medelec Sensor system was set up to collect the first 100 msec information after each stimulus but to reject those in which 10 microV was exceeded thereby filtering out effects due to muscle artefact. The signals were passed through a bandpass filter arrangement which was set with the

high pass filter at 10 Hz and the low pass filter at 3000 Hz. The results were then displayed on a screen which allowed the monitoring of the input or the averaged trace.

The averaged traces of each set of 1024 stimuli were then stored on a 5.25 inch floppy disc. This allowed data analysis and measurement to be done later. It was customary to do three runs of 1024 stimuli at each wrist but when work on the method was being done other acquisition parameters could be included and more runs collected. During stage 2 in eight of the forty infants the stimulus rate was varied on some occasions and data was collected with the stimulus delivered at 1 Hz or 3Hz and 256 or 512 stimuli were averaged. At the end of the study the electrodes were removed with the use of acetone.

The study was terminated if the baby did not settle after placement of the electrodes or if the mother was unhappy with the baby's reaction to the recording. It was a source of some surprise that early termination of the recording session was a rare event as the procedure was remarkably well tolerated by the babies. Indeed, many babies were apparently contented by the median nerve stimulus and began to be restive or cry when it was removed between runs of 1024 stimuli.

Access to full polygraphic recording facilities was not available and so sleep state could not be accurately determined but a visual assessment of wakefulness, quiet sleep and active sleep was made and noted.

The traces were independently assessed by the author and Dr V. Brezinova, Consultant Neurophysiologist, with respect to waveform and the latency of defined points on the response curve. Waveform was decided by simple visual inspection of the trace and latencies for defined points on each trace for right and left median nerve stimulation were calculated in each individual. Waveform analysis presented important difficulties and these are discussed below. Latency analysis was seldom a problem.

Subsequent statistical analysis of the data when only SEP measurements were involved (e.g. latencies of the SEP peak in different waveforms) was by parametric methods such as t test. Non-parametric methods (Chi squared, Spearman's rank correlation) were used for comparison of the SEP measures with the postmenstrual age. In addition, the main SEP differences were rechecked non-parametrically (Mann-Whitney test, Kruskal-Wallis test) to exclude effects of different sample size or variance.

6.4 Results

The SEP were easy to obtain in all 40 infants and data are available for right median nerve stimulation in 40, and left median nerve stimulation in 37 giving information on 77 somatosensory pathways in all. Appendix 1 lists the actual results for each parameter in each run of stimulation in each subject. Data will be discussed first for cervical potentials, then cortical potentials and then the central conduction time. There are two aspects of the somatosensory response to consider, namely the waveform or shape of the response and the latency of defined points on the waveform. Numerical data are shown in Table 6.2. When more than 3 runs of stimulation were performed in an individual infant only the first three runs on each median nerve were included in the general analysis of latencies and waveforms. This was to try to prevent bias from inclusion of many traces from these infants. The extra runs of stimulation occurred in those infants in which the effects of varying stimulus frequency were being investigated and their data were included in those specific analyses.

Cervical potentials

These were obtained in every instance. The early and reproducible portion consisted of a large negative deflection with up to three peaks within it followed by a deep positive wave. The highest amplitude peak was identified and was named C2 as it was most commonly the second peak. Even if only one peak was present or if the first of two peaks was of the largest amplitude it was still denoted C2. Any preceding peak or clear shoulder on the upstroke to C2 was named C1 and any peak or shoulder on the downstroke of C2 was given the name C3. The point of deepest deflection in a positive direction following the major cervical peaks was named Cp. The mean values for each parameter and their frequency of occurrence on any run in an individual infant are shown in table 6.2. Examples of cervical traces are shown in figures 6.1 to 6.4. There were no significant differences between right and left median nerve stimulation in any of the cervical response parameters.

The subsequent record from the cervically placed electrode showed more variation in character and was not subjected to detailed analysis.

Cortical potentials

Electrical information from both cortices were collected during stimulation of the median nerve. Most of the discussion relates to the findings on

examination of the trace from the contralateral cortex. The waveforms noted in this study for normal newborn infants differ markedly from those found in adults and older children. A number of forms came to be recognised and it was not unusual to find more than one form of response in the same child in a single recording session. There were a number of problems in the analysis of waveform.

In the total of 215 cortical SEP traces scored for general analysis there were four types of waveform recognised at the C"3 or C"4 electrode. There was a common pattern of each waveform beginning from a relatively positive position. There was then a negative wave of varying complexity before a fall back towards positive values. Those four main waveforms were identified as detailed below. Examples of each are shown in figures 6.1 to 6.4.

Waveform S (symmetrical) Fig 6.1 A broad negative wave, often of low voltage, which was symmetrical with both slow rise from and return to the baseline. The point of maximum amplitude is not distinct and is in the middle of the wave.

Waveform A (asymmetrical) Fig 6.2 Consisting of one broad negative wave of asymmetrical shape with a shorter rise time and prolonged fall back to the baseline or below into positivity. The maximum amplitude was more easily defined and lay at the peak of the short upstroke. This form was normally of larger amplitude than the form S.

Waveform P (plateau) Fig 6.3 This form was characterised by a sharp rise to a plateau without a clearly defined pinnacle. The descending part is also steeper than in S or A and may drop into positivity. The plateau was seldom ruler-flat and could undulate.

Waveform M (M shaped) Fig 6.4 This form was the most complex encountered. It consists of a series of fairly steep deflections with firstly a sharp rise to a clear negative peak followed by a fall which may reach to positive values before a rising wave to a second negative peak. The descent from this is normally more gentle and drops to positive values. Form M resembles the form seen in older infants and children.

It can be seen from the above that the waveforms described increase in complexity from S to M.

Out of the 215 SEP scored in the general analysis from the 40 subjects (111 from right median, 104 from left median) no recognisable peaks were found on 11 occasions (5%) in 5 infants. A response was present but poorly formed and not clearly fitting the above definitions on 12 occasions (6%). There were 17 (8%) in form S, 18 (8%) in form A, 78 (36%) in form P and 79 (37%) in form M. In no subject was there bilateral absence of response but in one infant of 37.5 weeks postmenstrual age (Infant 10) there was no demonstrable response on 3 runs of right median nerve stimulation at 5Hz. Unfortunately, slower stimulation frequency was not tried in this infant as he became restive and the study was terminated. The infants with runs of stimulation not resulting in a recognisable response were, in general the least mature infants studied and this finding may in part be explained by stimulus intensity and frequency (see below). The runs which did result in a cortical response in these immature infants tended to yield forms S and A.

It was found that the waveform was not constant within infants with waveform S found in 6 infants, waveform A in 7 infants, form P in 26 infants and form M in 26 infants. The number of different forms seen in an infants' study was 3 in two infants (Forms S, A and P and Forms A, P and M), 2 different waveforms in 24 infants and in 14 infants the waveform was consistent. The most common combination when two forms were present was of type P with type M (18 infants). In addition three children had combinations of A and P and one each of A and M and S and A. No infant had waveform S and waveform M. There was good agreement for waveform encountered on stimulation of right and left median nerve within infants.

In the measurement of latency values there were five variables considered. These were the latency of the small positivity preceding the first negative wave (P0); latency of the first negative wave at its peak (N1); rise time of the N1 peak (N1 latency-P0 latency); amplitude of N1 (amplitude difference N1-P0) and latency of the first positive peak after N1, called P1.

P0 was the latency of the peak of the positive deflection before the first negative wave or the starting point of that upstroke. The N1 could be defined as the first negative peak of the wave. In form S, this constituted the point of most negativity which normally lay in the middle of the wave. In form A the N1 was the end of the upstroke from P0. The position of N1 in form P was the end of the upstroke which was at the edge of the plateau. In form M the

N1 was again the peak of the upstroke and in this form it was much more clear cut. Examples of these forms and the definition of points is shown in figures 6.1 to 6.4. The cursor was run along the trace on the oscilloscope screen until the point at which polarity swing changed and these points were marked and their latency noted.

Table 6.2 shows the mean data for the right and left median nerve. All the left-right differences were not statistically significant. It is of note that the values for Cp and P0 are not significantly different suggesting that they may both represent the same (subcortical) electrical event.

There was striking variation in the latencies measured by the scalp electrodes as shown by the large standard deviation of the mean latencies. The main explanation for this was in the marked variation in waveform encountered. Table 6.3 shows the results for the main variables in each of the four cortical waveforms. A systematic shift of latency was found from the longest values in form S to the shortest latencies in form M. This was also true for the cervical peak C2 associated with each of the cortical waveforms. Significant differences between the groups are shown in table 6.4. The SEP with waveform M differed significantly from those with waveform S in most variables, as did those of waveform P. Differences between forms A and S were less prominent as were differences between forms A and M. The overall distribution of data among the four types of waveform were tested for the latencies of N1 and P1 peaks, P0-N1 rise time and central conduction time, and found significant in all instances ($p < 0.00001$ in Kruskal-Wallis test). Where more than one waveform was found in one infant there were no significant differences in N1 latency within those infants.

Examples of the waveforms with superimposition of repeated traces to show reproducibility are given in figures 6.1 to 6.4.

Interobserver and intraobserver variability

The waveform and latency data were scored independently by both the author and Dr V Brezinova, Consultant Neurophysiologist. A subsequent common 'discussed' scoring was agreed on and it is those data which have been analysed and discussed. There was variability in the scoring of both latency and form as should be understandable in view of the subjective nature of interpretation of SEP traces. The degree of agreement for scoring of the N1 was 82.3%. In the classification of waveform the pattern of interobserver variation was specific in that there was complete agreement on

the absent and S forms and virtual complete agreement on the category of form M. This is reflected by the fact that these two forms were significantly different in all major parameters. There was variability in scoring of forms A and P with the author more likely to score a wave as A. Intraobserver variation of waveform was assessed by scoring of waveform six months apart with just over 20% of forms changing scoring. The main difference was the creation of the category of indistinct waveform.

Factors influencing the cortical waveform

The mean intensity of stimulus used was 11.2±2.7 mA. No significant overall relationship was found between the intensity of the stimulus and the response waveform, the number of peaks in the cortical waveform, the latency of N1 or the N1 amplitude. However, in individual cases an absent or indistinct SEP was replaced by a definite form when the stimulus intensity was increased.

As detailed in Appendix 1, there were eight infants in whom the stimulus frequency was varied. Comparison was made of 3Hz stimulation with a 1Hz stimulus. Stimulus intensity did not significantly vary (10.3±2.7 mA and 10.5±2.6 mA respectively). With 3Hz there were absent SEP on three occasions but cortical waves were always obtained at 1Hz. On 4 occasions there was no change in form. It was also found that in four of the eight infants in whom different stimulus frequencies were employed a reduction in the stimulus frequency to 1Hz changed the waveform to a more complex one, normally form M. In three infants a cortical waveform was uncovered. It is of note that no infant had absent cortical response with a 1Hz stimulus. Reduction in stimulus frequency significantly increased the peak amplitude of N1 from 1.1±0.4 μV at 3Hz to 2.0±1.1 μV at 1Hz ($p<0.01$). There was no significant difference in latency of the N1 peak (32.7±8.5 at 3Hz and 35.0±9.9 at 1Hz) or of the P0-N1 rise time.

The measure of postmenstrual age (PMA), which is gestational age plus postnatal age was used in comparisons. The mean PMA for the 40 infants was 40.2±1.5 weeks (range 36.5 - 43 weeks). Distribution of the cortical SEP waveforms in relation to age is shown in table 6.5. An accumulation of absent responses and forms S and A is seen in the least mature infants. Waveforms P and M predominate in older infants with P commonest between 38.5 and 40.5 weeks and M between 40.5 and 43.5 weeks. The contingency distribution was significant in Chi2 test ($p< 0.001$). Rank

correlation of age with the main SEP variables was undertaken (Table 6.6). There was a significant negative correlation with postmenstrual age for C2, P0, N1 and P1 latencies, N1 rise time and central conduction time (CCT). Amplitude of the N1 peak did not significantly correlate with age.

The influence of sleep state was unclear and in the absence of polygraphic recording cannot be rigorously argued. Most of the infants did not markedly change sleep state during the recordings and change in waveform did occur within specific sleep states. In infants who remained in quiet sleep without apparent state changes throughout the study there were differences in waveform seen. In infants who moved from wakefulness to quiet sleep over the course of the study there was often a drop in amplitude of the response without marked change in waveform. In general, infants in a state of quiet wakefulness or who were alert had the more 'mature' waveforms M and P. It is possible that sleep state could be having some effect on the waveform but it is unlikely to be an important contributor to the variability seen.

Central Conduction Time

The CCT, which aims to give a measure of the intracranial part of the somatosensory pathway, was calculated from the difference between C2 and N1. As there were not major changes in the cervical response within the group of infants it follows that trends in CCT reflected changes in N1 latency.

Ipsilateral cortex

The main purpose of recording at the ipsilateral cortex was to confirm the unilateral nature of the near-field potentials in response to median nerve stimulation. An evaluation was made of the findings on the ipsilateral cortex.

A positive peaked wave similar in appearance and latency to the P0 potential on the contralateral cortex was noted on 149 of 215 recordings (69%). Right median nerve stimulation gave a latency of 16.8±1.2 msec and 17.0±1.3 msec on the left. This was not significantly different from the P0 latency on the contralateral cortex. In 103 SEP (49%) a low amplitude negative wave followed the P0 component. Its peak was 26.1±2.9 msec on right median nerve stimulation (24 infants) and 27.0±2.9 msec on the left (25 infants). Amplitude was low i.e. 0.5±0.1 μV on both sides. There was a highly significant difference ($p<0.0001$) between the ipsilateral and contralateral amplitude when a negative wave was seen in both, with a mean amplitude

0.8μV higher on the contralateral side. The wave seen was vague and floated back towards the baseline without a succeeding positive peak.

6.5 Discussion

In retrospect stage one of the study could have been performed on a more rigorous basis. A larger number of infants could have been studied with variation of parameters within rather than between infants. The question of stimulus frequency was, however, addressed in stage 2. This showed the importance of a slower rate of stimulation in the less mature infants. The number of stimuli was best to be as high as possible and a 5Hz stimulus gave a reasonable acquisition time. The constantly updated average was displayed on the oscilloscope during acquisition and so it could be observed that waves were not lost due to fatigue of response with the high number of stimuli. When a lower number were used with slower stimulation frequency the cervical waves were less clearly defined.

On theoretical grounds it was important to keep the bandpass as wide as possible (Desmedt et al 1974) and data in stage one showed that a high pass filter at 10Hz and a low pass filter at 3000Hz did allow the collection of data with acceptable levels of electrical interference and avoided distortion of components which would have occurred with lower low pass filter, which would also have prevented collection of cervical data.

The data collected in stage 2 allowed examination of the range of response with stimulus frequency and intensity, sleep state and postmenstrual age as potential influencing factors. As discussed in chapter 4.6 normal SEP data to upper limb stimulation in the newborn using a consistent technique have previously been reported by a number of authors (Hrbek et al 1968, Hrbek et al 1969, Desmedt and Manil 1970, Blair 1971, Hrbek et al 1973, Cullity et al 1976, Desmedt et al 1976, Pratt et al 1981, Laget 1982, Willis et al 1984, Gorke 1986, Zhu et al 1987, Laureau et al 1988, Klimach and Cooke 1988a, George and Taylor 1991). In this study an identifiable cortical response was measured in at least some runs in 39 of our 40 subjects (97.5%) which is higher than in most previous studies.

The mean latencies of the major cervical peak and of the early cortical potentials found in this study are generally longer than that of smaller series of infants previously reported (Willis et al 1984, Zhu et al 1987). Although part of the variation may be explained on the basis of method the main reason would appear to be the scatter of postmenstrual age and the

inclusion of less mature infants in this study. If only the SEP results with cortical waveform M are included these results would be in good agreement with previous series (see chapter 4.6). However, this work represents the study of 40 consecutive normal term infants and draws attention to the variability not previously reported in the literature. The large percentage of absent SEP in Willis and colleagues' study (1984) may be accounted for by rejection of less mature waveforms. Laureau et al (1988) in their study of changes in SEP over the course of early infancy noted that there were more marked differences with maturity in the cortical response than in the Erb's point and cervical potentials. The results of the present study suggest that even in the range of postmenstrual age around term there are marked changes in cortical SEP.

There are a number of factors known to affect EPs that are possible other variables in this study and need to be considered. Hypoglycaemia has been shown to affect the auditory evoked potentials of neonates and the SEP of older children by causing lengthening of latencies and even abolition of response (Koh et al 1988). By studying our infants within two hours of a feed this was unlikely to be a factor.

Temperature has a major effect on conduction in nerve pathways but the effect does not have a linear relationship. It has been shown that over the range of 30°C to 35°C there is little change in sensory conduction velocity (Todnem et al 1989). The infants in this study were wrapped in a cot in a warm hospital room. There was no clear trend in the latency of C2 and this value was remarkably constant within individuals. Only if this latency, representing peripheral sensory pathway conduction, was altering could one postulate changes in cortical waves affected by temperature. This was not so.

It was also undertaken to stimulate the median nerve above motor threshold with a short duration stimulus thereby ensuring repeated recruitment of the largest fastest conducting fibres to ensure that changes seen could not be accounted for by dispersion of the electrical stimulus within several fibre types and therefore changes in the nature of the travelling wave up the somatosensory system. Despite this, changes were seen with uncovering of cortical waveform with increase in stimulus intensity or decrease in frequency. It is likely the less mature infant's central pathway is less capable of responding to frequent stimuli as suggested by the uncovering of a response on reduction of stimulus frequency in some of the

least mature infants in this study. The only authors to have studied SEP in a large number of preterm infants (Klimach and Cooke 1988a) used a 1Hz stimulus.

As discussed in chapter 4.6 the effects of sleep state are variously reported in the literature. Sleep state can only reliably be determined by full polygraphic recording of the infant and this was not done in this study. Visual assessment of sleep state did not indicate any clear effect on latency. It may well be, however, that some of the variability in waveform may be accounted for by sleep state but this variable cannot be systematically analysed. There was a tendency towards the more mature forms in wakefulness. Interestingly a recent report (Laureau and Marlot 1990) has also reported variability in cortical waveform which was more marked on median nerve stimulation than tibial nerve stimulation. The authors speculate on differing maturation in fibre pathways but do not mention sleep state.

As described in chapter 4.1 the waveform measured at the cortical electrode in adults is thought to represent firstly the radiation of a dipole from a generator at the primary somatosensory cortex and then other electrical events including other generators. There is also data from principal component analysis of neonatal SEP (Karniski 1992) to support the view that the first negative peak of the SEP measured from "cortical" scalp electrodes is from a tangential dipole located in the post-central gyrus. Obviously variation in waveform will occur if the 'viewing' electrode moves significantly in relation to the dipole. This would be a possible explanation for changes in waveform encountered. The author believes that this is not the explanation as in the small number of infants studied at C3, C'3 and C"3 there was no change in waveform. In addition, there was good agreement between left and right within infants with respect to waveform. The visual examination of a waveform has a large subjective element, particularly in defining the transitional forms P and A. However, significant differences in most measured parameters were found between the form M and P on one side and the form S on the other side. Table 6.5 shows a clear trend of waveform with maturity. It would therefore appear that the inevitable slight differences in spatial relation of the scalp electrode and the primary somatosensory cortex are not the explanation for differing waveform.

These data are cross-sectional and infants were not studied serially over a prolonged period to study the day to day variability. However, several runs over each median nerve were collected as is good practice in all EP studies.

It was found that variability occurred even in the course of a two hour recording session with the possible influences as discussed. These results would stress the need for repeat studies in SEP in the newborn as in any other subject.

Possible explanations of waveform variability

As outlined in chapter 2, there are important changes in the nervous system before and around birth that may well offer explanations of some of the findings of this study. In the immediate postnatal period there is explosive development of the dendritic tree with a rapid increase in length, size and degree of branching. Studies of fetal sheep (Bernhard and Meyerson 1972, Persson 1973) have correlated cortical neuron development with cortical EPs. These studies showed positive first potentials thought to be due to blind ending afferents with no cortical connection. Subsequent development of positive-negative swings were associated with differentiation of cortical layers IV, V and VI and increasing complexity was associated with further cortical differentiation and dendritic development.

Other factors influencing the shape of cortical waveforms are changes in cortical neuronal function as discussed in chapter 2.8. Immature cortical neurons have slower rise time and longer duration of excitatory postsynaptic potentials (Purpura and Shofer 1972). The long duration is likely to be accounted for by temporal dispersion of the afferent volley in immature fibres and from the relative density of synapses on the soma and dendritic tree of the neuron.

There is good evidence from the results to postulate that there is a progression of waveform from S as the most primitive through A and P to the mature form M. The trend of latencies is clear and the grouping of the forms S and A to the least mature infants and P and M to the more mature is also strong evidence. When more than one form was found during an infant's study it was almost always of two adjacent forms, especially of P and M. In the infants with runs without a clear response the other runs which did show an identifiable waveform were normally of form S, the postulated least mature form. No infant had forms S and M.

The least mature waveform has a slow time course and is relatively simple suggesting that it is not a composite of several different events. The long duration of the depolarisation and the slow rise time of immature fibres would account for the S waveform observed in the least mature infants in this study.

With the development of intercortical connections and proliferation of synapses and soma/dendrite development the responses will become faster and more defined. This could give rise to a clearer faster wave such as waveform A. This waveform was also of a greater amplitude which may reflect an increasing number of functioning elements or a more concerted electrical event due to lessening dispersion of signal within the pathway with increasing neuronal maturity.

Other electrical events may be occurring within the first 50 msec in the maturing infant after median nerve stimulation and other components with a positive polarity may cause a distortion of the peak with the truncation of the negative rise and thereby leading to form P. Form M was the most mature and was not dissimilar to an adult response over a longer time course and therefore it may represent activity in two cortical dipoles served by the thalamocortical radiation with consequent positive-negative swings.

As has been discussed in chapter 2, myelination is also rapidly progressive at this time and is occurring at a time of growth and maturation of neurons. This would contribute to the decrease in N1 with increasing complexity of the waveform.

The bilateral representation of the P0 peak in 69% of SEP measured from a scalp electrode is consistent with the idea of it being a far-field potential arising from subcortical structures. The appearance of a negative wave on the ipsilateral cortical trace is also suggestive of far-field components which may be subcortical and may also be making a contribution to shaping the waveform on the contralateral cortex. The significantly greater amplitude of the contralateral negative wave bearing the N1 would suggest it to be near-field activity in the primary sensory cortex, although clearly not orientated such that a volley was directed at the recording electrode. There may well be substantial contributions from subcortical structures to the neonatal 'cortical' waveform.

The statistically significant relationship between the complexity of the cortical waveform and increasing postmenstrual age is in agreement with the known incomplete maturation of the intracerebral part of the somatosensory pathway, particularly the thalamocortical fibres (Yakolev and Lecours 1967). While the cervical potentials have the complexity and form of the adult response the cortical potentials are very variable particularly in their later components. Multiple generators are known to contribute to the conformation of the short latency adult SEP (Desmedt and Cheron 1981b, Deiber et al

1986, chapter 4.1). The small number of recording channels employed in this study could not give information about the origin and homology of differing components. It is interesting to speculate whether techniques such as brain mapping may allow us to determine if the increasing complexity of the waveform is due to increasing complexity of the response of the primary somatosensory cortex or to the slotting in of different generators into a basic primitive waveform, presumably from the primary somatosensory area. It may be that if the sweep time was increased a second negative wave as seen in the M form may have been uncovered in those with the less mature form.

An altered form of evoked potential is sometimes seen in pathological circumstances, although less important than abnormal latency of loss of response (Jones 1982b). The change of form may be accounted for by abnormal dispersion of conduction velocities in the relevant pathway and/or fall out of some conducting fibres. In the human neonate it has been stated that the appearance of a more primitive pattern can be observed in spontaneous electrical brain activity in pathological states (Ellingson 1980). It is therefore very important to have a knowledge of the range of normal waveform and latencies in the healthy newborn in order to make valid interpretation of the SEP in neurologically sick infants.

It has been shown that SEP can be consistently measured in term infants, but that the response is variable between and within infants and reflect the great changes taking place in neurological pathways around term. The main determinant of cortical SEP is the maturity of the infant as expressed by the post menstrual age.

Table 6.2

SEP variables measured in the 40 infants

Parameter	No. Observations	Range msec	Mean msec	S. D. msec
Right C1	38	7.8-10.8	8.9	0.7
Left C1	35	7.8-11.0	8.9	0.7
Right C2	40	9.0-12.6	10.1	0.7
Left C2	37	9.0-12.6	10.2	0.7
Right C3	30	10.4-14.8	12.1	1.0
Left C3	23	10.6-14.4	12.2	1.0
Right Cp	40	14.4-19.0	16.5	1.0
Left Cp	37	14.4-19.6	16.8	1.0
Right P0	39	13.8-19.2	16.8	1.2
Left P0	37	15.4-29.4	17.5	2.7
Right N1	39	22.8-58.8	29.3	6.7
Left N1	37	22.8-51.0	30.1	6.8
Right CCT	39	13.0-47.8	19.2	6.3
Left CCT	37	13.4-39.8	19.9	6.5

Two or three runs are averaged for each subject.

All left-right differences are non-significant in t test for paired observation.

Table 6.3

Right	Left		Difference			
	Mean	s.d	Mean	s.d.	Mean	s.d.
C2 latency	10.1	0.7	10.2	0.7	0.2	0.2
P0 latency	16.8	1.2	17.5	2.7	1.2	1.5
N1 latency	29.3	6.7	30.1	6.8	1.8	2.1
P0-N1 rise time	12.4	6.1	12.6	5.1	2.0	2.2
CCT	19.2	6.3	19.9	6.5	1.8	2.2
N1 amplitude	1.3	0.5	1.3	0.5	0.4	0.3

Two or three runs are averaged for each subject.

All left-right differences are non-significant in t test for paired observation.

Table 6.4

SEP variables measured within cortical waveforms.

Variable	S (n=6) mean ± s.d.	A (n=7) mean ± s.d.	P (n=26) mean ± s.d.	M (n=26) mean ± s.d.
C2	11.0 ± 0.7	10.3 ± 0.5	10.1 ± 0.6	9.9 ± 0.7
P0	21.0 ± 4.0	18.3 ± 3.1	17.1 ± 1.2	16.9 ± 1.1
N1	44.9 ± 7.9	32.6 ± 5.3	28.1 ± 2.6	26.7 ± 2.2
P0-N1	27.4 ± 10.0	14.8 ± 3.3	10.9 ± 1.7	10.0 ± 1.9
CCT	37.2 ± 10.0	22.4 ± 4.9	18.0 ± 2.4	16.9 ± 1.8
P1	81.8 ± 10.7	58.5 ± 9.8	56.6 ± 9.4	37.5 ± 5.0
N1 amplitude (μV)	1.0 ± 0.2	1.6 ± 0.6	1.3 ± 0.5	1.3 ± 0.3

Mean and standard deviation of each variable in msec for each waveform.
Data from identical waveforms are averaged in each subject.
n = number of subjects.

Table 6.5

Comparison of cortical peak latencies between cortical waveforms.

Variable	M-P	M-A	M-S	P-A	P-S	A-S
C2 latency			0.01		0.05	
N1 latency			0.001*		0.001*	0.01
N1 amplitude			0.01		0.02	
P0-N1 rise time		0.05	0.001*		0.001*	0.001*
CCT			0.001*		0.001*	0.02
P1 latency	0.001*	0.001*	0.001*	0.01	0.001*	

Data from identical waveforms are averaged in each subject.

For each parameter, prominent differences (in t test) between waveforms are shown with their p values. As 6 comparisons are made for each variable, a p value smaller than 0.008 (0.05/6) indicates an overall significance of the differences for the variable (Dunn-Bonferroni). Significant differences, confirmed in a non-parametric test (Mann-Whitney) are denoted by an asterisk.

Table 6.6

Distribution of cortical waveforms across the postmenstrual age range.

Age	Absent, S or A	P or M
36.5 to 38 weeks	29	0
38.5 to 40 weeks	21	74
40.5 to 43 weeks	8	83

Chi squared value (for 2x2 table, 36 to 40 weeks combined) is 24.4, $p < 0.001$

Table 6.7

Correlation of SEP variables with postmenstrual age in the 40 neonates.

Variable	Correlation coefficient	p <
C2 latency	-0.529	0.01
P0 latency	-0.683	0.001
N1 latency	-0.705	0.001
P1 latency	-0.507	0.01
N1 amplitude	-0.142	not significant
P0-N1 rise time	-0.730	0.001
CCT	-0.805	0.001

Data from right and left median nerve are arithmetic means in each subject. Spearman's rank correlation coefficient is shown.

6.6 Conclusion

The normal SEP in term infants ?

What then do we designate as a normal response in view of the findings above ? It is clear that the postmenstrual age of the infant must be taken into account and that acquisition parameters must be as detailed above. In previous work on SEP in child and adult subjects there have been two main types of abnormal response noted; latency and/or waveform outwith the normal range or complete absence of response.

A clearly abnormal response would be the absence of recognisable cortical waveform on repeated runs with the stimulus intensity clearly above motor threshold, the stimulus frequency varied to include runs at 1Hz and the sweep time increased to allow measurement of potentials in the first 200msec after the stimulus. If these manoeuvres fail to uncover a cortical response it would appear reasonable to declare the SEP absent.

The identification of abnormality when a cortical response is present is obviously less clear cut. This is further discussed in the following chapter.

It would appear that the first two parts of the hypothesis have been shown to be correct in that SEP have proved measurable and a normal response has been established. However, that response is variable and defining abnormality is clearly a less precise undertaking.

Figure 6.1
Right median nerve stimulation. Superimposed traces of cervical and cortical SEP in a 37 weeks PMA infant Waveform S. Infant 22.

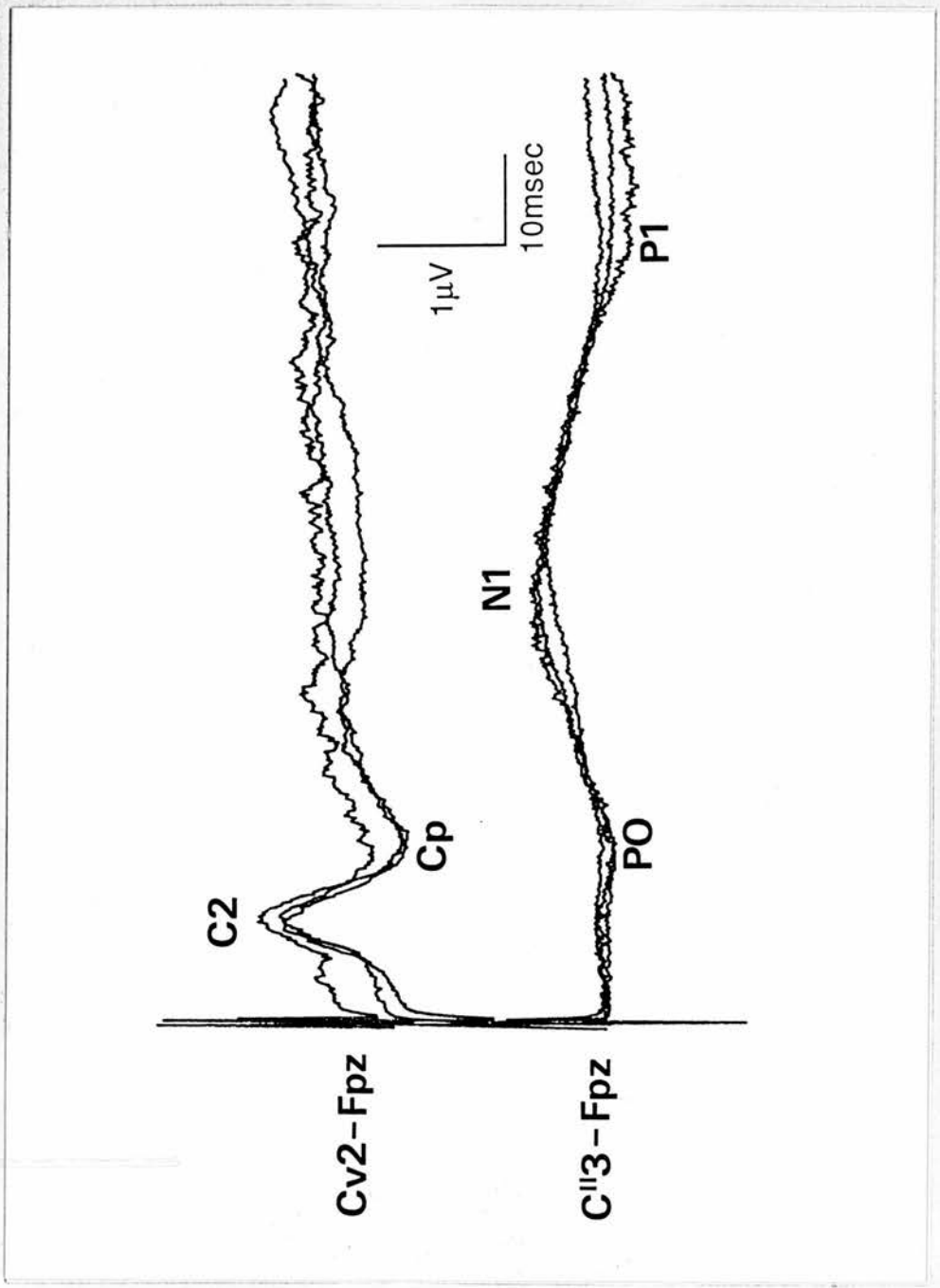


Figure 6.2
Right median nerve stimulation. Superimposed traces of cervical and cortical SEP in a 41 weeks PMA infant Waveform A. Infant 26.

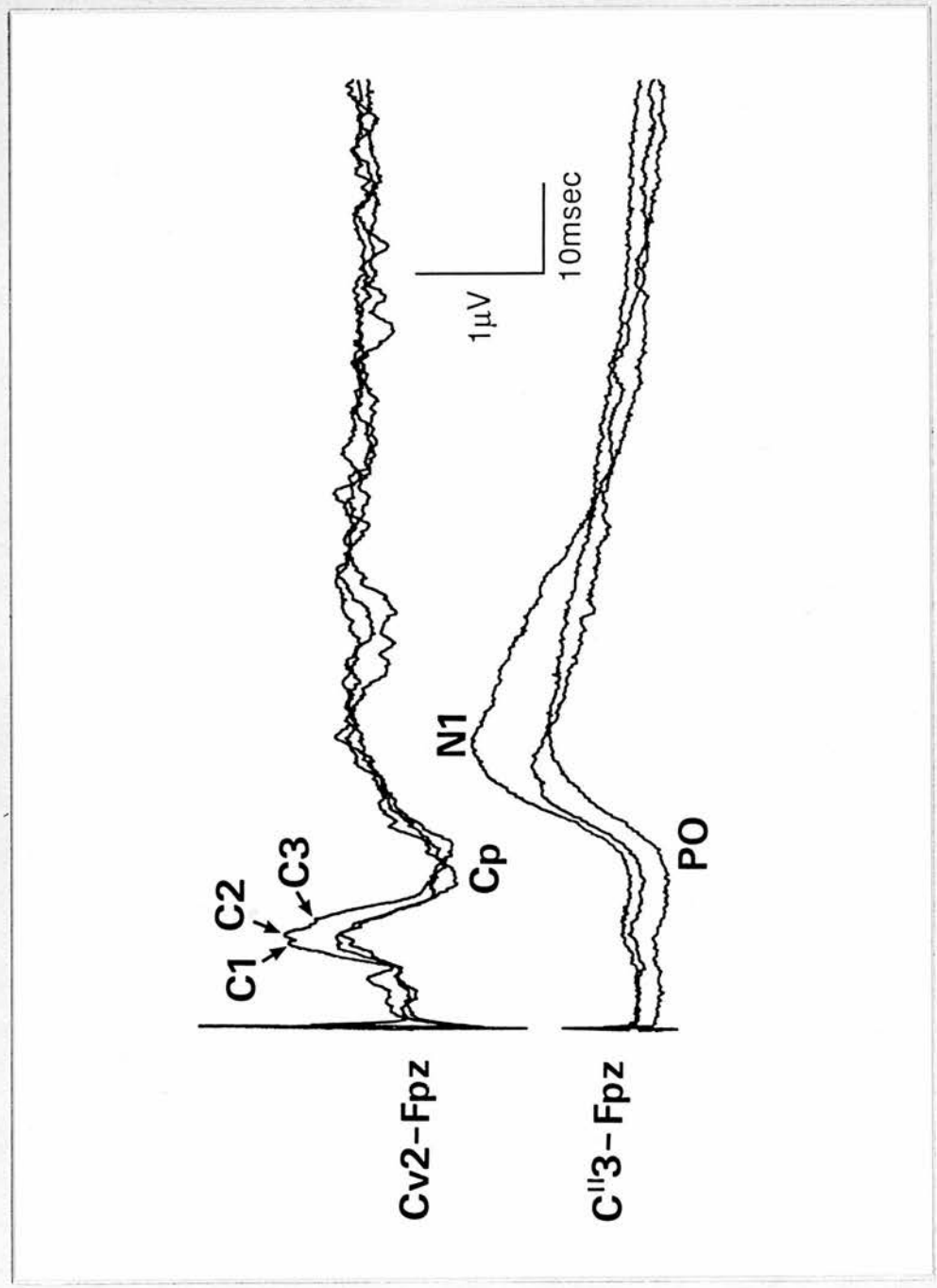


Figure 6.3
Right median nerve stimulation. Superimposed traces of cervical and cortical SEP in a 40 weeks PMA infant Waveform P. Infant 6.

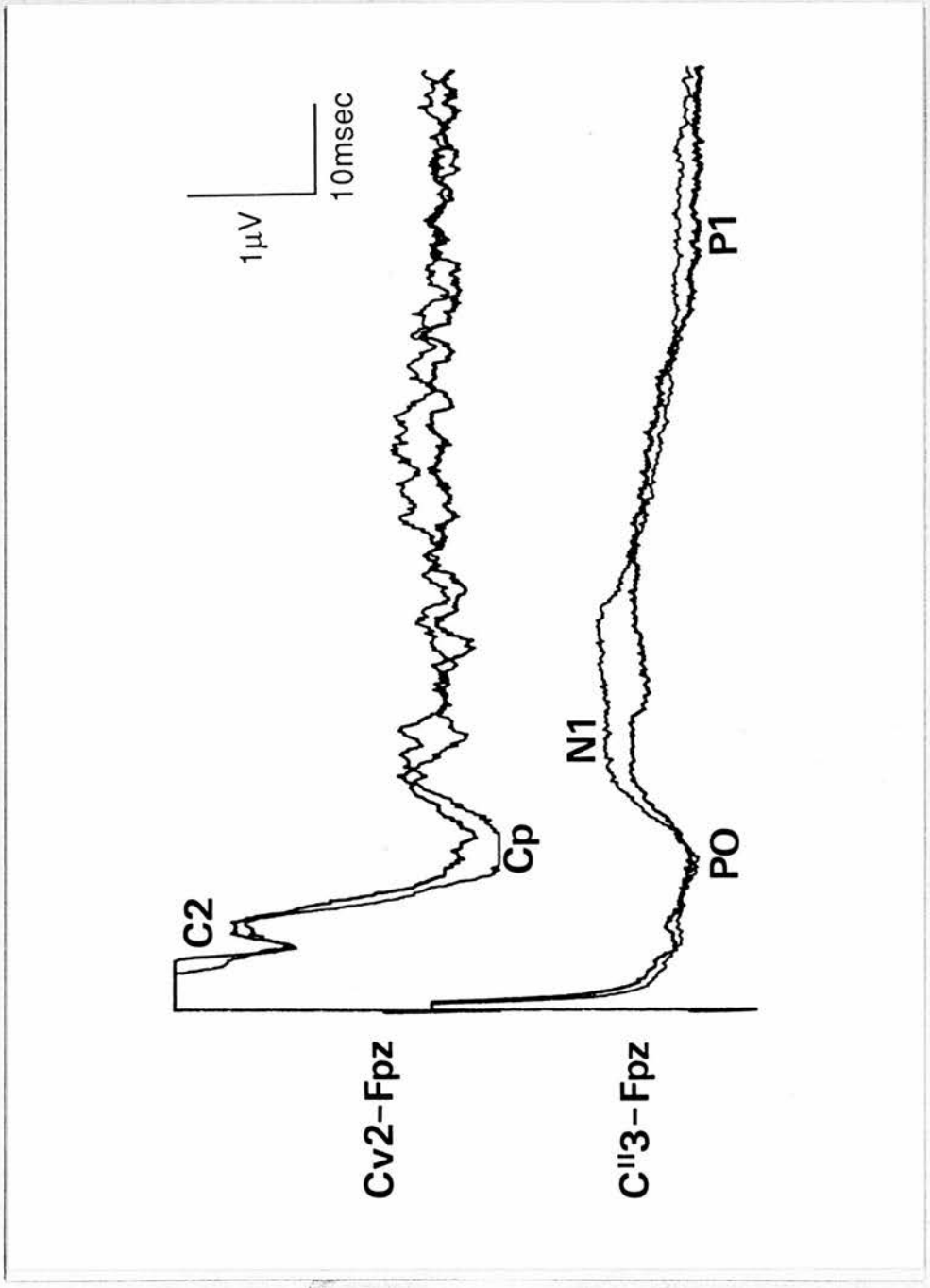
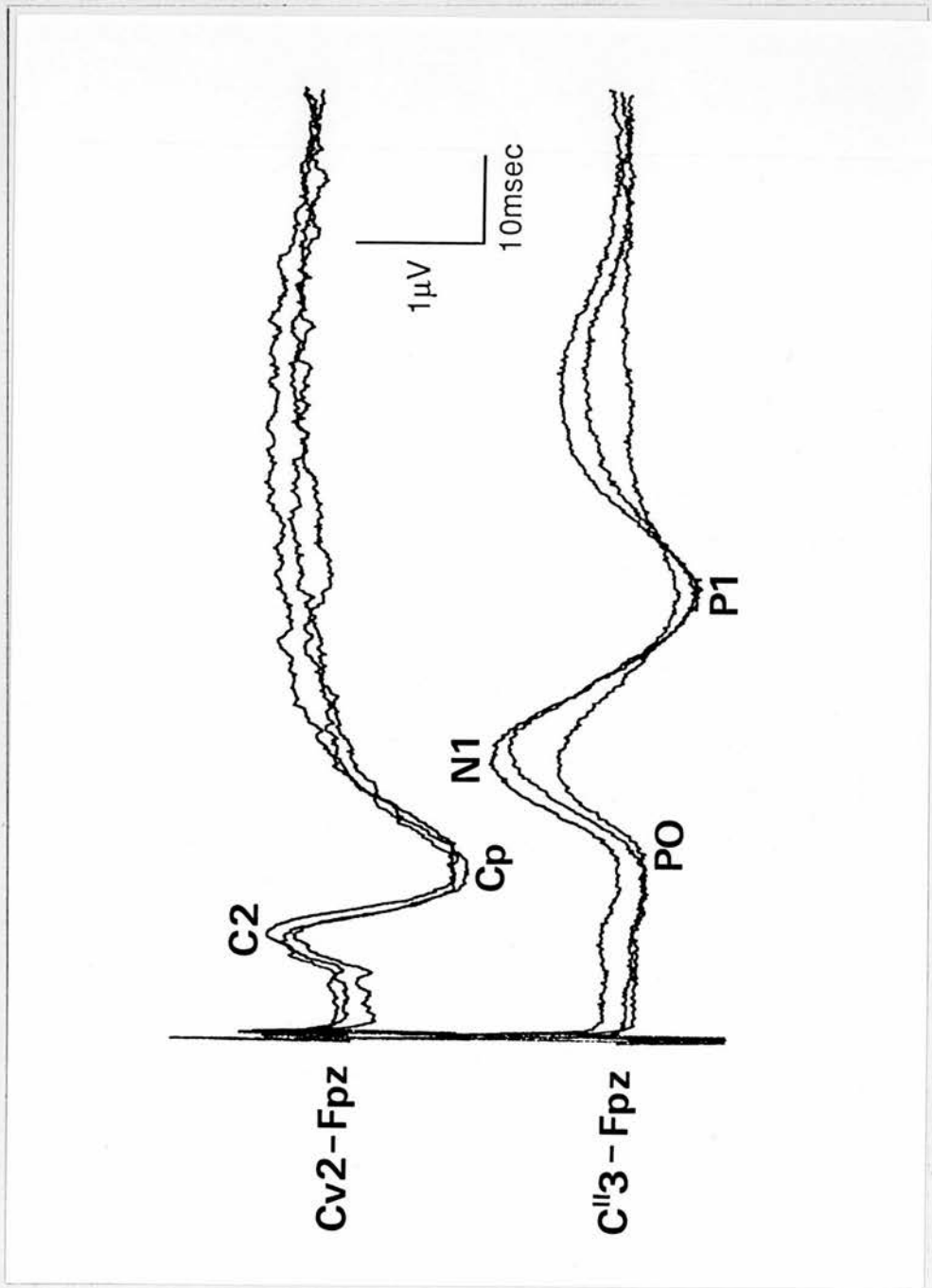


Figure 6.4
Right median nerve stimulation. Superimposed traces of cervical and cortical SEP in a 40 weeks PMA infant Waveform M. Infant 13.



Study of asphyxiated infants

This chapter describes the part of the study concerned with the assessment of asphyxiated term infants by SEP. An account will be given of infant selection, clinical management and the methods and investigation of the cohort of asphyxiated term infants included in the study. The results of SEP measurement are described and discussed as are the clinical features of these infants.

7.1 Selection of subjects

All the subjects in this part of the study population were term infants admitted to the Neonatal Unit of Leicester Royal Infirmary between May 1987 and December 1988. All had a clinical diagnosis of perinatal asphyxia. During the above study period there were 32 infants who fulfilled the following criteria for such a diagnosis.

(1) The infants had a perinatal history suggestive of compromise e.g. abnormal cardiotocograph (CTG), abnormal scalp pH measurements, the presence of meconium staining or more obvious problem such as uterine rupture or cord prolapse. Some of the infants had a history of collapse in the immediate postnatal period.

(2) In addition, as explained in detail in chapter 1.3, they all had to have abnormal neurological signs in the early neonatal period with a pattern of behaviour consistent with the clinical syndrome of hypoxic/ischaemic encephalopathy.

There were a number of infants suggested for enrolment by unit staff who were not included. Any infant who was admitted for observation after resuscitation in Labour Ward and who exhibited only jitteriness but fed normally and was discharged before 12 hours was excluded from this study. It was not felt that this particular clinical picture constitutes significant hypoxic/ischaemic encephalopathy. This judgement is based on the author's clinical impression and the widespread experience of neonatal neurologists described in the available literature, which is detailed in chapter 1.3.

The parents of infants fulfilling the study entry criteria were approached as soon as possible after admission to the Unit and informed consent for the

study of SEP in their infant was sought. Parents were, in general, willing to allow participation and a number took advantage of the offer to be present during recording sessions.

Of the thirty two infants qualifying for admission to the study population only 30 were studied. One infant died within 3 hours of birth and was not at any time clinically stable enough to be studied before death and one set of parents did not give permission for their child to be entered into the study. This child (Infant no. 31) presents a rather interesting case as detailed in 7.8.

7.2 Clinical management

The individual care of the infants in this study was in the hands of the clinicians in the unit. The care was essentially supportive and was as necessary from the description below.

Respiratory:	Intubation for failure to maintain airway. Ventilation for pO2 < 8kPa in 60% O2 pCO2 > 8kPa
Cardiovascular:	Dopamine infusion for low BP. Volume support with plasma as clinically indicated.
Gastrointestinal /Nutrition:	Nasogastric feeding if unable to suck feeds. Appropriate feeding when tolerated. No infant developed necrotising enterocolitis.
Renal:	Management of fluid balance and electrolytes on the basis of blood and urine electrolyte and osmolality values. No infant developed overt renal failure.
Haematological:	Blood transfusion on clinical and laboratory grounds. Appropriate factor replacement in Disseminated Intravascular Coagulation.
Biochemical:	Careful monitoring of electrolytes and glucose homeostasis to avoid the deleterious effects of hypoglycaemia.
Neurological:	No routine intracranial pressure monitoring. Seizures managed with initial loading dose of 20mg/Kg Phenobarbitone followed by 6mg/Kg/day maintenance. Continued seizures then treated with Clonazepam bolus or infusion if control still not achieved. Cerebral Function Monitor (Criticon).

Skin:	Routine care.
Psychological:	Support and counselling of parents and siblings during the encephalopathy and follow-up.
	Bereavement counselling.

7.3 Clinical Details

Appendix 2 gives details of these infants and includes documentation of specific clinical features and any necessary treatment. As would be expected, this cohort of infants presents a very abnormal set of clinical features. In the antenatal period a number of infants were already identified as infants at risk. This was on the basis of poor fetal growth as assessed by antenatal ultrasound and/or maternal factors such as pregnancy induced hypertension.

The immediate perinatal period itself was complicated by documented signs of 'fetal distress' in 22 infants, most of the other infants not being monitored intensively during labour. This "distress" consisted in 10 infants of meconium staining of the thick 'pea soup' variety. Twenty-one of the infants had an abnormal cardiotocograph (CTG) which was normally manifest as deep decelerations with slow return to normal or by a fetal bradycardia. This was the evidence on which instrumental delivery was initiated in many cases. It must here be stated that during the period of this study there were numerous infants who underwent instrumental delivery for signs of fetal distress who were delivered in good condition and showed no signs of hypoxic/ischaemic encephalopathy. The debate rages on intrapartum monitoring (Lancet 1989b) but to the non-Obstetrician it is clear the specific test does not as yet exist.

The mode of delivery was also highly skewed towards instrumental delivery with almost half of the infants having operative delivery. The details are as follows.

12 Emergency Lower Segment Caesarean Section (LSCS)
2 Classical Caesarean Section for ruptured uterus
3 High Forceps
5 Low Forceps
3 Assisted Vaginal Breech Deliveries
5 'Normal' Vaginal Deliveries (2 with Shoulder Dystocia)

Apgar scores were often abnormal with 7 infants with scores of 0 at one minute and 21 having scores of ≥ 3 at one minute. Eight infants still had scores of ≥ 3 at 5 minutes of age. Resuscitation was therefore normally required in labour ward for these infants and some required full resuscitation by cardiopulmonary support and the use of bicarbonate and intracardiac and/or intratracheal adrenaline. After transfer to the Neonatal Unit the infants required varying degrees of supportive care as outlined above and detailed in Appendix 2.

The clinical features of one of the infants demand further discussion. The mother of infant no.23 suffered from poorly controlled diabetes mellitus during the course of her pregnancy and in addition smoked an average of 10 cigarettes a day. The day before delivery she suffered an hypoglycaemic attack which resulted in her being rendered unconscious for an unknown period of time before she was discovered and given Glucagon. The CTG was abnormal throughout labour and she had an LSCS for poor progress of labour and fetal distress. The infant's removal from the uterus was simple and without trauma. He demonstrated, in addition to the features of severe hypoxic/ischaemic encephalopathy, the clinical features of a thoracic spinal cord transection. His lower limbs retained a flaccid paralysis when his upper limb tone became hypertonic and his EMG showed a denervation pattern. Attempt at lower limb SEP was unable to generate cervical potentials although upper limb SEP did show normal cervical potentials. Spinal cord damage normally with obvious trauma, such as rotational forceps delivery, is well recognised (Towbin 1969, Wigglesworth and Silverman 1989, Mackinnon et al 1993) but has also been described before in perinatal asphyxia without trauma (Clancy et al 1984). A study of insulin dependent diabetes in pregnancy (Mimouni et al 1988) suggested perinatal asphyxia to be significantly correlated with maternal hyperglycaemia but not with hypoglycaemia in the immediate prenatal period.

7.4 Methods

All infants had their initial SEP study as soon as possible after admission to the Neonatal Unit and then it was planned to repeat studies every 2 days during the first week and then twice a week until discharge from the unit. Each study aimed to include collection of SEP data from each median nerve. The standard set-up of collecting the averaged response to 1024 stimuli at 5Hz was employed and if no cortical response could be obtained the

stimulus was first increased. Then the longer sweep time of 200msec was tried. Later in the study when the data from normal term infants had been studied it became customary to assess the response to the slower stimulus frequency of 1Hz for 256 or 512 stimuli The bandpass setting, filtering, averaging and electrode placement were all as for the normal range data as described in the preceding chapter (6.3).

Studies were performed on ventilated infants undergoing full intensive care in their incubator. In infants of this severity studies were performed with continuous measurement of transcutaneous oxygen and carbon dioxide levels and intermittent measurement of blood gases and appropriate measurement of blood sugar by BM Stix to ensure no infant was acutely hypoxic or hypoglycaemic. One infant developed significant hyperbilirubinaemia with a maximum level of 242 μmol/l and was studied while undergoing phototherapy. More stable infants were studied in a side room of the Neonatal Unit in a basinette cot. A study on a stable infant undergoing intensive care took from 45 to 90 minutes to perform. There were two reasons for inability to perform recordings on a few occasions. In one particular intensive care space within the Neonatal Unit 50Hz interference could not be surmounted despite cable screening. On two occasions infants were unable to be studied due to extreme neurological irritability which caused such marked muscle artefact and distress to the infant that it was not thought reasonable to proceed.

In addition to the SEP recording serial neurological examinations were performed on the infants based on the Dubowitz neonatal neurological examination (Dubowitz and Dubowitz 1981). This provided evidence for the grading of the hypoxic/ischaemic encephalopathy and also comparison with other studies in the literature which have used neurological examination prognostically.

The results of each recording session were recorded onto floppy disc for subsequent hard copy on paper and analysis. The parameters measured were the waveform and latencies of both cervical and cortical response. Measurement of C1, C2, C3 and Cp latencies were performed on the cervical traces. The cortical waveform was assessed and scored for presence or absence of identifiable waveform and the latencies of P0 and N1 with calculation of the CCT.

7.5 Results

These are detailed in Appendix 3. A total of 111 studies were performed on the 30 infants included giving a mean of 3.7 and a mode of 3 studies. Three infants only had one study before death and the largest number in any one infant was 10 studies. Eighteen infants were studied on day one, 7 were first studied on day two, with 4 first studied on day three and one on day seven.

Definitions

The traces obtained during each study were interpreted in relation to waveform and latencies obtained in the study of the neurologically normal term infants described in chapter 6.

The cervical responses were not markedly abnormal in the vast majority of infants except for some slowing of latency. It was clear that the major changes were with respect to the cortical waveform and latencies. It became clear that abnormal responses were variable and two groups of abnormal response were defined.

The unequivocal type of abnormal response was when there was complete absence of a recognisable cortical response on all runs with manipulations of method as described above to attempt to uncover a response. In the earliest infants the stimulus manipulations were not performed as the important findings of possible uncovering of a cortical waveform with a lowering of stimulus frequency described in chapter 6.4 had not been analysed.

The other type of abnormal response consisted of two broad groups when a response was present but deemed abnormal: either inappropriately long N1 for the encountered waveform i.e. a delayed response; or a very immature response for the infant's PMA. In view of the fact that there was a skew to the left in the normal data it was decided to use the value of the mean + 3 s.d. as the upper limit of normal for the N1 latency. The use of such a value is supported by a recent set of guidelines by the American EEG Society (AEEGS 1994). In some studies the separate runs did not yield the same waves each time and a result 'label' was assigned on the balance of results in each run i.e. one flat trace and two with form S at an appropriate N1 latency would be an Abnormal immature result at 42 weeks PMA. Therefore, the results in each individual study fell into three main types of response:

NORMAL Responses appropriate in both latency and waveform for the infant's postmenstrual age. Latency values were within a range Mean ± 3 s.d and appropriate for the waveform that was present in that trace.

ABNORMAL Measurable response with either a delayed N1 latency (> +3 s.d. from mean) for the encountered (appropriate) waveform or inappropriately Immature waveform with normal N1 latency.

ABSENT Complete absence of identifiable cortical response. i.e. flat traces

The results of each study are contained in Appendix 3. In most cases the SEP were fairly symmetrical, but in one interesting infant (no.20) marked asymmetry was consistently demonstrated and this is discussed below.

The pattern of response over time was very interesting. In the mildly asphyxiated infants the potentials were often persistently normal even if the infant were demonstrating quite marked abnormalities of muscle tone. In general the SEP results trended towards normality. In no infant did potentials become progressively more abnormal with the passage of time as potentials tended to remain abnormal or return towards normality.

Four patterns of SEP over the course of the encephalopathy were noted. The figures 7.1 to 7.4 (at end of this chapter) represent examples of the four patterns with superimposed traces to show reproducibility of each day's response.

(A) Persistently normal response - 11 infants.
(B) An initial abnormal response with all subsequent studies showing normal responses - 2 infants.
(C) Initial response flat or very abnormal followed by a period of flat/abnormal studies and then subsequent improvement towards normality - 9 infants.
(D) Persistently flat response - 8 infants.

It was noted in a number of infants that a P0 might be seen in some runs in the study before the return of identifiable cortical potentials. The Cp defection was always present in these infants in earlier studies.

In the more severely asphyxiated infants with periods of absent response the first studies during recovery with measurable response had delayed or immature waveforms. In some infants these persisted but in most the potentials matured rapidly over the next few studies.

Neonatal Stroke

Infant 20 provided the only instance of consistent marked asymmetry of SEP in the study. He had persisting absence of response on stimulation of the left median nerve until discharge from the unit at 17 days. There was improvement over time in the SEP measured from stimulation of the right median nerve with the initial study showing a mixture of flat and immature Form S traces. Subsequently the findings were of Form P with long latency and eventually normal traces with mature form were encountered before discharge. His CT scan appearances were consistent with neonatal stroke in the territory of the middle cerebral artery more marked on the right hemisphere than the left. The pattern of change over time in his right median nerve stimulation is shown in figure 7.3.

7.6 Discussion

There are potential difficulties with the definitions of abnormal waveform and latencies. The concept of latencies is relatively straightforward allowing for the decision to choose 3 s.d. because of the skewed nature of the normal infant latency data. The concept of appropriate waveform is contentious. The more mature infants in the normal infant study were increasingly unlikely to have the forms S and A. It was felt that these forms, especially if they were the only ones to be encountered in a recording session and might be associated with runs of stimulation resulting in no recognisable waveform, were inappropriately immature for an infant of 41 or more weeks PMA. The balance of all the runs performed in a single session had to be considered in view of the variability shown in the study of normal infants.

The general results of the SEP during the hypoxic/ischaemic encephalopathy are much as would be predicted from knowledge of the literature on similar insults in older children and adults (chapter 4.2 and 4.5). The range of different response in SEP was not great. The SEP was found to

be a fairly blunt instrument in that in the more severely asphyxiated infant the response was not present and abnormal but was absent. If the brain is suffering severe energy failure (chapter 1.1) it seems reasonable to suppose that a profound failure of function will also occur. Studies of clinical neurological examination during hypoxic/ischaemic encephalopathy agree with this idea. With clinical recovery the SEP appeared but seldom in a normal form initially. The return or appearance of measurable SEP in the more asphyxiated infants was often in a form that was immature or delayed for that infant. It has previously been reported (Ellingson 1980) that EEG in neonates may return in an immature form in the neonate recovering from a profound insult. This study may be demonstrating a similar phenomenon in evoked electrical activity in the neonatal brain.

In general the results showed a progression from abnormality to normality presumably with recovering neuronal function. However, there were three infants in whom there were SEP present at the very first recording during the first day of life at 16, 23 and 23 hours after birth, then subsequent recordings in these infants were flat for a variable length of time before showing the common pattern of recovery through immature/delayed forms. It is interesting to speculate whether these infants were displaying the same phenomenon as has been shown by 31P NMRS (chapter 1.4) of preserved brain energy status initially with subsequent loss and failure of function.

Data were included on the cervical response as the presence of a cervical response of normal form and latency shows that any abnormality in response measured at the cortex is due to factors higher in the pathway and not due to peripheral damage as may occur in shoulder dystocia. Interestingly in the two infants with shoulder dystocia the cervical potentials were normal, although it must be noted that neither infant showed any clinical evidence of a brachial plexus lesion.

The effects of sleep state and of drugs need to be considered as they are possible confounding factors in measurement of the SEP. They are features which can themselves have effects which may cloud the clinical picture and so make an objective clinical assessment of the asphyxiated infant difficult. The first line anticonvulsant used during this study was phenobarbitone and it has been shown in adults not to affect SEP (chapter 4.3). It was also noted that some of the infants who recovered from severe encephalopathy could have improving SEP over time in the presence of continuing maintenance treatment with phenobarbitone. As discussed in chapter 4.3, sleep state has

been described as having varying effects on SEP but probably has little effect on early cortical latencies. There is also the problem that recognisable changes of sleep state do not occur in severely encephalopathic infants. Asphyxiated infants have to be studied as best as is possible allowing for their frequently disordered neurobehavioural state. If SEP are to be a useful tool then they have to be robust enough to be used in such infants. It seems extremely unlikely that sleep state could have given rise to the profound abnormalities of SEP seen in this study as the studies of normal infants did not indicate major changes in SEP with change in state.

It was noted in a number of infants that a P0 might be seen in some runs in the study before the return of identifiable cortical potentials. The Cp defection was always present in these infants in earlier studies and this finding does challenge the idea mooted in chapter 6.5 that Cp and P0, which were not statistically different latencies in the cohort of normal infants, are expressions in different electrode pairs of the same phenomenon. It is possible that activity higher in the tract with a negative deflection is necessary for the P0 spike to stand out as a positive deflection in cortical traces and this might explain this finding of its detection before the full return of measurable cortical activity. It could alternatively be that the presence of the P0 potential but no subsequent potentials is due to the recording of the thalamocortical volley with a positivity directed towards the 'active' electrode which peters out amongst damaged fibres. This would be analogous to the first SEP recorded in fetal animals as described in chapter 2.7 (Persson 1973).

The reappearance of the cortical wave as an immature form would support the theory put forward in the preceding chapter that the complexity of the cortical waveform increases in the newborn due to the slotting in to the waveform of the electrical dipole swings of other generators. If generators are affected to differing degrees by the asphyxial insult then the waveform will change because of the removal of influences on the overall wave shape. Also, greater dispersion of neuron conduction velocity within the radiation because of asphyxial damage could be the cause of an immature form, as seen in normal immature infants. This would result in slow and delayed reception of impulses by cortical generators and the separation of their electrical effects. A much greater degree of detail in EP recording using multiple electrodes with bit-mapped SEP techniques or the use of isopotential maps would be necessary to investigate such questions. These

techniques are time and labour intensive and difficult to justify on ethical grounds because of the increased disturbance on a critically sick infant. The current method under discussion took around one hour to perform a recording from time of arrival at the incubator side to time of leaving the infant's intensive care space. Even this time and degree of disturbance needs considerable justification in terms of the information gained.

7.7 Therapeutic intervention ?

As discussed in chapter 1.1 the biochemical derangement of the cell heading towards death includes damage by oxygen free radicals and calcium influx. There has been continuing interest in therapeutic intervention in hypoxic/ischaemic injury with oxygen free radical scavengers and calcium channel blockers. Four of the infants described in this study (nos. 10, 14, 17 and 23) took part in an evaluation of the use of a calcium channel blocker, Nicardipine. The theoretical aspects of this hypothesis are covered in chapter 1.1. Several research teams have reported beneficial effects in terms of neuronal survival in dog (Steen et al 1984) and sheep (Thiringer et al 1987) from infusion of calcium channel blockers after hypoxic-ischaemic insult. There have been no previous reports of the use of these drugs in the human neonate. It was decided in view of the unknown effects of such drugs in the newborn to study only infants with a poor prognosis as defined by severe encephalopathy and the finding of abnormal Doppler cerebral blood flow velocity (CBFV) assessments (Archer et al 1986). Ethical approval was granted by the local ethical committee and a full explanation of the protocol was made to the parents before gaining written consent for study. We aimed to infuse Nicardipine at a dose of 5-10 μg/Kg/hr increasing by 5-10 μg every 60-90 minutes. Regular measurements of CBFV, arterial blood pressure from an indwelling arterial line, CFM trace and temperature and pulse were taken. SEP were recorded three or four times over the 3 to 5 hour course of the study. All of the infants had absent cortical responses before the Nicardipine study and continued to have absent cortical response throughout and in any subsequent study.

The findings of the study were alarming in that two of the infants who showed drops of 18% and 48% in their mean arterial pressure (MAP) associated with skin mottling and clinical deterioration in cardiovascular state. They required resuscitation with plasma. The other two infants showed changes of minus 8% and plus 17% during infusion. Drug levels were not at

potentially toxic levels in any of the infants. It was noted in the two infants showing profound drops in MAP that they had similar drops in CBFV suggesting that their cerebral blood flow was pressure passive and that they had lost the ability to autoregulate.

All four infants subsequently died of their asphyxia but it was not felt that this drug study was contributory in any of them. It must be stressed that these infants were at the most severe end of the spectrum of asphyxial injury. It is unlikely that a calcium channel blocker could make any positive difference to such an infant. It is possible that this effect seen in the worst infants would be due to the severe derangements in autoregulation consequent upon perinatal asphyxia and the potential of calcium channel blockers to depress myocardial function, a side-effect probably potentiated in post-ischaemic muscle. Perhaps, these effects would not be seen in 'survivable' infants, in whom calcium channel blockers could bring benefits. The conclusion reached from this small preliminary study was that any future attempts to use such drugs in the asphyxiated newborn should proceed only with extreme caution in order to avoid doing harm. The author is sceptical as to the potential for major therapeutic intervention in perinatal asphyxia. Further detail of this study can be found in the published report (Levene et al 1990) which is included in Appendix 5.

7.8 Unincluded infant

Infant number 31 presents an interesting case. She was a term infant who showed signs of fetal distress. Her mother had general anaesthesia for a Caesarean section and had a reaction to the injected anaesthetic thus becoming shocked. The infant was flat at delivery but responded well to resuscitation. She was extremely irritable for about 36 hours but settled. She clearly fitted the description of mild (grade 1) encephalopathy. On follow-up at a centre some distance from Leicester she was found to have cerebral palsy and delayed development. This child fulfilled the criteria for only grade one encephalopathy but had abnormalities at follow-up. It may be that there are other explanations for her handicap although this is thought unlikely. It is obviously regrettable that this infant did not form part of the study of SEP.

7.9 Conclusions

There are two further parts of the hypothesis which have been examined in this part of the study. Firstly, SEP have proved to be measurable in the

asphyxiated newborn and it appears that pathology in the relevant parts of the brain has been reflected in measurable abnormalities of the somatosensory pathway as assessed by the data obtained. This study has shown that the most profound abnormalities of SEP are found in the most severely asphyxiated infants and has identified patterns of abnormality over time. The follow-up data is described in the following chapter and then the correlation between SEP results and outcome is discussed in the concluding chapter allowing examination of the last two parts of the study hypothesis.

Figure 7.1
Infant No.4 on Days 1, 2 and 3.
Superimposed traces of response to left median nerve stimulation measured at C"4-Fpz (scalp).
Note consistently normal response of form P (Pattern A).

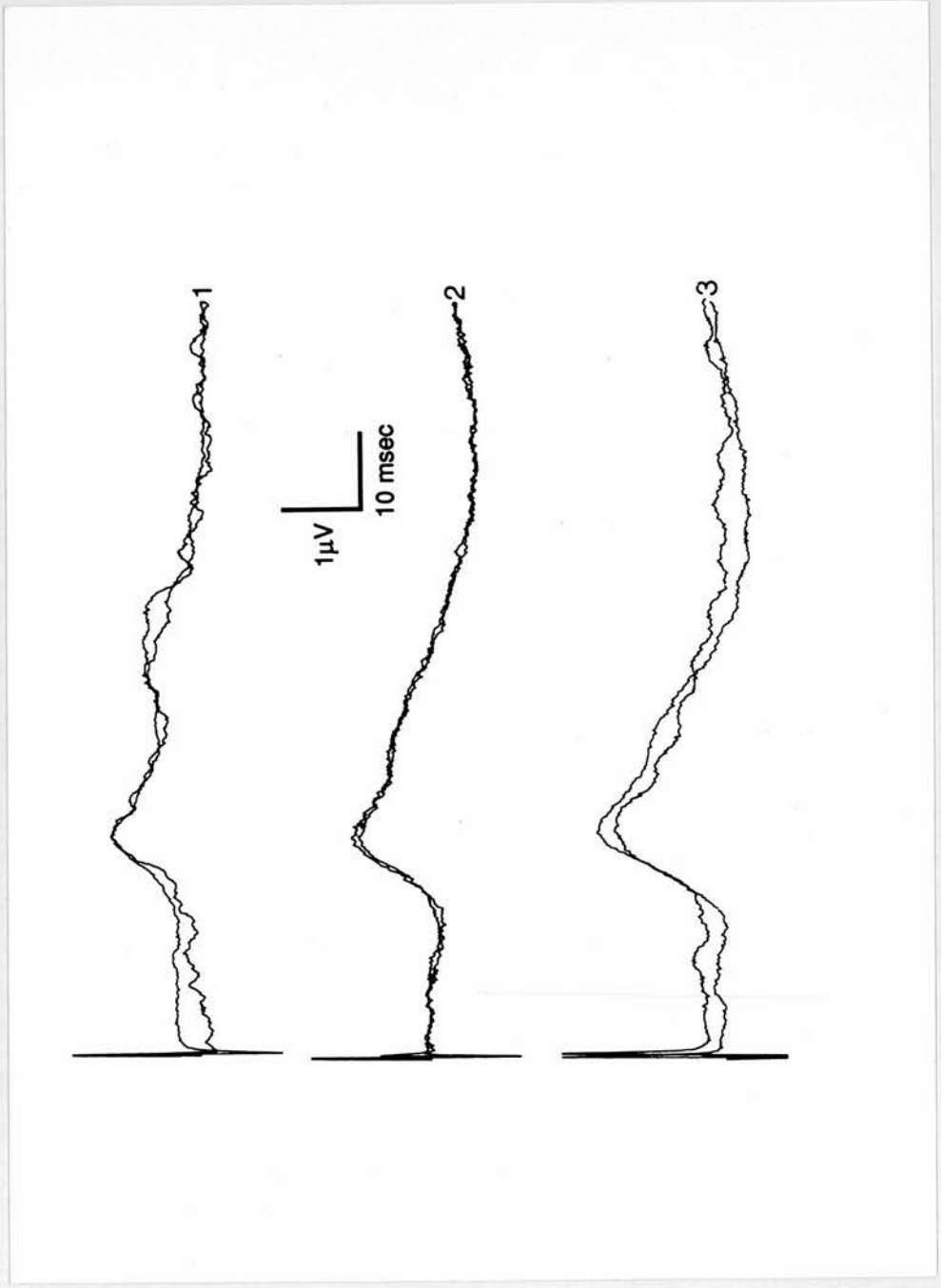


Figure 7.2
Infant No. 29 on Days 2 and 4.
Superimposed traces of response to left median nerve stimulation measured at C"4-Fpz (scalp).
Note indistinct trace of form S followed by normal response of form M (Pattern B).

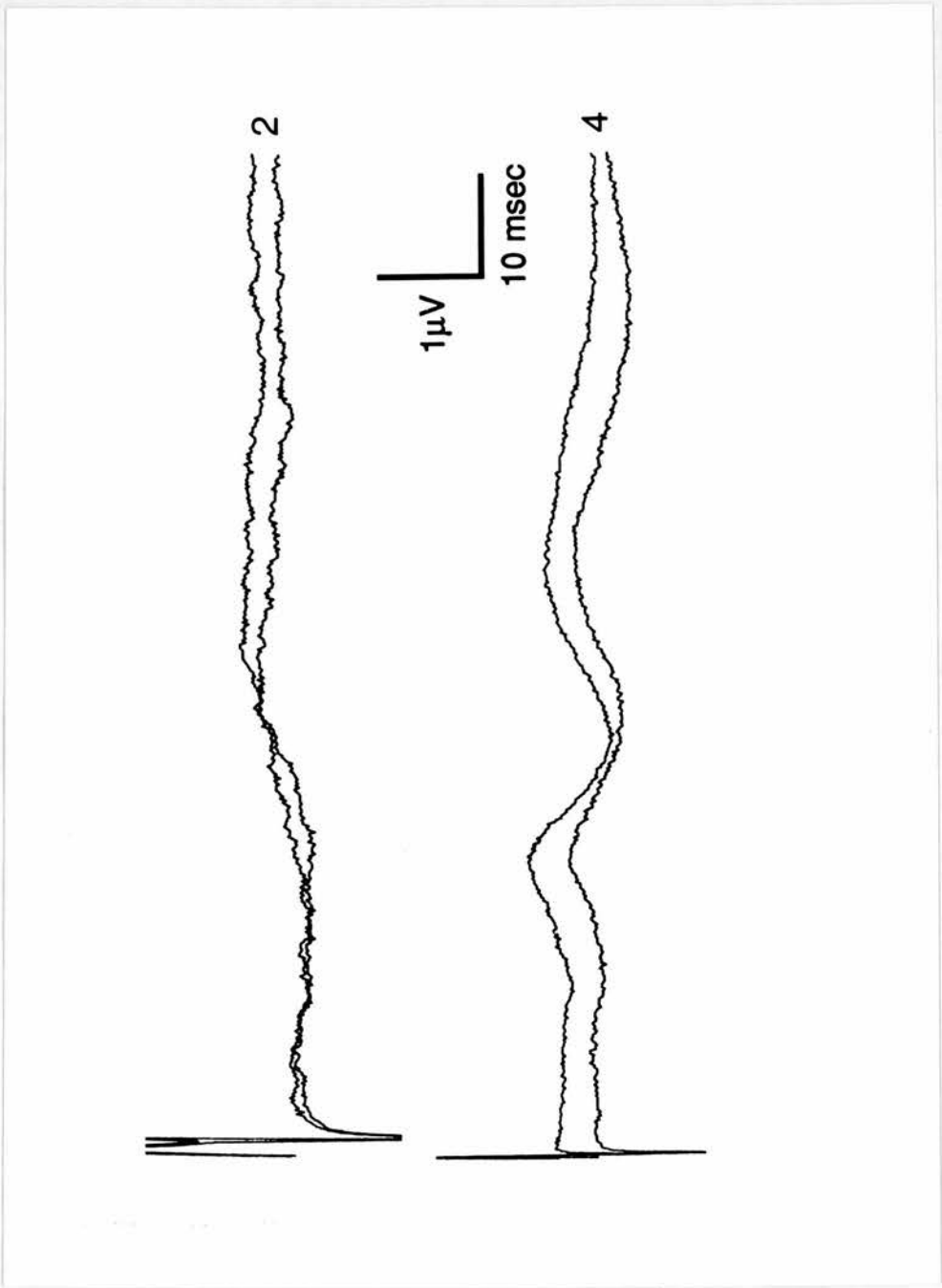


Figure 7.3
Infant No. 20 on Days 2, 4, 7 and 17.
Superimposed traces of response to right median nerve stimulation measured at C"3-Fpz (scalp).
Note trend towards normal response of form A (Pattern C).

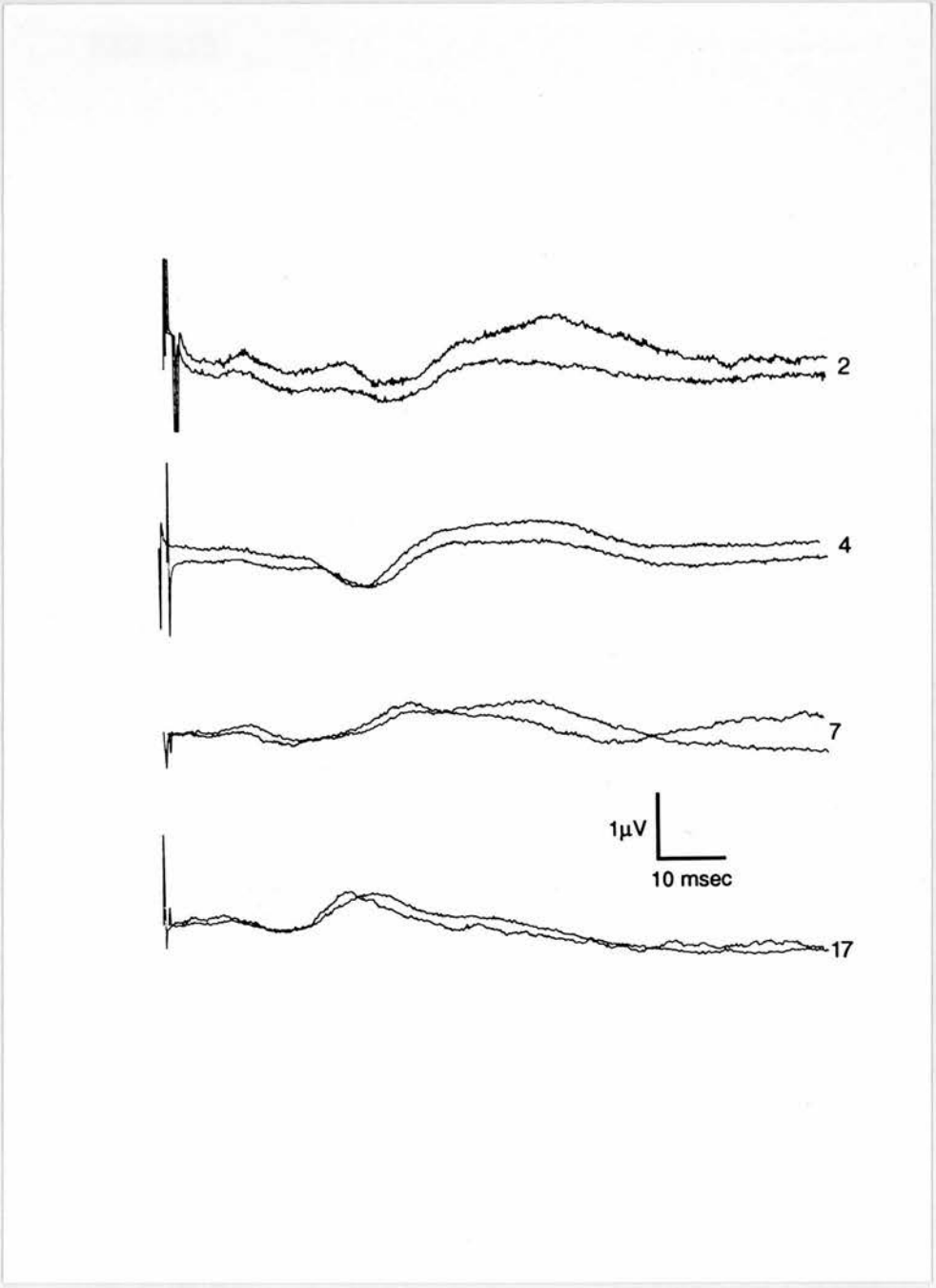
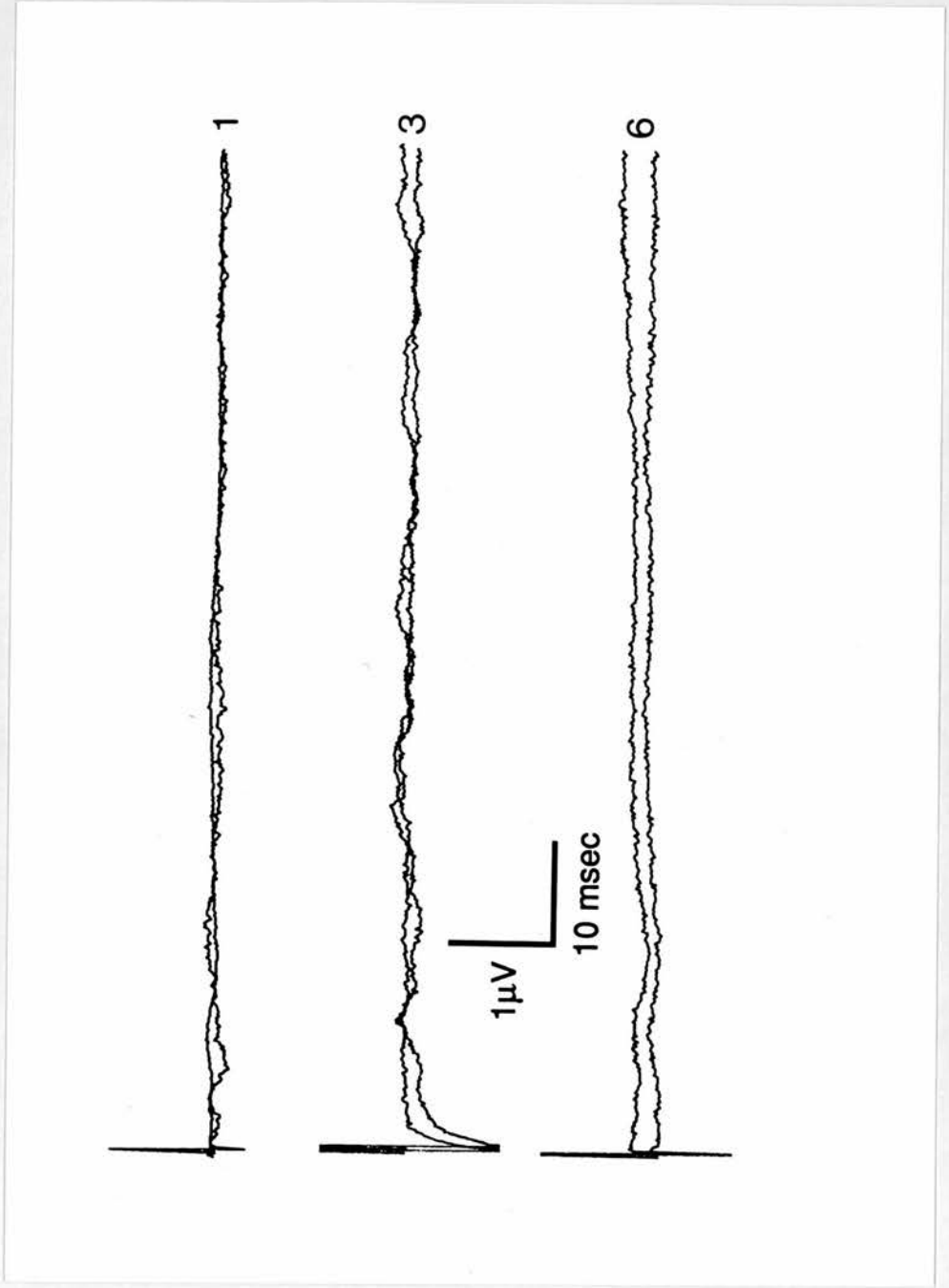


Figure 7.4
Infant No. 14 on Days 1, 3 and 6.
Superimposed traces of response to right median nerve stimulation measured at C"3-Fpz (scalp).
Note consistently abnormal flat response. (Pattern D).



Neurodevelopmental Follow-up

The most important feature of perinatal asphyxia and other neonatal illness is the ability to create adverse outcome of death or handicap. These sequelae are normally attributed to damage to developing neural tissue as a result of asphyxial injury. Any form of assessment of a technique in the sick newborn must include follow-up of the infants to document their outcome so that this may be related to the results of the neonatal assessment. This allows the examination of part five of the hypothesis.

Therefore, the surviving infants in this study underwent a follow-up examination at one year of age. This was performed in order to ascertain the progress of the infants with particular regard to: the presence or absence of cerebral palsy or neurological dysfunction; and to assess the developmental achievements of the infants.

8.1 Methods - Developmental assessment

All but one of the examinations were carried out by Dr. Margaret Graham as described below. The parents of one infant were unwilling to allow a separate assessment and information was therefore gained from routine hospital review of the child's development and neurology at one year of age by the local consultant paediatrician. The method chosen for the developmental information was the Griffiths Assessment. A general neurological examination was also performed.

The families of the infants were contacted just prior to the first birthday or, in two cases, the date of leaving the Leicestershire area. Arrangements were then made to see each child in his or her own home in familiar surroundings. From this part of the study three pieces of information were therefore to be documented: the Griffiths developmental assessment; the Griffiths General Quotient; and the findings on neurological examination.

Although essentially a rather artificial exercise it is necessary in research of this nature to have a formalised system for scoring or grading the child's developmental progress. The assessment that a Paediatrician makes in routine clinical practice is largely subjective and unsuitable if a careful comparison between subjects is desired. It is therefore usual to make use of one or other of the standardised developmental scales. This allows a 'score' to be given and provides numerical data for analysis rather than a verbal word based report. The Griffiths method was chosen for reasons stated

below but it is accepted that others could have been employed. Other possible tests are discussed below together with reasons for the decision to use the Griffiths assessment.

The Denver Developmental Screening test is a much used technique which is based on the results of testing 1036 American children in the mid 1960s. There are four components: gross motor; fine motor-adaptive; language; and personal-social individual behaviour. It is based on 105 items and it is claimed to be so easy to administer that it can be used without specific training. It was designed particularly to show up those infants who are delayed with respect to the age range at which specific skills are normally acquired. It was not thought suitable for this study because it takes no account of patterns of development. Such patterns may have given useful information on asphyxiated infants.

The Gesell Developmental Scales are also based on American data but have been modified by Illingworth's extensive study of development in British children (Illingworth 1983). They are a more concrete form of the normally subjective methods of developmental assessment employed by general and developmental Paediatricians in their everyday practice. It is a valuable tool in the handicapped infant as those tests with rigid scoring systems can give a falsely low score in the handicapped due to a specific delay in one aspect of development dragging down the overall score.

Another test is the Bayley Infant Intelligence Scale which is widely used in the United States. This has two scores, for mental and motor development, and is based on mean and standard deviation of months at which a particular stage of development is reached.

8.2 The Griffiths Assessment

The Griffiths test was chosen for this study for a number of reasons. Firstly, the scales are based on careful work on the abilities of English children, although it can be argued that they are in need of some updating. Secondly, it relies on a single examination and the option of taking account of the mother's history is a useful adjunct to the formal testing. Thirdly, the separation into subscales may have been potentially useful in highlighting particular areas of difficulty in the individual infant and the provision of an overall G.Q. is invaluable in follow-up work of this nature. Lastly, at an important and relevant practical level, our research group in Leicester have

previously used the scales and our investigator has confidence and experience in their use.

The Griffiths Mental Development Scales (Griffiths 1954 and 1970) are a set of standardised scales of infant and young child development based on study of a sample of over 600 English children in the interwar years. Practitioners wishing to use the scales in developmental assessment are required to attend a course in their theory and use. They consist of a formalised development questionnaire and practical test which aim to assess the infants' abilities in five sub-scales of development up to 2 years of age, thereafter a sixth subscale is available. These subscales are :

A locomotion
B personal-social
C hearing and speech
D hand and eye
E performance
(F practical reasoning)

They allow the representation of developmental data on the infant as a set of scales which may highlight a specific problem area e.g. in scale C when speech is delayed due to a specific auditory problem. The results can be presented as a profile or series of scores for the five categories and as a global score or General Quotient (G.Q.), related to the normal derived from Griffiths' original studies.

Only one assessment was to be made of the infants in the study and so care was necessary to ensure that a faithful representation of the child's abilities was documented. The environment in which any developmental work is carried out is most important. It was decided to assess the infants in his or her own home in order to maximise compliance. This decision was based on Dr. Graham's experience in a previous study (Graham et al 1987). In his or her own home an infant is in familiar surroundings with parent(s) present: the examiner and her assessment kit being the only foreign elements. However, in the clinic setting everything except the parent is foreign, and infant may well take longer to settle and cooperate. As much as possible, other siblings, toys and any other possible distractions were removed.

The child was seated on the parent's lap, at a table, with the examiner opposite as the testing commenced. The Griffiths apparatus comes as a kit and contains the necessary equipment for assessment of infants up to two years of age. The details of the kit are included in Appendix 4. The objects are all standardised because if, for instance, the bricks or other such object varied significantly in size, weight or texture from the standard then the element of comparison with normal inherent in the Griffiths test would be weakened.

The assessment itself could perhaps be described as part science and part art. It combines both objectivity (e.g. manages one circle board) with a degree of 'measurable subjectivity' (e.g. looks at pictures in book with interest, likes adult to show book). The examiner has to be able to observe carefully and score the 'scientific' part but also to gain an overall impression of the child's abilities and to allow the child the optimal framework to demonstrate what he/she can do.

Each of the five subgroups of development is arranged as a column of items. These items are arranged in an order decided by the testing used to set up the Griffiths assessment, in increasing order of difficulty. They are also grouped into 3 month periods. An item approximately appropriate to the child's age is presented and the examiner is guided up or down the scales by the child's reactions. The endpoint of the subscale is found when six consecutive items are failed. In general, the examiner tries to complete each subscale before beginning the next but this is difficult to achieve. It is extremely difficult to gain the sustained cooperation of an infant if a rigid approach is employed and this is where experience in the administration of these scales becomes invaluable. Each pass counts as a score of one and these are summated for each subscale. The scores in all 5 subscales can then be added and a mental age calculated. If this figure is then divided by the chronological age a General Quotient (G.Q.) is revealed. Dividing the subscale scores by two gives the mental age for that subscale. If these, in turn, are divided by the chronological age to form a percentage, the individual subscale quotients are revealed. This allows investigators to see if an infant scored particularly poorly in one or other of the subscales.

The Locomotor scale (A) measures achievement in the skills necessary for achieving upright posture and subsequently walking, running, climbing, etc... The items around one year of age are crawling, pulling to stand, side

stepping, cruising, walking with support, standing, walking alone and climbing up one step or stairs.

The Personal-Social scale (B) attempts to assess the infants interaction with other people and objects. It includes, at around one year, such items as finger-feeding, waving "bye bye," playing patacake, obeying simple requests and helping with dressing.

The importance of the Hearing-Speech scale (C) is self explanatory. It assesses the use of meaningful babble, words and musical sounds in the child of 12 months.

The Hand-Eye scale (D) gives an idea of the infants' progress in manipulative skills and takes account of the visual inspection a young infant employs before the stage of exploration with the fingers, and assesses the way in which the hand is used. A child who is functioning at around a year will be given credit for such items as pointing with his/her index finger, playing-rolling a ball, showing interest in and ultimately playing with a toy car and use of a pencil including the grasp employed.

The Performance scale (E) sets a number of practical test situations to the child and looks for the ingenuity and readiness to respond that is displayed. It can be looked upon as a synthesis of elements of the other scales and reflects the degree of cooperation of which the child is capable. The elements of this scale important for the one year old focus on the performance of tasks involving removing bricks from boxes, clicking bricks together, accepting a third brick without dropping, unwrapping a hidden toy and the one circle form board.

The neurological examination was normally performed after the Griffiths assessment and consisted of testing vision and hearing, the cranial nerves and the examination of the child's posture, tone, power and reflexes.

8.3 Results

Ten of the babies in this study died. Nine of these died in the neonatal period between 4 hours and 14 days of birth of whom one was the baby with Spinal Muscular Atrophy. The one infant who survived the neonatal period (no. 23) but ultimately died at 70 days of age was cared for by his parents at home with considerable input from community services. His death resulted from his overwhelming neurological dysfunction.

Of the 20 survivors one did not have a Griffiths assessment. This infant (No. 25) was assessed by his local Paediatrician. He had been transferred to

Leicester from another centre and had presented one of the more interesting sets of SEP results (see Appendix 3). He was seen at 12 months of age and was found to be well within the normal range of abilities for his age and also to show no signs of neurological dysfunction or abnormal tone. The one infant whose parents did not give consent for SEP study (no. 31, see chapter 7.8) was shown to have clear signs of cerebral palsy at 18 months of age with marked developmental delay on follow-up by a neurodevelopmental paediatrician in the area to which she moved. This is not in keeping with the benign nature of mild encephalopathy reported in the literature and it is most unfortunate that this infant did not take full part in the study.

Nineteen survivors were therefore available for more detailed follow-up and were seen at a mean age of 12 months (range 9.5 - 14.5), thirteen of the children being seen within two weeks of their first birthday. The results of their Griffiths assessments are detailed in Tables 8.1 and 8.2.

Table 8.1

Results of Griffiths Assessment

Infant	Locomotor A	Personal -Social B	Hearing -Speech C	Hand -Eye D	Performance E
1.	96	104	100	104	108
2.	100	108	108	96	100
6.	124	116	120	116	132
7.	105	84	68	68	100
8.	79	96	79	92	92
12.	124	110	100	100	121
13.	108	117	121	112	117
16.	127	114	132	105	100
18.	83*	108	121	117	112
19.	100	91	130	96	113
20.	125	96	117	104	108
21.	67	75	67	75	75
22.	58	71	67	62	62
24.	135	123	115	112	108
26.	121	112	112	108	112
27.	117	112	117	108	112
28.	96	92	79	88	96
29.	146	112	133	104	121
30.	67	75	75	71	75

* This infant is a bottom shuffler (as was his father).

Table 8.2
Follow-up details

Infant	Age when seen (months)	Mental age	G Q	Neurology
1.	13	13.3	102	Normal
2.	13	13.3	102	Normal
6.	12.5	15.2	122	Normal
7.	9.5	8.1	85	Doubtful
8.	12	10.5	88	Doubtful
12.	14.5	16.1	111	Normal
13.	12	13.8	115	Normal
16.	11	12.7	115	Normal
18.	12	13.0	102	Normal
19.	11.5	12.2	106	Normal
20.	12	13.2	110	Left hemiplegia
21.	12	8.6	72	Spastic quadriplegia
22.	12	7.7	64	Spastic quadriplegia
24.	13	15.4	118	Normal
26.	12	13.6	113	Normal
27.	12	13.6	113	Normal
28.	12	10.8	90	Doubtful
29.	12	14.8	123	Normal
30.	12	8.7	72	Dystonic

Table 8.3

Details of all infants with any subscale score below 80, with scores.

Infant Number	Locomotor	Personal -Social	Hearing -Speech	Hand -Eye	Performance
7			68	68	
8	79		79		
21	67	75	67	75	75
22	58	71	67	62	62
28			79		
30	67	75	75	71	75

No child was found to have a significant loss of function in the special senses of vision or hearing. Distraction tests were performed in the six infants with depressed scores in subscale C and found to be normal. The results of neurological assessment were normal in 12 of the 19 infants, all of whom had G.Q. above 100. There were two groups within the seven others, all of whom had G.Q. of 90 or less. Three infants clearly had cerebral palsy. Two had spastic quadriplegia (Nos. 21 and 22) with pan-depressed Griffiths assessments and one had a left hemiplegia (No. 20) which did not appear to impair his development. Four infants had more subtle abnormalities. Infant no. 7 had no clear cut neurological abnormalities but was slow with poor hand-eye coordination and was clearly less 'bright' and able than her twin. Infant no. 8 had slightly increased tone in her hamstrings and also seemed "dull." Infant 28 had marked asymmetry of upper limb function although no gross tone differences. The last infant (No.30), in addition to his markedly depressed G.Q., was dystonic with increased tone in all four limbs, more marked in his lower limbs, no saving reactions and poor fine motor function.

The subscale scores in Table 8.3 show that only six infants had a score for any of their subscales whose value was below 80. These six infants all fell into the abnormal outcome group. The only infant with abnormal outcome and consistently normal subscale scores is the infant with the left hemiplegia. Three infants have pan-depressed profiles with low values for each subscale

and those are the two infants with spastic quadriplegia and the dystonic infant. No other infant had a low score in scales B or E. Infant 7 underperformed in Hand-eye and Hearing-Speech and infant 8 in Locomotor and Hearing-Speech. Infant 28 had a depressed score for Hearing-Speech. Subscale C was therefore depressed in all the infants with abnormal outcome except the infant with the isolated left hemiplegia.

8.4 Discussion

This study has produces a good outcome rate (normal survival) of 43% and a poor outcome rate (death or cerebral palsy) of 43%, with the remaining 16% doubtful. These results are not surprising, especially in view of the high proportion of infants with severe encephalopathy, and are in line with the experience reported in the literature and discussed in chapter 1.3.

Criticism could be levelled at the choice of one year as a time for assessment of the survivors. The ages of 18 months and two years are often used in short term neonatal follow-up work. The age of one year was chosen firstly as it minimised the possible effects of external environment and parenting on the developmental progress thus allowing minimal extraneous influences. In addition, it is usually possible to clearly delineate those infants with cerebral palsy at this age but difficult to do so with certainty at a younger age. Similarly, at one year those infants who are to be unscathed from their neonatal insult can be clearly identified as normal. Finally, the detailed follow-up of such infants can prove difficult due to geographical movements of families; the longer follow-up is left, the harder it is to achieve 100% success. With a small sample full ascertainment is even more important.

The group of 'doubtful' infants represents an interpretative and scientific problem. It must be remembered that the neurodevelopmental assessment was done by an investigator blind to the SEP results and that those infants in this category were spontaneously identified as giving cause for concern. It is likely that with time they will come to fall either in the normal category or become more markedly abnormal, although environmental influences will play more and more of a part in their progress. It is extremely likely that infant 30 will tend towards abnormality but with the others it is likely that they will fall into the broad group of infants at normal school.

This question has been addressed before. Piper and co-workers (1988) studied 115 preterm infants at potential risk of neurodevelopmental sequelae with the Griffiths Scale at 6 and 12 months and a neurological assessment at

12 and 24 months. They used 3 categories of finding: normal, suspect and abnormal. At one year 25% of their subjects were considered suspect but this proportion had fallen to 12% by two years. The only appreciable movement in the cohort between 12 and 24 months was the movement from suspect category in either direction. Interestingly, they found that the best predictor of which way a suspect infant would go was the personal-social subscale of the Griffiths assessment at 6 months. All four of the 'doubtful' group had personal-social scale scores (at one year) below 100 as did the three with cerebral palsy, and one normal infant.

In conclusion, it has been shown that the infants in this study had an outcome in keeping with the literature reports of mortality and morbidity in perinatal asphyxia. Death occurred in 10 infants, cerebral palsy in 3, questionable neurodevelopmental features in 4 and 13 infants were unequivocally normal at one year of age. The correlation between these findings and the SEP data will be discussed in the final chapter.

Discussion and Conclusions

The previous chapters of this thesis have outlined the background to this project and then detailed and discussed the findings of each of the relevant parts of the study. Having discussed the SEP results in themselves and detailed the findings of the neurodevelopmental follow-up it is now relevant to seek correlation between these two data to test the final part of the hypothesis presented in the introduction. This chapter will therefore, examine whether SEP have any prognostic value in perinatal asphyxia in the term newborn and compare this with other methods of neonatal assessment.

9.1 Other Prognostic Indicators

As extensively discussed in chapter 1.4 a number of other tests have previously been shown to give a guide to prognosis in perinatal asphyxia. Some of these were employed in the infants in this study. The management of all the infants was under the control of their clinicians and it was not part of the protocol of this study to compare the prognostic information of any other test directly with SEP. Therefore the information is patchy. However, careful clinical examination was performed on all the infants on a regular basis using the Dubowitz neonatal neurological examination and neurobehavioural data is available.

Encephalopathy Grade

The relation between this clinical parameter and outcome is shown in table 9.1. There were 16 grade 3 infants of whom 10 died, one was normal, 2 have spastic quadriplegic cerebral palsy and 3 are doubtful. As the literature suggests grade 2 was the most varied in that of the 6 infants 4 are normal, one has a left hemiplegia and one is doubtful. In our study's 8 other infants we confirmed that grade 1 HIE has a universally good outcome.

Table 9.1 Comparison of encephalopathy grade and outcome

HIE grade	Normal	Doubtful	CP	Died	Total
1 Mild	8	0	0	0	**8**
2 Moderate	4	1	1	0	**6**
3 Severe	1	3	2	10	**16**

This shows that a diagnosis of grade one HIE is only 62% sensitive for a good outcome but is 100% specific. The figures for the ability of grade 3 HIE to predict bad outcome are 88% sensitive and 92% specific.

CT Scan

Seven infants had CT scans in the second week of life. Only one had asymmetrical changes (No.20) with hypodensity much more marked in the right middle cerebral artery territory. He has developed a left hemiplegia. The other 6 infants had scans with diffuse hypodensity of whom one (extensive) died, two have spastic quadriplegia and the others are in the doubtful category, one of whom had extensive hypodensity and is the markedly dystonic child with a G.Q. of 72 (Infant 30). The experience in these infants with CT also therefore accords with the literature that this investigation is accurate in its prediction of outcome.

Electroencephalography

Only 4 of the study infants had an EEG performed. In two the background was normal and both these infants are normal on follow-up. Of the two with flat background traces, one died and the other is infant 30. This would be in accord with the literature experience of the prognostic ability of this investigation.

Doppler

Using the concept of abnormally high P.R.I. (see chapter 1.4) all the infants with this finding either died or had abnormal outcome in accordance with previous studies in Leicester.

Apgar Scores

Seven infants had a one minute Apgar score of zero, of whom 5 died and two are completely normal on follow-up. The other 5 infants who died had Apgar scores of 1, 1, 2, 5 and 10 at one minute. At 5 minutes an Apgar score of 3 or less predicted adverse outcome in 7 out of 8 infants (5 dead, one CP, one doubtful). However there remained a false negative rate for prediction of adverse outcome by this method. This study is again in accord with the literature that the Apgar score is not an accurate predictor of outcome.

As stated above these data are patchy and do not allow any detailed comparison of their findings with the prognostic ability of SEP. It was not part of the study design to compare SEP systematically with any investigation other than neonatal neurological examination. It would have been quite unreasonable to devote the resources necessary to compare and contrast various modes of imaging and EEG with SEP. None of the other prognostic assessment tests discussed in chapter 1.4 such as biochemical assessment of cord blood samples or CSF or assessment of cerebral brain energy status was employed in Leicester during the course of this study.

9.2 Correlation of SEP data with outcome

Firstly it is appropriate to compare the 4 patterns of SEP over time with the outcome of the infants with these patterns. The outcome data have been separated into four groups for this purpose.

Table 9.2

Comparison of SEP pattern and outcome

	Normal	Doubtful	CP	Dead	Total
A Always normal	10	0	0	1*	**11**
B Initially delayed then normal	2	0	0	0	**2**
C Trend towards normality	1	4	3	1	**9**
D Always flat	0	0	0	8	**8**

* Infant with Spinal Muscular Atrophy

The infant with the normal SEP who died was the infant who had Spinal Muscular Atrophy and his death was clearly not wholly attributable to his asphyxia. It can be deduced from Table 9.2 that all other infants who had persistently normal responses or whose responses were only delayed on the first recording all had normal outcome. The outcome was much more variable in those with the pattern of a period of absent cortical SEP followed by a trend to normal waveforms and latencies. All of the infants whose studies revealed no cortical responses at any time died of their asphyxia. The prognostic ability of pattern A or B to predict good outcome is therefore 92% sensitive and 94% specific. Pattern D is 100% specific for death but only 80% sensitive.

It is then pertinent to look at the timing of changes on cortical SEP in the infants whose SEP changed over the course of their encephalopathy, pattern C. This reveals that the one infant with pattern C who had normal outcome (no. 25) had early rapid changes. He had bilateral absent response on day 1. On the second day he had a normal response on the left and a clearly delayed response on the right and on day 3 had a response on the left with a mature form and an N1 latency well within the normal range for all control infants and 0.1 msec more than the mean + 3 s.d. for waveform P. This was accompanied by a normal right sided response. Therefore, he had had normal responses on each side by day 4 of age. All the other infants with normal response by 4 days of age were in the groups A and B. Therefore, normal cortical SEP by 4 days of age was associated with normal outcome.

Looking further at group C did not show any clear difference in SEP between those with cerebral palsy and those in the doubtful category. All of these infant had long periods of absent SEP followed by a long period of delayed or immature responses. There was no cut off point. The possible exception was that the infant with the left hemiplegia (no 20) did not have any cortical response on stimulation of his left median nerve on any of his studies up till 17 days. Meanwhile his right sided response went from absence to delay to normality. Unfortunately his parents were unwilling for any further SEP study.

Therefore, this study showed that persistently normal cortical SEP correlated with normal outcome at one year following perinatal asphyxia and persisting absence of response correlated with death from asphyxial damage. Those infants with changes in the response towards normality who survived unequivocally intact had normal SEP by 4 days after birth.

Direct comparison with the grade of encephalopathy shows little difference. Both early normal SEP examination and mild encephalopathy grade are highly specific for normal outcome but SEP is more sensitive. The advantage of SEP is the ability to pick out those with moderate encephalopathy in whom a good outcome can be predicted. It is argued that the additional use of SEP can improve the sensitivity of neonatal neurological examination.

9.3 Comparison with other studies

Neonatal SEP

The results of this study confirm and expand on the findings of the previous studies in the literature (chapter 4.7). Like Hrbek et al (1977) it was found that the most abnormal SEP were found in the most asphyxiated infants (grade 3). In addition, this study shows the pattern over time particularly with regard to the recovery of response in surviving infants. In the other earlier report (Willis et al 1987), it was shown that SEP in infancy at 2, 4 and 6 months had good predictive ability but the present study takes the predictive abilities of SEP into the neonatal period.

The results described by the Toronto group (Taylor et al 1992) in their study of 57 term infants are very similar to that of the present study. This group uses an SEP technique with a slower stimulation frequency and less sweeps but very similar bandpass. They also found that normal cortical SEP on either side by three days was highly specific for normal outcome but that prediction of adverse outcome by results later in the encephalopathy was less precise. Similarly the Dutch group (de Vries et al 1991) using the technique and normal values of Klimach and Cooke (1988a) came to identical findings. They did not systematically make sequential study of each of their infants but showed patterns of persistently absent SEP associated with poor outcome and normal SEP by the second week followed by normal outcome. As in the present study, delayed latencies, even into the second week, could be associated with several outcome categories.

Although there are elements of the present study which could be criticised, in particular the use of a high stimulus frequency, it is interesting to note that the results are confirmed by other workers using a similar technique except in respect of stimulus frequency.

Other features

There are a number of other features of the study population and their characteristics which merit comparison with the available literature as described in chapter 1.4. There were 3 infants in the present study with IUGR (birthweight < 2.5 Kg at 38 weeks or more). This is a group in whom the literature suggests a worse outcome (Dweck et al 1974). This is confirmed in that 2 have spastic quadriplegia and one is doubtful. This explanation for this may lie in the likelihood that growth retarded infants have

suffered chronic asphyxia in utero perhaps with placental insufficiency resulting in poor growth.

As discussed in chapter 4.2, SEP have been evaluated in adult coma (Brunko and Zegers de Beyl 1987, Walser et al 1985). It was found that persistently absent N20 (analogous to neonatal N1) correlated with death and persistent normal cortical response led to good outcome. The papers discussed in chapter 4.5 on SEP in childhood coma describe similar patterns of SEP to those found in adult studies. The Toronto studies (DeMeirleir and Taylor 1987) of 73 children show SEP results in close accordance with this study and their own study of infants with perinatal asphyxia. They showed death to be associated with absence or gross abnormality of SEP. Their normal survivors had persistently normal SEP or abnormalities only on the first study and abnormal survival was associated with improvement in SEP that was slow or incomplete.

In this study 10 infants died, of whom 8 had no recovery of SEP. The other two died non-cerebral deaths (Spinal muscular atrophy and pulmonary hypertension). Normal outcome was associated with persisting SEP normality or rapid improvement and slow or incomplete improvement of SEP correlated with abnormal survival. As in studies in older subjects it was noted that the return of function mirrors neurological function. This is expected as the evoked response is dependent on cerebral function as is neurological recovery.

9.4 Withdrawal of care in severe brain injury

Timing of prediction of outcome by SEP in this study is in the first week of life. It is now accepted practice in British neonatology that infants known to be severely and irreparably damaged may have their intensive care withdrawn after full informed consultation with the parents. In two infants in this study (nos. 3,14) this was done. SEP results in this study played no part in this decision. It would seem that SEP will not be able to become a part in this decision making process. This is because SEP does not differentiate degrees of abnormal outcome. An infant with absent cortical response on day 5 may still have any of three outcomes: death, major handicap or mild developmental delay at one year. The main role of SEP suggested by the results of this study are that it may be useful to allow a few infants who do not have grade one (mild) encephalopathy and have persisting neurological abnormality who have a questionable prognosis on other criteria to be put

firmly in a good prognostic group on the basis of their normal SEP by 4 days of age.

9.5 Hypothesis revisited

The author believes the data contained within this thesis to have shown the hypotheses to be correct with some important reservations. Somatosensory evoked potentials have proved to be measurable in the term newborn and in the asphyxiated term neonate. A normal range of response using a specific technique was established. However, this range of response was marked within individuals as well as between individuals. The intraindividual variability may be related to technical factors, and in particular, the use of a high stimulus frequency and possible small effects of sleep state. The interindividual variability was shown to correlate highly with the postmenstrual age of the subjects.

The degree of abnormality of the SEP in the asphyxiated infants was related closely to the degree of encephalopathy suggesting SEP to be a good marker of severity of hypoxic/ischaemic encephalopathy. The outcome of the infants was in accord with similar series in the literature. The pattern of SEP over the first week of life correlated with broad outcome criteria. This study showed that the grade of encephalopathy is very specific for outcome in perinatal asphyxia but that SEP may have additional advantage in improving the sensitivity.

9.6 Study Conclusions

1. Somatosensory evoked potentials have proved measurable in the term newborn although with a wide range of normal response with some intrasubject variability and considerable intersubject variability.

2. The response becomes more complex in its waveform and of shorter latency with increasing postmenstrual age.

3. Study of asphyxiated term infants revealed that the more asphyxiated the infant the more abnormal were the SEP results.

4. There was a tendency for SEP results to trend from abnormality towards normality over the course of the hypoxic/ischaemic encephalopathy.

5. Infants whose response was normal by 4 days of age had a normal outcome.

6. SEP did not discriminate between major and minor abnormalities at follow-up at one year of age.

7. The results of this study suggest that SEP have a role in the assessment of the asphyxiated term newborn infant but that they are not markedly superior to existing methods of assessment of such infants.

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Appendix 1

Results of studies on normal term infants.

Stage 1 Work on method of data collection.

Results: Most of the findings in this part of the study are qualitative not quantitative.

13 infants were studied and a descriptive summary is given of the findings and the parameters used.

Infant A
2 right median runs, 50 msec sweep
Cervical potentials low amplitude, highest peak 10.8 msec
Much interference on cortical trace, difficult to interpret
30-1500 Hz, 512 Stimuli

Infant B
1 run right median, 50 msec sweep
Cv7 potentials identified, Much interference
30-1500 Hz, 512 Stimuli

Infant C
2 runs right median, 50 msec sweep
Trilobed cervical peak on Cv7-Fpz
Fz-Mastoid sawtooth appearance
C"3-Fpz cortical wave, peak 32 msec
30-1500 Hz, 512 Stimuli

Infant D
2 runs right median, 50 msec sweep
Bilobed cervical peak, clearer than infants with narrower bandwidth
Fz-Mastoid sawtooth appearance
C"3-Fpz indistint wave
10-3000 Hz

Infant E
2 runs right median, 50 msec sweep
Cervical peak present
Fz-mastoid sawtooth appearance
C"3-Fpz clear cortical wave 32msec peak latency
10-1500 Hz

Infant F
3 runs right median, 50 msec sweep
Clear cervical peak on two runs
Fz-mastoid sawtooth appearance
Clear cortical wave around 21 msec
10-1500 Hz

Infant G
3 runs right median
100 msec sweep - cortical waves well contained within, Cervical easier to see.
Fz-Mastoid sawtooth
256 and 512 Stimuli, clearer waves with 512
Cortical peak at 26-32 msec
10-1500 Hz

Infant H
4 runs right median, 50msec sweep
Cv7 wave unclear
Fz-mastoid sawtooth
512 stimuli - jaggy trace
Cortical wave not clear
10-1500 Hz

Infant I
runs right median, 50 msec sweep
Cv7 electrode poorly separates components
Cortical peak at 20 msec. Higher amplitude at C'3 than C"3
512 stimuli, Bandpass not recorded

Infant J
2 runs each side, 50 msec sweep
Distortion at beginning of Cv7 trace
Fz-mastoid sawtooth
Cortical wave with peak at 22 msec left and right
Bandpass not stated

Infant K
2 runs each side
Cv2 and Cv7 recorded clearer separation of potentials on Cv2 trace
Clear cortical wave on 3 of 4 runs peak around 28 msec
1024 stimuli - much smoother traces
Bandpass not recorded

Infant L
3 runs right median, 100 msec sweep
Mid cervical Cv5 -Fpz with peak at 10 msec, 11.2 and 12.0 msec
C3 and C"3 to Fpz
Cortical wave on each run at C"3 but only on one run at C3
512 and 1024 stimuli - smoother traces with 1024
10-3000 Hz

Infant M
2 runs right median, 100 msec sweep
Cv2 - Fpz clear trilobed peak
C3, C'3 and C"3 compared, referenced to Fpz
Clear cortical waves with peaks within 0.4 msec on both runs
1024 stimuli 10-1500 Hz

Phase 2. Work on range of normal response.

Details on methods employed, analysis and definition of the waveform types and the defined latency points are given in detail in chapter 6.
Latency values are all in msec.

-	=	No point fitting the description identifiable
?	=	Unclear latency point
None	=	No identifiable cortical response
Indistinct	=	Cortical response appears to be present but the waveform does not conform to patterns seen and is indistinct
S,A,P,M	=	Defined cortical waveform responses

Infant 1 41.5 weeks postmenstrual age
Quiet sleep run2, moving run 3, quiet eyes open runs 1 and 4

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	8.4	10.0	-	15.2	16.0	26.4	16.4
	P	8.4	9.6	-	16.4	17.6	26.8	17.2
Left	M	-	10.4	-	16.8	16.8	26.0	15.4
	M	-	10.0	-	17.2	15.6	26.8	16.8

Infant 2 42.5 weeks postmenstrual age
Quiet awake on all 4 runs

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	8.0	10.8	-	16.4	17.2	29.6	18.6
	M	8.0	9.2	-	18.0	16.0	24.8	15.6
Left	M	-	?	-	15.2	15.6	23.2	?
	M	-	9.2	-	16.4	16.4	22.4	13.2

Infant 3 41.5 weeks postmenstrual age

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	-	9.2	12.0	15.6	16.0	28.0	18.8
	P	8.0	9.2	-	17.6	16.4	25.6	16.4
Left	M	8.0	8.8	-	16.4	15.6	26.8	18.0
	M	7.6	9.2	-	16.0	15.6	26.4	17.4

Infant 4 39.5 weeks postmenstrual age
Quiet awake throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	8.8	9.6	-	16.8	16.8	34.0	24.4
	P	8.8	9.6	-	16.4	19.6	31.2	21.6
Left	P	8.4	9.6	11.6	16.8	20.8	35.2	26.6
	P	8.4	9.6	12.4	16.4	20.8	33.6	24.0

Infant 5 40.5 weeks postmenstrual age

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	8.4	9.6	-	18.4	16.4	27.6	18.0
	M	8.8	9.6	-	18.8	16.4	25.6	16.0
	M	8.4	9.6	-	15.2	15.6	27.6	18.0
Left	M	8.0	9.6	-	15.2	16.8	31.2	21.6
	M	8.4	9.6	-	16.8	15.2	38.0	28.4
	M	8.4	9.6	-	16.4	16.4	30.4	20.8

Infant 6 40 weeks postmenstrual age

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	9.2	10.4	-	16.4	15.6	28.0	17.6
	P	9.6	10.4	12.8	19.2	17.6	30.8	20.4
	M	9.6	10.4	12.0	17.2	17.6	29.6	19.2
Left	P	9.2	10.4	12.0	17.6	19.2	29.6	19.2
	P	9.2	10.4	11.6	16.8	18.0	28.4	18.0
	P	9.2	10.4	13.6	18.0	16.8	29.2	18.8

Infant 7 41.5 weeks postmenstrual age

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	8.4	10.0	-	18.4	16.0	23.2	13.2
	P	8.0	9.2	-	18.0	18.0	23.6	14.4
	P	8.8	10.0	-	16.4	16.4	22.8	12.8
Left	P	8.8	10.0	12.4	15.6	18.4	25.6	15.6
	P	8.4	10.0	12.4	17.2	15.6	26.8	16.8
	P	8.4	9.2	-	17.6	16.4	23.6	14.4

Infant 8 40.5 weeks postmenstrual age
Periods of quiet sleep and quiet wakefulness during recording session

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	8.0	9.6	11.2	18.0	17.2	27.2	17.6
	P	8.0	9.6	10.8	16.8	16.4	28.0	18.4
	P	8.0	9.2	11.6	16.4	16.0	29.2	20.0
LEFT	P	8.4	10.0	11.6	16.8	16.0	26.0	16.0
	P	8.0	9.6	11.2	17.2	14.8	26.8	17.2
	P	8.4	10.0	11.6	17.2	15.6	26.0	16.0

Infant 9 42 weeks postmenstrual age
Eyes open quiet throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	8.8	10.0	11.6	16.0	16.0	24.8	14.8
	M	8.8	10.0	12.0	17.6	15.2	25.6	15.6
	M	8.8	10.0	11.6	18.0	15.2	24.4	14.4
Left	M	8.8	10.0	-	16.4	16.8	26.0	16.0
	M	8.8	10.4	-	16.0	17.2	26.0	15.6
	M	8.4	9.6	11.6	16.8	15.6	25.2	15.6

Infant 10 37.5 weeks postmenstrual age
Deeply asleep during study

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	None	9.6	10.4	-	17.6	-	-	-
	None	9.2	10.4	-	16.4	16.8	-	-
	None	9.6	10.4	12.8	15.6	-	-	-
Left	S	8.8	10.8	-	17.2	27.2	50.4	39.6
	S	8.8	10.0	10.8	16.4	30.8	49.6	39.6
	S	9.2	10.0	10.8	16.4	30.4	50.4	40.4

Infant 11 43 weeks postmenstrual age
Quiet awake throughout

Side	Form	C1	C2	C3	Cp	p0	N1	CCT
Right	M	8.4	9.2	-	16.8	16.8	24.4	15.2
	P	-	9.6	-	14.4	14.4	26.8	17.2
	M	-	9.6	-	16.8	16.4	24.0	14.4
LEFT	P	8.4	9.6	10.4	17.2	15.6	25.2	15.6
	P	-	10.0	-	16.0	16.0	31.2	21.2
	P	8.0	9.2	10.8	16.4	16.8	26.8	17.6

Infant 12 41.5 weeks postmenstrual age
Alternated between quiet sleep and quiet wakefulness during study

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	8.8	10.0	-	14.4	13.6	28.0	18.0
	Indis	8.8	10.0	11.6	14.8	16.4	25.2	15.2
	Indis	-	10.8	-	13.2	13.2	27.6	16.8
Left	P	9.2	10.4	-	16.0	15.6	29.2	18.8
	P	-	10.0	-	16.8	18.0	30.4	20.4
	P	8.8	10.0	-	16.8	17.2	28.8	18.8

Infant 13 40 weeks postmenstrual age
Quiet sleep runs 2 and 3, quiet wakefulness runs 1, 4 and 5

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	8.8	10.0	-	18.4	16.4	26.0	16.0
	M	8.8	10.0	-	15.4	16.0	27.2	17.2
	M	8.0	9.2	11.2	15.0	17.6	26.4	17.2
Left	M	8.0	10.0	-	14.8	16.4	24.0	14.0
	P	8.0	10.0	-	16.8	15.6	25.2	15.2

Infant 14 41.5 weeks postmenstrual age
Quiet wakefulness throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	7.6	10.0	-	18.8	18.4	23.2	13.2
	M	8.4	9.6	-	14.8	15.6	22.4	12.8
	M	8.4	9.6	-	15.2	15.6	22.8	13.2
Left	M	8.8	10.0	-	16.4	16.4	23.2	13.2
	M	8.4	10.4	12.4	17.6	17.6	24.4	14.0
	M	8.8	10.4	-	15.2	14.8	24.4	14.0

Infant 15 41 weeks postmenstrual age
Quiet awake throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	9.6	10.4	11.6	18.0	19.6	26.4	16.0
	M	-	9.2	-	?	17.6	28.4	19.2
Left	M	8.8	10.2	12.0	17.6	17.6	28.8	18.6
	M	-	10.4	13.2	?	17.6	29.2	18.8
	P	8.8	10.8	-	16.8	19.6	31.2	20.4

Infant 16 38 weeks postmenstrual age
Quiet sleep throughout recording

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	Indis	11.2	13.2	-	17.2	17.2	39.4	26.2
	Indis	10.8	12.0	14.0	18.0	22.4	?	-
	Indis	10.4	12.4	14.0	18.0	17.6	40.4	28.0
Left	S	11.2	12.8	-	18.8	18.4	54.4	41.6
	S	10.8	12.8	-	18.0	18.0	32.0	19.2
	S	10.8	12.0	-	18.0	18.0	38.4	26.4

Infant 17 38.5 weeks postmenstrual age
Quiet sleep throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	A	8.4	9.6	-	15.2	15.6	28.4	18.8
	A	8.0	9.6	10.8	15.2	16.0	28.8	19.2
	A	8.0	9.2	10.4	14.8	16.4	28.4	19.2
Left	A	-	9.6	-	14.8	14.4	28.4	18.8
	A	-	9.6	11.2	16.4	16.4	28.4	18.8
	A	8.8	9.6	-	16.0	15.6	27.6	18.0

Infant 18 41 weeks postmenstrual age
Quiet sleep throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	8.8	10.0	-	16.0	15.6	24.0	14.0
	M	-	10.0	11.2	16.0	16.0	25.2	15.2
	M	8.4	10.0	-	18.0	15.6	26.8	16.8
Left	M	8.4	9.6	-	16.0	14.8	26.0	16.4
	M	8.4	9.6	-	16.0	15.2	27.6	18.0
	A	8.4	9.6	-	16.8	16.8	26.8	17.2

Infant 19 40.5 weeks postmenstrual age
Quiet awake throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	9.2	10.8	12.0	16.8	16.4	30.4	19.6
	M	8.8	10.4	-	17.2	15.6	30.4	20.0
	M	9.2	10.8	-	16.4	16.4	29.6	18.8
Left	M	-	10.4	12.0	17.2	16.4	30.4	20.0
	M	-	10.8	12.0	17.2	20.8	28.4	17.6
	M	9.2	10.4	12.0	16.8	16.8	29.2	18.8

Infant 20 41.5 weeks postmenstrual age
Quiet awake throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	8.8	10.0	-	15.6	14.8	28.8	18.8
	P	-	10.0	12.4	14.8	15.2	28.8	18.8
	P	8.8	10.4	-	16.4	14.0	29.2	18.8
Left	M	8.8	10.8	-	17.2	16.4	27.2	16.4
	M	9.6	10.8	-	17.2	15.2	26.4	15.6

Infant 21 40 weeks postmenstrual age
Quiet sleep throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	9.6	10.8	-	18.0	16.8	30.8	20.0
	P	9.6	10.8	-	17.6	16.8	25.6	14.8
	P	9.6	10.8	-	17.2	16.0	30.8	20.0
Left	M	9.2	11.2	-	16.0	17.2	27.2	16.0
	P	9.6	10.8	-	18.0	16.0	27.6	16.8
	P	9.6	10.4	-	15.2	18.0	29.6	19.2

Infant 22 37 weeks postmenstrual age
Quiet asleep/awake varying during runs

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	S	10.0	11.2	-	18.0	19.2	50.4	39.2
	S	10.0	11.2	-	18.4	17.6	48.4	38.2
1HZ 256 STIM	S	10.0	11.2	-	17.6	18.4	45.6	35.4
3HZ 512 STIM	S	9.6	11.2	13.2	19.6	21.6	48.0	36.8
	S	9.6	11.2	12.8	19.6	19.2	46.4	35.2
Left	S	9.6	11.2	13.6	18.4	20.0	49.2	38.0
	S	9.6	11.2	13.6	18.0	21.2	50.8	39.6
	S	9.6	11.2	13.2	18.4	22.0	52.8	41.6

Infant 23 39 weeks postmenstrual age
Quiet awake during recording

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	Indis	8.8	10.4	-	15.6	16.4	25.6	15.2
	Indis	8.8	10.8	-	16.0	17.2	27.2	16.4
3Hz 512 Stim	M	-	10.4	12.0	15.2	18.0	26.8	16.4
Left 3HZ 512 STIM 1HZ 256 STIM	P	-	10.0	12.0	16.4	16.4	30.4	20.4
	P	9.2	10.4	11.6	16.8	18.0	30.4	20.0
	Indis	8.8	10.4	12.0	16.0	18.8	28.8	18.4

Infant 24 40 weeks postmenstrual age
Quiet sleep throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	8.4	9.6	-	15.6	15.6	26.0	16.4
3Hz 5 12 STIM	M	8.0	9.6	-	14.8	17.2	28.8	19.2
3Hz 1 024 Stim	M	8.4	9.6	-	15.6	16.8	26.8	17.2
3Hz 512 STIM	A	8.4	9.6	-	17.2	17.6	27.6	18.0
1Hz 256 Stim	A	8.8	9.6	-	17.6	16.8	30.4	20.8
1Hz 256 Stim	A	8.0	9.6	10.8	16.8	16.0	30.0	20.4
	A	8.0	9.6	10.8	16.8	15.2	26.4	16.8
Left	P	8.0	9.6	-	15.6	15.6	25.2	15.6
	M	8.4	9.6	11.6	16.0	15.6	27.2	17.6
	M	8.4	9.6	-	15.6	16.4	26.4	16.8

Infant 25 39.5 weeks postmenstrual age
Active during recording

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	8.0	9.6	11.2	16.4	16.8	25.6	16.0
	M	8.0	?	-	14.8	18.8	25.6	?
	P	8.0	10.0	11.2	17.6	16.8	28.0	18.0
	P	8.8	10.0	11.2	18.0	18.0	27.2	17.2
	P	8.4	10.0	11.6	17.2	16.4	28.4	18.4

Infant 26 41 weeks postmenstrual age
Quiet awake throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	A	8.8	9.6	11.2	18.0	16.0	29.6	20.0
	A	8.8	10.0	11.2	14.4	15.6	27.2	17.2
	A	8.8	9.6	11.2	15.2	15.6	30.8	21.2
Left	P	8.0	10.0	10.8	12.4	18.0	27.6	17.6
	A	8.8	9.6	10.8	16.4	16.4	30.8	21.2
	A	8.8	10.0	11.2	14.4	16.4	30.0	20.0

Infant 27 40.5 weeks postmenstrual age
Very restive

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	8.4	10.4	11.6	16.8	16.4	28.0	17.6
	P	8.8	10.0	11.6	16.4	17.6	26.8	16.8

Infant 28 41 weeks postmenstrual age
Quiet sleep

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	8.4	10.0	-	16.8	17.2	25.6	15.6
	M	8.4	9.6	-	16.0	16.8	26.8	17.2
3Hz 512 Stim	M	8.0	9.6	12.8	16.8	18.0	28.0	18.4
3Hz 512 Stim	M	8.4	10.0	-	16.8	16.8	25.2	15.2
1Hz 256 Stim	M	8.4	9.6	11.6	17.2	16.0	26.8	17.2
1Hz 256 Stim	M	8.4	9.2	14.0	17.6	17.2	27.2	18.0
	P	8.4	9.2	11.2	17.6	18.0	29.2	20.0
Left	M	8.4	9.6	-	16.8	16.4	26.4	16.8
3Hz 512 Stim	M	8.0	9.6	10.8	16.8	18.0	27.2	17.6
3Hz 512 Stim	Indis	8.4	9.6	11.2	14.4	-	-	-
1hz 256 Stim	M	8.0	9.2	10.4	15.6	18.4	26.4	17.2

Infant 29 38.5 weeks postmenstrual age
Quiet sleep throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	Indis	-	10.4	12.0	16.4	15.6	30.0	19.6
	S	9.6	10.8	12.8	18.0	18.0	48.4	37.6
	Indis	9.6	11.2	-	16.8	16.8	31.6	20.4
Left	-	9.6	10.8	-	15.6	17.2	-	-
	A	9.6	10.8	13.2	17.2	24.8	32.4	21.6
	-	-	10.4	11.6	15.6	-	-	-

Infant 30 42 weeks postmenstrual age

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	-	10.0	12.0	15.2	14.8	24.0	14.0
	P	8.8	10.0	12.4	15.6	15.6	26.4	16.4
3Hz 512 STIM	P	8.4	10.4	13.2	14.8	16.4	46.4	36.0
3Hz 512 STIM	P	8.8	10.0	-	18.4	16.8	28.0	18.0
1Hz 256 Stim	M	9.2	10.4	-	14.4	13.6	26.0	15.6
1Hz 256 Stim	M	8.8	10.0	-	16.4	16.4	27.2	17.2
Left	P	10.0	10.8	12.8	15.2	15.2	23.6	12.8
	P	8.8	10.0	-	14.8	15.2	25.6	15.6
	P	9.6	10.8	-	14.8	18.0	26.4	15.6

Infant 31 40.5 weeks postmenstrual age
Crying

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	9.6	10.8	12.4	18.0	17.2	27.2	16.4
	M	9.2	10.8	-	16.8	17.6	28.0	17.2

Infant 32 39.5 weeks postmenstrual age
Quiet awake

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	9.6	11.6	-	18.8	18.4	42.0	30.4
	Indis	9.6	11.6	13.2	18.4	17.2	40.0	28.4
	A	9.6	10.8	12.0	20.0	20.8	42.0	31.2
Left	P	-	10.8	12.0	19.6	21.2	34.8	24.0
	P	10.0	12.0	14.0	18.8	18.8	34.0	22.0
	P	10.8	11.6	13.6	18.0	22.0	31.2	19.6

Infant 33 39 weeks postmenstrual age
Quiet sleep throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	-	9.6	11.2	14.4	16.0	-	-	-
	S	10.0	11.2	14.4	18.0	18.4	34.0	22.8
1Hz 256 Stim	A	10.0	10.8	12.0	17.2	17.2	30.4	19.6
Left	P	10.0	10.8	12.8	16.8	18.4	27.2	16.4
	Indis	10.0	11.2	-	17.6	18.4	27.2	16.0
1Hz 256 Stim	S	-	10.8	12.8	16.4	18.8	31.2	20.4

Infant 34 38.5 weeks postmenstrual age
Quiet sleep

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	8.8	10.4	-	18.0	15.2	32.8	22.4
	P	8.4	10.0	-	17.6	16.4	31.2	21.2
Left	A	8.8	10.4	-	17.2	17.2	31.2	20.8
	A	8.8	10.4	-	17.6	16.4	34.4	24.0
	A	8.8	10.4	12.0	17.2	17.2	34.8	24.4

Infant 35 40.5 weeks postmenstrual age
Quiet awake 1,2 and 3. Quiet sleep 4, 5 and 6

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	8.8	9.6	10.8	16.8	16.4	26.0	16.4
	P	8.8	9.6	10.8	16.0	16.0	27.6	18.0
	P	-	9.6	-	15.6	15.6	28.8	19.2
Left	P	8.8	9.6	-	14.8	16.0	26.0	16.4
	P	8.8	10.0	11.6	16.0	16.4	28.4	18.4
	P	8.8	10.0	-	16.4	16.8	28.8	18.8

Infant 36 38.5 weeks postmenstrual age
Quiet sleep

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	-	10.4	-	16.0	17.2	24.8	24.4
	P	8.8	10.0	11.6	18.0	18.4	25.6	15.6
1Hz 256 Stim	M	-	10.8	12.4	16.0	21.6	32.8	22.0
1Hz 256 Stim	M	8.8	10.4	13.6	16.8	19.2	31.6	21.2
1Hz 256 Stim	M	9.2	10.0	-	16.4	18.4	30.0	20.0
Left 1Hz 256 Stim	P	9.2	10.8	-	16.8	16.8	32.4	21.6
1hz 256 Stim	P	10.0	10.8	-	15.6	18.0	34.8	24.0
	Indis	8.8	10.8	-	17.6	17.2	31.6	21.8

Infant 37 41 weeks postmenstrual age
Quiet sleep

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	P	10.0	10.8	-	16.8	18.4	26.0	15.2
	P	10.0	10.8	-	16.4	16.4	28.8	18.0
	M	-	10.0	-	15.6	16.4	28.4	18.4

Infant 38 39.5 weeks postmenstrual age
Quiet sleep throughout

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	9.2	10.8	-	17.6	18.0	30.4	19.6
	M	9.2	10.4	-	18.8	18.4	28.8	18.4
	M	9.2	10.4	-	16.4	18.4	28.4	18.0
Left	P	8.8	11.2	-	17.6	16.8	29.6	18.4
	P	8.8	10.8	-	18.4	18.8	29.2	18.4
	P	-	10.8	-	18.4	16.4	29.2	18.4

Infant 39 41.5 weeks postmenstrual age
Alert awake

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	M	8.8	10.0	-	17.2	16.0	26.8	16.8
	P	8.8	10.4	-	18.0	17.2	27.6	17.2
	P	8.8	10.4	-	17.6	17.6	26.8	16.4
Left	M	8.8	10.4	-	17.2	17.6	26.0	15.6
	M	9.2	10.4	-	17.6	16.8	26.4	16.0
	M	9.2	10.4	-	16.8	16.8	28.0	17.6

Infant 40 36.5 weeks postmenstrual age
Quiet sleep

Side	Form	C1	C2	C3	Cp	P0	N1	CCT
Right	None	9.6	10.8	-	18.0	-	-	-
	None	-	10.8	-	17.6	-	-	-
1Hz 512 Stim	S	-	11.2	12.4	18.8	18.8	58.8	47.6
Left 1Hz 512 Stim	S	10.0	11.2	-	18.4	18.4	48.4	37.2
	None	10.0	11.6	-	20.8	-	-	-

Clinical details of asphyxiated infants

List of abbreviations at end of Appendix

Number	1.	Male	HIE Grade 1
D.O.B.	29/5/87		
Birthweight.	3.96 Kg		Gestation 40 weeks
Race.	Caucasian		
Family History.	Nil of note		
Antenatal period.	No problems		
Labour.	14 hrs 35 mins then 3 hrs 3 mins.		
	Meconium. Type 1 dips		
Delivery.	Kiellands Rotation		
Resuscitation.	Intubation. Washout of Meconium. Good response		
Apgar.	2 at 1 minute, 5 at 3, 8 at 5.		
Neonatal Course.	Initial Headbox Oxygen then settled		
	Course of antibiotics then to Postnatal ward on day 4.		
Drugs.	Ampicillin/Gentamicin only		
Other diagnoses.	Mild Meconium Aspiration.		
Neurology.	Initially jittery and irritable then settled		
Laboratory Results.	Nil abnormal		
Radiology.	Chest X Ray clear		
CT scan and EEG.	Not done		
Outcome.	Normal		GQ 102

Number	2.	Male	HIE Grade 2
D.O.B.	30/5/87		
Birthweight.	4.58 Kg		Gestation 41 weeks 4 days
Race.	Caucasian		
Family History.	Obesity		
Antenatal period.	Borderline hypertension		
Labour.	Artificial rupture membranes post-term		
	13 hrs 40 mins		
Delivery.	Em. LSCS for flat CTG		
Resuscitation.	None required		
Apgar.	9 at 1 minute.		
Neonatal Course.	Admitted to NNU at 33 hours fitting and poor feeding		
	Right focal fits. Poor feeding for first 5 days.		
	Full infection screen including LP		
Drugs.	Ampicillin/Gentamicin. Phenobarbitone		
Other diagnoses.	None		
Neurology.	Increased tone on left, normal R arm and hypotonic R leg		
	Then hypotonic and improved to normal tone		
Biochemistry.	Phenobarbitone level 26 on 5/6/87		
	Sodium down to 127		
Microbiology.	Corynebacterium in blood		
	CSF -ve for bacteria, viruses and Tuberculosis		
Radiology.	None		
CT scan and EEG.	Not done		
Outcome.	Normal		GQ 102

Number	3.	Male	HIE Grade 3
D.O.B.	23/6/87		
Birthweight.	2.24 Kg		Gestation 37 weeks
Race.	Asian		
Family History.	None		
Antenatal period.	Polyhydramnios Otherwise normal		
Labour.	9 hrs 50 then 41 mins. Type 2 dips, baseline bradycadia		
Delivery.	Neville Barnes forceps		
Resuscitation.	Intubation IPPV. Cardiopulmonary Resuscitation Adrenaline. Bicarbonate. Heart Rate below 100 for 8 mins No respiratory effort until 15 mins		
Apgar.	0 at 1 minute, 0 at 5, 5 at 10.		
Neonatal Course.	Transferred to NNU from Leicester Gen. Hosp. at 4 hrs Brain orientated intensive care ICP, Mannitol etc..... Intensive Therapy withdrawn after discussion with parents		
Drugs.	Mannitol. Phenobarbitone. Antibiotics		
Other diagnoses.	None		
Neurology.	Floppy arms, increased tone in legs initially Then profound hypotonia		
Genetics	Normal 46XY		
Laboratory Results.	Nil abnormal		
CT scan and EEG.	Not done		
Doppler.	Abnormal		
Outcome.	Died.		

Number	4.	Female	HIE Grade 3
D.O.B.	5/8/87		
Birthweight.	3.5 Kg		Gestation 41 weeks
Race.	Asian (parents first cousins)		
Family History.	As above (subsequent child also died of SMA.)		
Antenatal period.	Mass on Right side of abdomen on antenatal ultrasound Polyhydramnios Reduced fetal movements.		
Labour.	Failure to induce		
Delivery.	LSCS		
Resuscitation.	Slow HR then cardiac arrest. Cardiac massage, Adrenaline, Bicarbonate. No breath until 1 hour		
Apgar.	0 at 1 minute, 1 at 5, 3 at 10.		
Neonatal Course.	Ventilated, pneumothoraces Intensive care withdrawn when diagnosis known		
Drugs.	Phenobarbitone, Antibiotics		
Other diagnoses.	**Spinal Muscular Atrophy**		
Neurology.	Always floppy		
Biochemistry.	Normal urine metabolic screen		
Microbiology.	Pseudomonas from chest drain tip		
Radiology.	Normal abdo U/S		
CT scan and EEG.	Not done		
EMG.	Median Nerve Conduction Velocity normal. Fibrillations. Consistent with Lower MotorNeuron damage		
Doppler.	Normal		
Outcome.	Died.		

Number	5.	Female	HIE Grade 3
D.O.B.	10/8/87		
Birthweight.	3.64 Kg		Gestation 40 weeks
Race.	Caucasian		
Family History.	Mother on Sodium Valproate and Phenytoin		
Antenatal period.	Nil of note		
Labour.	type 1 dips, bradycardia, meconium 3 hrs 45 then 2 hours 26 mins.		
Delivery.	Assisted breech		
Resuscitation.	Intubated for 3 mins, clearing of meconium, picked up quickly		
Apgar.	5 at 1 minute, 8 at 5.		
Neonatal Course.	Sudden collapse 32 hrs Postnatal ward.(seen 15 mins before) Ventilated. Fits and deterioration		
Drugs.	Phenobarbitone, Antibiotics		
Other diagnoses.	**Group B Streptococcus septicaemia**		
Neurology.	Hypotonic with fits		
Haematology.	Initial WBC = 27		
Microbiology.	Group B Beta haem Streptococcus ear and blood		
CT scan and EEG.	Not done		
Outcome.	Died.		

Number	6.	Female	HIE Grade 1
D.O.B.	23/7/87		
Birthweight.	2.65 kg	Gestation 42 weeks	EDD = 6/7/87 by U/S
Race.	Caucasian		
Family History.	nil of note		
Antenatal period.	Uneventful		
Labour.	5 hrs 45 mins then LSCS		
Delivery.	Em. LSCS for fetal distress and meconium		
Resuscitation.	Thick meconium cleared. Bag and mask with response		
Apgar.	4 at 1 minute, 7 at 5.		
Neonatal Course.	IV fluids overnight then slowly onto feeds		
Drugs.	None		
Other diagnoses.	None		
Neurology.	Hypotonic and lethargic and then normal		
Haematology.	WBC 36		
CT scan and EEG.	Not done		
Outcome.	Normal		GQ 122

Number	7.	Female	HIE Grade 3
D.O.B.	28/8/87		
Birthweight.	2.83 Kg	Gestation 38 weeks	EDD = 8/9/87
Race.	African		
Family History.	Mum is Hepatitis B e Ag +ve		
Antenatal period.	Hypertension and oedema		
Labour.	First twin was SVD, delay of 30 mins. Bradycardias with poor recovery		
Delivery.	Neville Barnes Forceps		
Resuscitation.	20 mins intubation and IPPV. Bicarbonate. First breath at 15 mins		
Apgar.	2 at 1 minute, 3 at 5, 7 at 15.		
Neonatal Course.	Ventilated 5 days for poor effort and apnoeas Intracranial pressure monitoring		
Drugs.	Phenobarbitone and clonazepam		
Other diagnoses.	None		
Neurology.	Hypotonic then improved very slowly after discharge		

Laboratory Results.	Nil abnormal.
Radiology.	Chest XRay - slight shadowing in right zones
CT scan.	Mild hypodensity in both parietal areas
EEG.	None
Outcome.	Doubtful GQ 85

Number	8. Female HIE Grade 2
D.O.B.	16/9/87
Birthweight.	3.28 Kg Gestation 40 weeks EDD = 15/9/87
Race.	Caucasian
Family History.	Nil of note
Antenatal period.	General Practitioner care. No problems
Labour.	Only monitoring was intermitent auscultation Bradycardia at 2nd stage. Meptid pain relief 13hours 40 mins then 10 mins. Meconium
Delivery.	SVD. Shoulder dystocia
Resuscitation.	Narcan. Bag and Mask IPPV 4 mins. Good response
Apgar.	3 at 1 minute, 7 at 5.
Neonatal Course.	Initial O2 for ? Meconium Aspiration with tachypnoea Started feeds day 2
Drugs.	Phenobarbitone
Other diagnoses.	Mild Meconium Aspiration.
Neurology.	Initial hypotonia then differential tone with jitters. Gradual return to normal over a week
Biochemistry.	Normal. Phenobarbitone 31 on 23/9/87
Haematology.	WBC 21 and 35 on days 1 and 2.
CT scan and EEG.	Not done.
Doppler.	Normal
Outcome.	Doubtful GQ 88

Number	9. Female HIE Grade 3
D.O.B.	4/12/87
Birthweight.	3.58 Kg Gestation 37 weeks EDD 19/12/87 by U/S
Race.	Caucasian
Family History.	None
Antenatal period.	Breech noted at 37 weeks
Labour.	6 hrs 40 then 5 mins
Delivery.	Assisted breech
Resuscitation.	Intubated IPPV first respiratory effort at 6 mins Slow to respond and ventilated to NNU
Apgar.	1 at 1 minute, 1 at 5, 4 at 10.
Neonatal Course.	Ventilated and then CPAP until extubated at 8 days
Drugs.	Phenobarbitone
Other diagnoses.	Dysmorphic with course facies, cleft palate distal digital hypoplasia
Neurology.	Hypotonic
Genetics.	46 XX
Laboratory Results.	Nil of note
CT scan and EEG.	Not done
Outcome.	Died.

Number	10.	Female	HIE Grade 3
D.O.B.	10/12/87		
Birthweight.	2.86 Kg		Gestation 39 weeks 4 days
Race.	Caucasian		
Family History.	Nil of note		
Antenatal period.	Unremarkable. Admitted for LSCS for previous LSCS		
Labour.	Spontaneous onset in antenatal ward Fetal bradycardia on admission to Labour ward.		
Delivery.	Emergency LSCS Ruptured uterus Baby stillborn.		
Resuscitation.	Intubated IPPV, CPR, Bicarbonate, Still no apex at 5 mins Calcium, Plasma, Bicarbonate. No resp effort by 30 mins.		
Apgar.	0 at 1 minute, 1 at 5, 2 at 10.		
Neonatal Course.	Flaccid, No response, Fits +++		
Drugs.	Ampicillin/Gentamicin. Phenobarbitone, Clonazepam. NICARDIPINE		
Other diagnoses.	None		
Neurology.	Flaccid throughout. No bulbar reflexes		
Laboratory Results.	Nil of note		
CT scan and EEG.	Not done		
Doppler.	Abnormal		
Outcome.	Died.		

Number	11.	Male	HIE Grade 3
D.O.B.	16/12/87		
Birthweight.			Gestation c 42 weeks (dates)
Race.	Asian		
Family History.	Nil relevant		
Antenatal period.	Decreased fetal movements for 2-3 days before delivery Membranes ruptured at home with thick meconium Attended Antenatal clinic as planned in afternoon		
Labour.	Found to have flat unreactive CTG		
Delivery.	Emergency LSCS.		
Resuscitation.	CPR, IPPV, Bicarbonate		
Apgar.	2 at 1minute, 5 at 5, 7 at 10.		
Neonatal Course.	Stiff, legs >> arms, hyperreflexic. Fits +++		
Drugs.	Antibiotics. Phenobarbitone		
Other diagnoses.	None		
Neurology.	Hypertonic, Hyperreflexic. Then hypotonic		
Laboratory results.	Nil abnormal		
CT scan and EEG.	Not done		
Doppler.	Abnormal		
Outcome.	Died.		

Number	12.	Female	HIE Grade 1
D.O.B.	6/2/88		
Birthweight.	3.25 kg	Gestation 40 weeks 4 days	EDD = 2/2/88
Race.	Caucasian		
Family History.	Mother Obese		
Antenatal period.	Borderline CTG		
Labour.	Spontaneous onset, Thick Meconium, Bad decelerations		
Delivery.	Emergency LSCS		
Resuscitation.	IPPV for 3 mins, suction and CPR		
Apgar.	2 at 1 minute, 5 at 3, 7 at 5.		

Neonatal Course.	Initially to postnatal ward but not feeding so to NNU Nasogastric feeds for 3 days. Large right Cephalhaemotoma
Drugs.	None
Other diagnoses.	None
Neurology.	Hypotonic, floppy, irritable then stiff limbs with truncal hypotonia and then return to normal
Laboratory Results.	Nil abnormal
CT scan and EEG.	Not done
Outcome.	Normal GQ 111

Number	13. Female HIE Grade 1
D.O.B.	13/2/88
Birthweight.	3.42 Kg Gestation 41 weeks by scan EDD = 4/2/88
Race.	Caucasian
Family History.	Nil of note
Antenatal period.	Nil abnormal
Labour.	Meconium staining Type 1 dips, fetal bradycardia to 90
Delivery.	Simpson's Forceps
Resuscitation.	Facial Oxygen. Meconium sucked out
Apgar.	6 at 1 minute, 9 at 5.
Neonatal Course.	Temperature imbalance Responded to treatment
Drugs.	Ampicillin/Gentamicin
Other diagnoses.	**Group B Streptococcal meningitis** (+ve CSF and Blood)
Neurology.	Hypotonia Irritability ++ Poor suck initially Still hypotonic at day 3 legs >> arms
Biochemistry.	Urea 9.2 on day 2
Haematology.	WBC 19.2 on day 2
Microbiology.	B haem Strept from ear, blood and CSF
Radiology.	Clear
CT scan and EEG.	Not done
Outcome.	Normal GQ 115

Number	14. Male HIE Grade 3
D.O.B.	21/3/88
Birthweight.	4.08 Kg Gestation Term plus 4 days by scan
Race.	Caucasian
Family History.	None
Antenatal period.	Uneventful. Previous section
Labour.	Spontaneous onset. Trial of Labour. After 4 hours fetal bradycardia + lower abdo pain Ruptured uterus
Delivery.	Emergency LSCS
Resuscitation.	Intubation, IPPV, CPR. First heart beat at 2 mins First resp effort at 20 mins. Gas at 30 mins pH 7.0
Apgar.	0 at 1 minute, 4 at 5, 4 at 10.
Neonatal Course.	Severe encephalopathy. Fits +++ Intensive care withdrawn
Drugs.	Phenobarbitone, Paraldehyde, Clonazepam NICARDIPINE
Other diagnoses.	None
Neurology.	Hypotonia, tremors, abnormal movts. Poor bulbar eflexes.
Laboratory Results.	Nil abnormal

CT scan.	Not done
EEG.	CFM flat or burst supression
Doppler.	Abnormal
Outcome.	Died

Number	15. Male HIE Grade 3
D.O.B.	27/3/88
Birthweight.	2.10Kg Gestation Term IUGR
Race.	Asian
Family History.	None
Antenatal period.	Nil abnormal
Labour.	Large APH, mother had hypoxic/ischaemic episode on intubation. Fetal bradycardia
Delivery.	Emergency LSCS
Resuscitation.	Intubated IPPV 10 mins pH 7.06 Bicarbonate, ventilated to Special Care at Leic. Gen.Hosp.
Apgar.	1 at 1 minute, 4 at 5, 8 at 10.
Neonatal Course.	Paralysed, ventilated 10 days. Very unstable. Fits on CFM
Drugs.	Phenobarbitone, Tolazoline, Dopamine, Pancuronium, Antibiotics
Other diagnoses.	Persistent fetal circulation
Neurology.	Pancuronium but would twitch when wearing off.
Biochemistry.	Persistent high urea, low sodium at first
Haematology.	Normal clotting and blood count
Microbiology.	Staphylococcus albus in blood
Radiology.	widespread alveolar shadowing on Chest X Ray
CT scan and EEG.	Not done
Outcome.	Died of persistent fetal circulation/pulmonary hypertension

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Number	16. Male HIE Grade 2
D.O.B.	30/3/88
Birthweight.	3.54 Kg Gestation 39 weeks EDD = 6/4/88
Race.	Caucasian
Family History.	Nil of note
Antenatal period.	Unremarkable
Labour.	Spont. onset ARM in labour. CTG reactive. Epidural
Delivery.	SVD
Resuscitation.	Bag and Mask O2
Apgar.	2 at 1 minute, 5 at 2, 8 at 3, 9 at 5.
Neonatal Course.	Admitted from antenatal ward with cyanotic episode ? fit on second day. Ventilated for apnoea with fits +++ Fits for over a week. Discharged at 2 weeks
Drugs.	Phenobarbitone, Clonazepam, Pyridoxine (no effect)
Other diagnoses.	None
Neurology.	Hypotonic generally with improvement Normal tone by discharge
Biochemistry.	Nil of note including Electrolytres, Magnesium Amino acids, urine screen,
Microbiology.	Nil of note
Radiology.	Chest X Ray normal
CT scan.	Not done
EEG.	No epileptiform activity seen. Normal background activity
Outcome.	Normal GQ 115

Number	17.	Male	HIE Grade 3
D.O.B.	9/4/88		
Birthweight.	3.61 Kg	Gestation 39 weeks 2 days	
Race.	Asian		
Family History.	Nil of note		
Antenatal period.	Uneventful		
Labour.	Spont. onset 6hrs 15 mins then 2hrs 24 mins. Meconium and decelerations		
Delivery.	Neville Barnes Forceps for fetal distress		
Resuscitation.	None required		
Apgar.	10 at 1 minute, 10 at 5.		
Neonatal Course.	Found collapsed on postnatal ward at 15 hours of age. Resuscitated. Full intensive care		
Drugs.	Phenobarbitone, Clonazepam infusion. Ampicillin/Gentamicin NICARDIPINE		
Other diagnoses.	Pulmonary haemorrhage		
Neurology.	Hypotonic, Gasping, Tremulous		
Laboratory Results.	Nil abnormal		
CT scan.	Not done		
EEG.	Flat CFM - isoelectric		
Doppler.	Abnormal		
Outcome.	Died.		

Number	18.	Male	HIE Grade 2
D.O.B.	4/5/88		
Birthweight	3.17 Kg	Gestation 40 weeks EDD = 5/5/88	
Race.	Caucasian		
Family History	None		
Antenatal period.	Spotting at 7 weeks only		
Labour.	14 hrs 30 then 75 mins No fetal distress		
Delivery.	SVD		
Resuscitation.	None required		
Apgar.	7 at 1 minute, 10 at 5.		
Neonatal Course.	Fits at 33 hrs on postnatal ward. Nasogastric feeds		
Drugs.	Phenobarbitone		
Other diagnoses.	None		
Neurology.	Jittery, increased tone then changed to differential tone then normal tone. Fits		
Laboratory Results.	Nil abnormal		
CT scan.	None		
EEG.	Normal with no focus		
Doppler.	Normal		
Outcome.	Normal		GQ 102

Number	19.	Female	HIE Grade 1
D.O.B.	8/5/88		
Birthweight.	3.06 Kg	Gestation 39 weeks	
Race.	Caucasian		
Family History	Nil of note		
Antenatal period.	No problems noted		
Labour.	SRM. Known breech. Epidural. 8 hours 45 mins then 55 mins.		

Delivery.	Body delivered easily. 8 minute delay for head with forceps.
Resuscitation.	No HR, blue, floppy. Intubated IPPV 5 mins extubated at 8 mins. Good HR and gasping by 3 mins.
Apgar.	0 at 1 minute, 4 at 5, 7 at 10.
Neonatal Course.	Cold, infection screen. Intravenous fluids but settled well. To postnatal ward on day 4.
Drugs.	Ampicillin/Gentamicin
Other diagnoses.	None.
Neurology.	Irritable. hypotonic at first but improved over 3 days
Laboratory Results.	Nil abnormal
Radiology.	Normal hip ultrasound
CT scan and EEG.	Not done
Doppler.	Normal
Outcome.	Normal GQ 106

Number	20. Male HIE Grade 2
D.O.B.	21/5/88
Birthweight	3.04Kg Gestation 39 weeks EDD = 27/5/88
Race.	Caucasian
Family History	None
Antenatal period.	Normal
Labour.	9 hours then 49 mins Membranes ruptured 12 hours Type 1 dips, bradycardia in 2nd stage. Pethidine, Entonox
Delivery.	Kielland's rotation and Simpson's Forceps
Resuscitation.	None required
Apgar.	8 at 1 minute, 9 at 5.
Neonatal Course.	Admitted to NNU at 29 hours with R focal fits Lots of fits, tonal changes
Drugs.	Phenobarbitone, Clonazepam, Antibiotics
Other diagnoses.	Stroke Right > Left. Large cephalhaematoma
Neurology.	Increased reflexes and tone generally at first Then differential tone legs > arms increased leg tone Gradual improvement over 2 weeks. Feeding by 9 days On discharge at 10 days still floppy with head lag
Biochemistry.	Phenobarbitone levels therapeutic.
Haematology.	Hb 11.1 initially (cephalhaematoma)
Radiology.	Skull X Ray normal
CT scan.	Bilateral extensive areas of low attenuation in MCA territory. Right worse than Left. Appearances are that of bilateral cerebral infarcts.
EEG.	Not done
Doppler.	Normal no difference in MCA signals.
Outcome.	Left hemiplegia. GQ 110

Number	21. Male HIE Grade 3
D.O.B.	9/6/88
Birthweight.	2.51 Kg Gestation 41 weeks EDD = 2/6/88
Race.	Caucasian
Family History	None
Antenatal period.	Essential hypertension on Atenolol and Nifedipine
Labour.	Flat CTG with decelerations pH 6.8
Delivery.	LSCS
Resuscitation.	IPPV 12 mins
Apgar.	1 at 1 minute, 3 at 5, 8 at 10.

Neonatal Course.	Ventilated, very sick.
Drugs.	Dopamine, Phenobarbitone
Other diagnoses.	Poor myocardial function. Coagulation problems. Jaundice
Neurology.	Hypotonic then differential tone then improved
Haematology.	Low platlets
CT scan.	Hypodensity periventricularly
EEG.	Not done
Doppler.	Abnormal
Outcome.	Spastic Quadriplegia GQ 72

Number.	22. Female HIE Grade 3
D.O.B.	10/6/88
Birthweight.	2.06Kg Gestation 40 weeks EDD = 10/6/88
Race.	Caucasian
Family History	None of note
Antenatal period.	Small for dates. Known IUGR. Low Oestriols
Labour.	Admitted for CTG = flat Cervix favourable, to Labour Ward, Prostin pessary. ARM = thick meconium + blood. Also fetal bradycardia
Delivery.	Em. LSCS
Resuscitation.	Flat, Heartrate 20, covered in thick old meconium Intubated IPPV. CPR for 3 mins. First gasp at 6 mins
Apgar.	1 at 1 minute, 6 at 5.
Neonatal Course.	Ventilated for 6 days, early fits
Drugs.	Phenobarbitone, Clonazepam infusion.
Other diagnoses.	Small for Dates
Neurology.	Initially hypertonic, then hypotonic with fits +++ Then more normal tone. Tone Left > Right at 11 days
Laboratory Results.	Nil of note
CT scan.	Mild hypodensity
EEG.	Not done
Outcome.	Spastic Quadriplegia GQ 64

Number	23. Male HIE Grade 3
D.O.B.	1/7/88
Birthweight	3.42 kg
Gestation.	38 weeks EDD = 6/7/88
Race.	Caucasion
Family History	Nil of note
Antenatal period.	Mum very poorly controlled diabetic. Smokes 10/day Major hypoglycaemia the day before delivery
Labour.	Admitted for induction. 10 hours. Pethidine + Entonox Type 2 decelerations, bradycardias down to 70
Delivery.	Em. LSCS for poor progress and fetal distress
Resuscitation.	Intubated. External Cardiac Massage. Intracardiac Adrenaline. First cardiac output at 18 mins, 1st gasp 30 mins. Reasonable resp effort at 45 mins.
Apgar.	0 at 1 minute, 0 at 5, 6 at 18.
Neonatal Course.	Ventilated, hypoglycaemia, poor temp control. Went home on tube feeding before death
Drugs.	Phenobarbitone, Clonazepam NICARDIPINE
Other diagnoses.	**?? spinal cord injury**
Neurology.	Initial hypertonia and jitters and fits. Profound hypotonia Never any lower limb movement

	Increased arm tone latterly with decorticate movements
Biochemistry.	Urea as high as 11 otherwise nothing significant
Haematology.	Normal. No clotting abnormality documented
Radiology.	U/S sacrum and lower spine normal U/S renal tract normal
CT scan.	Diffuse hypodensity with loss of definition (week 2)
EEG.	Flat CFM (but on Phenobarbitone)
Doppler.	Persistently abnormal
Outcome.	Died at 70 days.

Number	24.	Female	HIE Grade 1
D.O.B.	28/7/88		
Birthweight.	2.64 Kg	Gestation 40 weeks	EDD = 30/7/88
Race.	Caucasian/Asian		
Family History	None		
Antenatal period.	Breech		
Labour.	Tachycardia with type 2 dips		
Delivery.	Emergency LSCS Head stuck for 7 mins		
Resuscitation.	Intubated, IPPV for 8 mins first breath at 2 mins CPR for 4 mins, regular resps at 6 mins.		
Apgar.	2 at 1 minute, 6 at 5, 9 at 10.		
Neonatal Course.	Settled in 2 days		
Drugs.	none		
Other diagnoses.	none		
Neurology.	Initially hypertonic and jittery. Settled by 3 days		
Laboratory results.	Nil abnormal		
CT scan and EEG.	Not done		
Outcome.	Normal		GQ 118

Number	25.	Male	HIE Grade 3
D.O.B.	12/9/88		
Birthweight.	3.5 Kg	Gestation Term and 3 days by scan	
Race.	Caucasian		
Family History	none		
Antenatal period.	Breech		
Labour.	Type 2 dips in 2nd stage		
Delivery.	Em. LSCS head stuck for several minutes. Fetal HR lost		
Resuscitation.	IPPV, CPR, Bicarbonate, Plasma. First HR at 5 mins First resp effort at 8 mins		
Apgar.	0 at 1 minute, 1 at 5, 6 at 10.		
Neonatal Course.	Transferred from Sheffield ventilated Had been overventilated to CO_2 = 0.95 Improved quickly so was feeding at 5 days on return		
Drugs.	Phenobarbitone		
Other diagnoses.	None		
Neurology.	Hyperreflexia to hypotonia to normal tone. 2 definite fits R focal		
Laboratory Results.	Nil abnormal		
CT scan and EEG.	Not done		
Doppler.	normal		
Outcome.	Normal.		

Number	26.	Female	HIE Grade 1
D.O.B.	13/10/88		
Birthweight.	2.35 Kg	Gestation 36 weeks	
	EDD = 11/11/88 by scan		
Race.	Caucasian		
Family History	none		
Antenatal period.	No problems		
Labour.	Type 1 and 2 dips in 2nd stage		
Delivery.	SVD, cord round neck		
Resuscitation.	Intubated IPPV good response		
Apgar.	1 at 1 minute, 5 at 5.		
Neonatal Course.	Settled quickly on NNU. Slow to feed		
Drugs.	None		
Other diagnoses.	none		
Neurology.	Jittery poor neck tone then improved		
Laboratory Results.	Nil abnormal		
CT scan andEEG.	Not done		
Doppler.	Not done		
Outcome.	Normal		GQ 113

Number	27.	Male	HIE Grade 1
D.O.B.	24/10/88		
Birthweight.	4.03 Kg	Gestation 38 weeks	EDD = 6/11/88
Race.	Caucasian		
Family History	none		
Antenatal period.	Normal Glucose Tolerance Test at 28 weeks		
Labour.	6 hrs 15 then 53 mins		
Delivery.	SVD, cord round neck, difficulty in delivering shoulders		
Resuscitation.	Facial O2, Narcan, HCO3		
Apgar.	2 at 1 minute, 5 at 5.		
Neonatal Course.	Settled over 3 days when feeding		
Drugs.	None		
Other diagnoses.	None		
Neurology.	Jittery and hypertonic then settled Thought by clincians to have asymmetry ?R hemiplegia Investigator opinion - normal neurology on discharge.		
Laboratory Results.	Nil abnormal		
CT scan.	Not done		
EEG.	CFM normal		
Outcome.	Normal		GQ 113

Number	28.	Male	HIE Grade 3
D.O.B.	31/10/88		
Birthweight.	1.79 Kg	Gestation 37 weeks	
Race.	Caucasian		
Family History	Nil of note		
Antenatal period.	Known IUGR. Decreased fetal movts the day before delivery		
Labour.	2nd CTG flat. Fetal pH = 6.9		
Delivery.	Em. LSCS		
Resuscitation.	Bag and mask IPPV. Bicarbonate, pH 7.1 on admission to NNU		
Apgar.	4 at 1 minute, 5 at 5, 7 at 10.		
Neonatal Course.	Ventilated for 2 days then HBO2. FFP +++ for clotting problems		
Drugs.	Phenobarbitone, clonazepam, FFP, plats		

Other diagnoses.	DIC, IUGR, Lactose intolerance
Neurology.	Hypotonic to Extensor hypertonus. Fits +++ Very irritable on discharge
Biochemistry.	Nothing remarkable
Haematology.	Abnormal clotting screens (DIC)
Radiology.	Normal abdo films and ultrasound
CT scan.	Extensive hypodensity
EEG.	Not done
Doppler.	Abnormal
Outcome.	Doubtful GQ 90

Number	29. Female HIE Grade 2
D.O.B.	14/12/88
Birthweight.	3.91 Kg Gestation 40 weeks
Race.	Caucasian
Family History	None
Antenatal period.	Uneventful
Labour.	5 hours. Pethidine. Meconium +++ Type 2 and 3 decelerations in 2nd stage
Delivery.	Forceps for failure to progress
Resuscitation.	Sucked out
Apgar.	7 at 1 minute, 9 at 5.
Neonatal Course.	Admitted from postnatal ward with fits. Improved over 3-4 days
Drugs.	Phenobarbitone
Other diagnoses.	None
Neurology.	Initial hypertonus then normal tone. Left focal fits
Biochemistry.	Normal. Normal urine metabolic screen
Radiology.	Normal Chest XRay
CT scan and EEG.	Not done
Doppler.	Not done
Outcome.	Normal GQ 123

Number	30. Male HIE Grade 3
D.O.B.	19/12/88
Birthweight	2.89 Kg Gestation 37 weeks EDD = 10/1/89
Race.	Caucasion
Family History	Nil of note
Antenatal period.	Very abnormal. 7 admissions for raised BP etc ..... Persistently flat, unreactive CTG. Smokes 15/day Decreased fetal movts near delivery
Labour.	Induced 5 hours then 58 mins. Absolutely flat CTG throughout. Pethidine 6 hours predelivery
Delivery.	Lift out forceps
Resuscitation.	Intubated. Narcan (little effect). Picked up slowly. Deteriorated again at 15 mins
Apgar.	3 at 1 minute, 5 at 5, 7 at 10.
Neonatal Course.	Ventilated for poor resp. effort
Drugs.	Phenobarbitone, Clonazepam
Other diagnoses.	Plasma exchange. Phototherapy for Bilirubin 242 RSV +ve chest infection
Neurology.	Hypotonia to Extensor Hypertonia. Fits +++
Biochemistry.	Urine amino acids, pH, reducing subs, cystine, ketoacids - All Normal. Serum amino acids Normal. Phenobarbitone 28 and 24
Haematology.	Normal INR 1.6 Plats 80ish initially
Microbiology.	Serratia, Pseudomonas, RSV isolated

Chromosomes	Normal
Radiology.	Chest XRays normal
CT scan.	Extensive hypodensity
EEG.	Low amplitude consistent with Cortical dysfunction.
Doppler.	Abnormal
Outcome.	Frankly Dystonic, Doubtful. GQ 72

Number	31. Female HIE Grade 1
D.O.B.	10/6/87
Birthweight.	3.70 Kg Gestation 41.5 weeks EDD = 31/5/87
Race.	Caucasion
Family History	Nil of note
Antenatal period.	Minor vaginal bleed at 12 weeks
Labour.	Elective LSCS for breech Mother had anaphylactoid reaction on anaesthetic induction with a period of 20 mins of hypotension.
Resuscitation.	Intubated. CPR. IPPV for 4 mins. HR > 100 by 2 mins Resp effort at 5 mins, extubated at 7 mins. To NNU at 10 mins
Apgar.	1 at 1 minute, 4 at 3, 7 at 5, 8 at 10.
Neonatal Course.	Vomiting and feeding difficulties at first. To post natal ward at 5 days breast feeding.
Drugs.	None
Other diagnoses.	None
Neurology.	Initially hypertonic. Remarkably irritable, too much so to do SEP. Settled in 3 days
Laboratory results.	Nil abnormal
CT scan and EEG.	Not done
Doppler.	Not done
Outcome.	Cerebral Palsy with truncal hypotonia, dribbling, slightly delayed milestones and mild ataxia (Seen by Dr. J.M. Hockaday in Oxford)

Abbreviations

APH	Antepartum haemorrhage
ARM	Artificial rupture of membranes
BP	Blood pressure
CFM	Cerebral function monitor
CPAP	Continuous positive airways pressure
CPR	Cardiopulmonary resuscitation
CSF	Cerebrospinal fluid
CT	Computed tomogram
CTG	Cardiotocograph
DIC	Disseminated intravascular coagulation
D.O.B.	Date of birth
EDD	Expected date of delivery
EEG	Electroencephalogram
Em.LSCS	Emergency lower segment Caesarian section
El.LSCS	Elective lower segment Caesarian section
FFP	Fresh frozen plasma
GQ	Griffiths Quotient
HIE	Hypoxic ischaemic encephalopathy
HR	Heartrate
ICP	Intracranial pressure
INR	International normalised ratio
IPPV	Intermittent positive pressure ventilation
IUGR	Intrauterine growth retardation
LP	Lumbar puncture
MCA	Middle cerebral artery
NNU	Neonatal Unit
U/S	Ultrasound
SMA	Spinal muscular atrophy
SRM	Spontaneous rupture of membranes
SVD	Spontaneous vertex delivery
WBC	White blood cell count

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT

Appendix 3

SEP results of asphyxiated infants.

The technical parameters are

Stimulus intensity	Sufficient to just excede motor threshold (6-20 mA)
Stimulus rate	5 Hz or as stated in left hand column
Number of Stimuli	1024 or as stated in left hand column
Bandpass	10-3000 Hz
Sweep time	Mostly 100msec, some at 200 msec

INFANT 1

Day 1									
Right	A	9.6	10.8	11.6	16.4	20.0	26.0	6.0	15.2
	A	9.6	10.8	11.6	16.0	19.6	26.0	6.4	15.2
Left	A	9.6	11.2	12.0	16.0	18.8	30.0	11.2	18.8
	A	9.6	11.2	-	16.4	16.4	28.0	11.6	16.8
Day 3									
Right	M	9.2	10.4	-	17.2	17.2	24.4	7.2	14.0
	M	8.8	10.8	-	17.6	17.6	25.2	7.6	14.4
Left	M	9.6	10.8	-	18.0	16.4	27.6	11.2	16.8
	M	9.2	10.4	12.8	18.4	18.0	27.2	9.2	16.8
Day 5									
Right	M	9.2	10.8	12.0	17.6	16.0	27.6	11.6	16.8
	M	9.2	10.8	-	18.4	16.8	28.0	11.2	17.2
Left	A	9.2	10.4	-	17.6	16.4	27.2	10.8	16.8
	A	8.8	10.4	-	16.2	15.6	27.6	12.0	17.2

INFANT 2

Day 2									
Right	A	9.2	11.2	12.4	18.8	19.2	34.0	14.8	22.8
	A	9.6	11.2	-	18.4	18.4	29.4	11.0	18.2
3Hz 514 stim	A	-	11.2	-	17.6	18.0	28.0	10.0	16.8
Left 3Hz	A	9.2	10.8	12.4	17.6	18.8	30.0	11.2	19.2
	A	10.0	10.8	-	16.0	15.2	29.6	14.4	18.8
Day 3									
Right	P	10.0	11.2	-	18.4	18.0	27.6	9.6	16.4
	P	9.6	11.2	-	18.4	18.4	28.8	10.4	17.6
Left	A	9.6	11.2	-	20.0	19.6	32.0	12.4	20.8
	A	10.0	11.2	-	18.8	18.0	30.4	12.4	19.2

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 6									
Right	A	-	11.6	-	18.4	18.0	29.6	11.6	18.0
	A	10.0	11.6	-	18.4	18.0	29.2	11.2	17.6
Left	A	9.2	11.6	-	19.2	17.6	30.0	12.4	17.4
	A	10.0	11.2	13.6	19.6	18.8	31.6	12.8	20.4
INFANT 3									
Day 1									
Right	FLAT	12.0	14.0	-	19.6	-	-	-	-
	FLAT	12.0	12.8	14.0	22.0	-	-	-	-
	FLAT	12.4	13.6	16.8	20.8	-	-	-	-
Left	FLAT	13.2	14.8	-	21.6	-	-	-	-
	FLAT	12.0	14.0	-	23.6	-	-	-	-
	FLAT	12.0	13.6	-	20.4	-	-	-	-
Day 2									
Right	FLAT	-	13.2	14.4	24.0	-	-	-	-
	FLAT	-	13.2	14.8	24.0	-	-	-	-
Left	FLAT	-	14.0	-	-	-	-	-	-
	FLAT	-	14.4	15.6	18.0	-	-	-	-
	FLAT	12.0	14.0	-	23.0	-	-	-	-
Day 3									
Right	FLAT	12.0	14.8	17.2	-	-	-	-	-
	FLAT	14.0	16.4	-	22.0	-	-	-	-
Left	FLAT	12.0	14.0	-	-	-	-	-	-
	FLAT	8.8	12.4	-	-	-	-	-	-
INFANT 4									
Day 1									
Right	M	-	10.0	-	16.0	15.6	27.6	12.0	17.6
	M	-	9.6	-	18.0	17.6	28.0	10.4	18.4
1Hz 200 Stim	M	-	9.6	-	17.6	16.8	26.0	9.2	16.4
2Hz 256 Stim	M	-	10.0	-	16.4	16.4	26.4	10.0	16.4
3Hz 256 Stim	M	-	9.6	-	16.8	14.4	27.2	12.8	17.6
	M	-	9.6	-	18.0	18.0	28.4	10.4	18.8
Left	M	-	9.6	-	16.4	18.0	28.4	10.4	18.8
	M	-	9.6	10.8	20.4	18.0	29.2	11.2	19.6
	P	9.2	10.0	-	16.4	15.6	28.8	13.2	18.8

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 2									
Right	P	-	10.0	-	18.8	18.4	29.6	11.2	19.6
	P	8.8	10.0	12.8	18.0	18.4	30.0	11.6	20.0
	P	-	10.0	12.8	18.4	17.6	30.0	12.4	20.0
Left	P	-	9.6	10.4	17.2	16.0	29.2	13.2	19.6
	P	-	9.2	10.0	19.6	19.6	29.6	10.0	20.4
	P	-	9.6	12.4	19.6	19.2	28.4	9.2	18.8
Day 3									
Right	P	-	10.0	12.0	16.8	18.4	29.2	10.8	19.2
	P	-	9.2	10.0	17.6	18.0	28.8	10.8	19.6
	P	8.8	10.0	12.0	16.8	16.0	29.6	13.6	19.6
Left	P	9.6	10.4	-	19.2	18.8	30.0	11.2	19.6
	P	-	10.0	-	20.0	19.2	30.0	10.8	20.0
	P	9.6	10.4	-	16.8	18.0	29.2	11.2	18.8

INFANT 5

Day 2
Floppy disc error. Data lost before detailed analysis. Cervical latencies were noted as 'NORMAL' and note made that no identifiable cortical potentials were recorded.
Day 3
Floppy disc error. Data lost before detailed analysis. Cervical latencies were noted as 'NORMAL' and note made that no identifiable cortical potentials were recorded.

Day 4									
Right	FLAT	8.0	9.2	10.4	15.6	-	-	-	-
	FLAT	8.8	9.2	-	16.4	-	-	-	-
	FLAT	-	8.8	12.0	16.8	-	-	-	-
Left	FLAT	-	9.6	10.8	16.4	-	-	-	-
	FLAT	-	9.2	10.0	17.6	-	-	-	-
	FLAT	-	9.2	10.0	17.6	-	-	-	-

INFANT 6

Day 1									
Right	M	-	9.2	11.6	18.8	18.0	27.6	9.6	18.4
	A	10.8	12.0	-	19.6	15.6	28.0	12.4	16.0
	P	9.2	12.0	-	19.6	17.6	26.0	8.4	14.0
Left	P	9.6	10.4	11.6	20.0	20.8	24.8	4.0	14.4
	P	8.8	9.6	11.6	19.6	18.0	28.8	10.8	19.2
	P	9.6	12.0	-	19.6	20.4	27.6	7.2	15.6
	P	9.6	11.2	-	18.8	18.8	28.0	9.2	16.8
Day 2									
Right	M	7.6	8.8	10.4	17.2	16.8	28.0	11.2	19.2
	M	9.2	10.4	-	19.2	16.4	27.2	10.8	16.8
Left	M	9.2	10.4	13.2	17.6	16.4	29.6	13.2	19.2
	M	-	8.4	10.8	18.4	12.4	26.8	14.4	18.4

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
INFANT 7									
Day 1 (4 hours)									
Right	FLAT	-	11.2	13.6	19.2	-	-	-	-
	FLAT	-	10.4	12.0	19.2	-	-	-	-
	FLAT	10.4	11.6	-	20.4	-	-	-	-
	FLAT	10.4	11.2	13.6	19.6	-	-	-	-
Left	FLAT	10.4	12.4	-	22.4	-	-	-	-
	FLAT	10.8	12.0	-	21.2	-	-	-	-
	FLAT	10.4	12.0	-	22.0	-	-	-	-
Day 1 (17 hours)									
Right	FLAT	9.6	11.2	12.8	20.0	-	-	-	-
	FLAT	9.2	11.2	13.2	18.8	-	-	-	-
	FLAT	10.0	11.2	12.8	19.6	-	-	-	-
Left	FLAT	9.2	10.8	12.8	18.8	-	-	-	-
	FLAT	9.2	10.8	12.8	19.6	-	-	-	-
	FLAT	9.6	10.8	12.4	17.6	-	-	-	-
Day 3									
Right	FLAT	10.0	11.2	12.8	19.2	-	-	-	-
	P	10.0	11.2	-	20.4	22.0	31.6	9.6	20.4
	FLAT	10.0	11.2	12.6	20.8	-	-	-	-
Left	FLAT	-	10.4	11.6	16.4	-	-	-	-
	FLAT	10.4	11.6	13.2	18.8	-	-	-	-
	FLAT	10.0	11.2	12.8	18.8	-	-	-	-
Day 5									
Right	FLAT	9.6	10.8	-	18.8	19.2	-	-	-
	FLAT	9.6	11.2	-	19.2	-	-	-	-
	FLAT	9.6	11.2	-	19.6	-	-	-	-
Left	FLAT	9.6	11.2	-	18.0	-	-	-	-
	FLAT	9.2	11.2	-	18.8	-	-	-	-
	FLAT	9.2	10.8	-	18.4	-	-	-	-
Day 7									
Right	S	9.6	11.2	12.4	18.4	21.0	49.2	28.2	38.0
	S	9.6	10.8	-	19.2	20.6	53.6	33.0	42.8
	S	-	10.4	-	20.0	20.0	54.4	34.4	44.0
Left	S	9.6	10.8	12.4	19.2	19.2	38.4	19.2	27.6
	S	9.2	10.8	-	18.8	-	54.8	-	44.0
	FLAT	9.2	10.8	-	17.6	-	-	-	-
Day 10									
Right	FLAT	9.6	10.4	-	16.8	-	-	-	-
	S	9.6	10.4	-	18.8	18.8	58.0	39.2	47.6
	S	-	10.4	-	17.6	17.6	56.0	38.4	45.6
Left	S	9.2	10.8	-	18.4	-	41.2	-	30.4
	FLAT	9.2	10.4	-	19.2	-	-	-	-
	S	-	9.6	-	18.4	-	38.4	-	28.8

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 13									
Right	FLAT	9.2	10.4	-	17.6	-	-	-	-
	S	8.8	10.8	13.6	16.4	21.6	44.8	23.2	34.0
	S	-	10.4	-	16.0	19.2	44.0	24.8	33.6
	S	-	10.4	-	18.4	20.8	41.6	20.8	31.2
	S	9.2	10.4	-	16.8	18.0	47.2	29.2	36.8
Left	S	9.2	10.8	-	17.6	20.8	40.4	19.6	29.6
	S	9.6	10.8	-	18.0	18.0	38.0	20.0	27.2
	FLAT	-	10.4	-	20.0	-	-	-	-
	S	9.6	10.4	-	20.0	19.2	36.8	17.6	26.4
Day 17									
Right	S	8.8	10.0	-	18.8	18.8	43.6	24.8	33.6
	S	8.8	10.4	-	20.4	20.4	44.4	24.0	34.0
	S	8.8	10.4	-	16.0	15.2	44.0	28.8	33.6
	S	-	9.6	-	17.6	16.8	29.6	12.8	20.0
Left	S	9.2	10.4	-	15.2	19.2	34.0	14.8	23.6
	S	8.8	10.4	-	14.8	20.8	36.8	16.0	26.4
	S	9.2	10.0	12.0	15.2	21.2	40.4	19.2	30.4
6 weeks									
Right	P	8.0	9.2	-	16.0	16.0	27.6	11.6	18.4
	P	8.0	9.2	-	16.4	16.4	32.0	15.6	22.8
	M	8.0	9.2	-	16.0	18.8	35.2	16.4	26.0
Left	M	7.6	8.8	-	16.0	18.0	26.0	8.0	17.2
6 months									
Right	M	7.6	8.8	10.4	13.6	17.2	26.8	9.6	18.0
	M	7.2	8.8	10.4	14.8	16.4	26.4	10.0	17.6
	M	7.2	8.8	10.4	14.8	18.0	27.6	9.6	18.8
Left	M	7.2	8.4	10.4	15.2	12.4	22.8	10.4	14.4
	FLAT	7.2	8.8	10.0	15.6	-	-	-	-
	M	7.2	8.8	10.0	14.8	12.0	23.6	11.6	14.8
INFANT 8									
Day 1									
Right	S	8.8	10.4	-	16.4	15.6	35.6	20.0	25.2
	S	9.2	10.4	-	16.4	16.4	31.6	15.2	21.2
	S	8.8	10.4	-	16.4	17.2	39.6	22.4	29.2
	S	9.2	10.0	-	17.6	16.8	33.6	16.8	23.6
Left	S	8.8	10.0	-	14.8	20.4	36.4	16.0	26.4
	S	10.0	11.2	-	17.2	18.4	40.4	22.0	29.2
	S	9.2	10.4	-	16.4	17.2	36.4	19.2	26.0
	S	8.8	10.0	-	16.0	18.8	35.2	16.4	25.2
Day 3									
Right	FLAT	9.2	10.4	-	17.2	18.8	-	-	-
	FLAT	9.2	10.4	-	16.8	17.2	-	-	-
	FLAT	9.2	10.4	-	17.2	17.2	-	-	-
Left	FLAT	9.2	10.4	-	16.0	18.8	-	-	-
	FLAT	9.6	10.8	-	17.6	17.6	-	-	-
	FLAT	-	10.4	-	17.6	18.4	-	-	-

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 5									
Right	FLAT	9.2	10.4	-	16.0	16.4	-	-	-
	FLAT	9.2	10.4	-	18.4	20.8	-	-	-
	S	9.2	10.0	-	18.4	17.2	35.6	18.4	25.6
Left	FLAT	-	9.2	10.4	18.8	20.4	-	-	-
	FLAT	-	10.4	11.6	19.2	18.4	-	-	-
Day 7									
Right	A	8.8	10.4	-	15.6	17.6	34.0	16.4	23.6
	A	9.2	10.4	-	18.0	16.4	35.2	18.8	24.8
	A	9.6	10.4	-	16.8	17.2	35.2	18.0	24.8
Left	S	8.4	10.4	-	16.8	20.4	33.2	12.8	22.8
	S	9.2	10.4	-	17.6	16.4	43.6	27.2	33.2
	S	9.2	10.4	-	18.0	18.8	32.0	13.2	21.6
7 weeks									
Right	P	8.0	9.6	-	16.0	14.8	24.0	9.2	14.4
	P	7.6	9.6	-	14.0	14.0	23.6	9.6	14.0
	A	8.4	9.6	-	16.0	15.6	30.0	14.4	20.4
6 months									
Right	M	6.0	8.4	-	15.6	13.6	17.6	4.0	9.2
	M	7.2	9.6	-	13.6	13.6	18.0	4.4	8.4
	M	-	9.2	12.4	16.8	-	15.6	-	6.4
Left	M	-	8.4	-	12.8	12.8	18.8	6.0	10.4
	FLAT	7.2	8.4	-	13.6	-	-	-	-
	M	8.0	8.4	-	14.4	12.0	18.8	6.8	10.4
	M	-	8.4	-	12.4	12.0	18.4	6.4	10.0

INFANT 9

Day 7
No identifiable potentials on three runs of 1024 stimuli delivered at 5Hz to each median nerve. Recording of epochs of 100 and 200 msec were made. This infant died only a few hours later.

INFANT 10

Day 1									
Right	FLAT	7.6	10.4	11.6	20.0	-	-	-	-
	FLAT	7.2	10.4	11.2	19.6	-	-	-	-
	FLAT	7.2	9.6	10.8	18.8	-	-	-	-
Left	FLAT	-	9.2	12.0	22.0	-	-	-	-
	FLAT	-	9.6	12.0	22.0	-	-	-	-
	FLAT	-	9.6	12.4	20.8	-	-	-	-
	FLAT	-	9.6	12.0	24.0	-	-	-	-

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
INFANT 11									
Day 1									
Right	FLAT	9.2	11.2	13.6	19.2	19.2	-	-	-
	FLAT	9.6	10.4	11.6	17.2	-	-	-	-
	FLAT	-	11.2	-	20.0	-	-	-	-
Left	FLAT	9.6	11.2	13.6	20.4	-	-	-	-
	FLAT	9.2	10.8	13.6	18.8	18.8	-	-	-
	FLAT	-	10.8	13.6	18.4	21.0	-	-	-
INFANT 12									
This patient had a large cephalhaematoma over the right side of the skull and had low amplitude response to left median nerve stimulation.									
Day 1									
Right	P	9.2	10.4	-	16.0	14.8	25.6	10.8	15.2
	P	9.2	10.4	-	17.6	17.6	29.2	11.6	18.8
	P	9.2	10.4	-	17.6	19.2	30.4	11.2	20.0
Left	P	9.2	10.8	-	18.4	19.2	27.6	8.4	16.8
	P	9.6	10.4	11.6	18.4	18.0	32.4	14.4	22.0
	P	8.8	10.4	-	22.4	22.4	28.8	6.4	18.4
	P	8.0	9.6	10.8	16.8	17.6	28.4	10.8	18.8
Day 3									
Right	P	7.6	10.0	-	18.4	17.2	25.6	8.4	15.6
	P	7.6	10.0	12.0	17.6	16.8	28.4	11.6	18.4
	P	8.4	10.0	11.6	17.2	18.8	29.6	10.8	19.6
Left	P	9.6	10.8	12.4	18.4	-	32.8	-	22.0
	P	9.6	10.4	-	19.2	-	32.0	-	21.6
Day 11									
Right	P	7.2	9.6	11.2	14.8	14.8	24.0	9.2	14.4
	P	8.4	10.0	-	15.2	14.8	29.2	14.4	19.2
Left	P	8.8	10.0	-	14.4	-	26.4	-	16.4
	P	8.0	10.0	-	15.6	14.4	28.4	14.0	18.4
	P	-	9.6	-	16.4	-	24.8	-	15.2
INFANT 13									
Day 2									
Right	M	10.4	11.2	-	20.0	19.2	27.2	8.0	16.0
	P	9.6	10.4	11.2	14.4	20.4	24.8	4.4	14.4
	M	8.8	11.2	-	18.4	17.6	25.6	8.0	14.4
Left	M	8.8	10.0	11.2	15.6	15.2	26.8	11.6	16.8
	P	8.4	9.6	11.2	17.6	17.6	26.4	8.8	16.8
	P	8.8	10.4	11.6	18.0	18.8	26.4	7.6	16.0

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 4									
Right	P	10.4	11.6	-	18.4	18.0	33.6	15.6	22.0
3Hz	S	10.0	11.2	-	18.0	18.4	38.0	19.6	26.8
512 Stim									
1Hz	S	10.4	11.2	-	18.0	19.6	37.6	18.0	26.4
256 Stim									
	P	-	10.8	11.6	16.8	18.8	31.2	12.4	20.4
Left	P	-	9.6	11.6	18.4	19.2	30.4	11.2	20.8
	P	10.0	11.2	12.4	16.4	15.2	26.0	10.8	14.8
	P	10.0	11.2	-	17.6	16.8	30.8	14.0	19.6
INFANT 14									
Day 1									
Right	FLAT	-	10.4	-	16.8	-	-	-	-
	FLAT	-	10.4	-	-	-	-	-	-
	FLAT	8.8	10.4	12.2	16.8	-	-	-	-
	FLAT	9.2	10.4	12.0	15.2	-	-	-	-
Left	FLAT	-	9.6	-	-	-	-	-	-
1Hz	FLAT	10.4	11.6	-	18.0	-	-	-	-
256 Stim									
	FLAT	9.2	10.4	14.0	18.8	-	-	-	-
Day 3									
Right	FLAT	9.6	10.4	-	21.6	-	-	-	-
	FLAT	9.6	10.4	13.2	16.0	-	-	-	-
	FLAT	9.2	11.2	13.2	16.0	-	-	-	-
Left	FLAT	-	11.2	-	16.8	22.0	-	-	-
	FLAT	-	10.8	-	18.0	-	-	-	-
	FLAT	-	11.2	-	17.6	-	-	-	-
Day 4 NICARDIPINE									
Right	FLAT	9.2	10.8	13.2	16.8	-	-	-	-
	FLAT	-	9.6	11.2	19.2	-	-	-	-
	FLAT	-	9.6	10.8	-	-	-	-	-
	FLAT	-	9.6	-	19.6	-	-	-	-
	FLAT	10.0	11.2	13.6	20.0	-	-	-	-
Day 6									
Right	FLAT	-	9.6	-	17.6	17.6	-	-	-
	FLAT	-	9.6	10.8	17.2	-	-	-	-
	FLAT	9.2	10.0	11.8	17.2	-	-	-	-
Left	FLAT	9.2	10.0	11.2	16.4	-	-	-	-
	FLAT	9.6	10.8	-	16.8	-	-	-	-
	FLAT	-	9.6	-	17.6	-	-	-	-

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
INFANT 15									
Day 3									
Right	M	-	10.4	13.6	17.2	17.6	29.6	12.0	19.2
	M	-	10.4	-	17.6	17.6	29.2	11.6	18.8
Left	S	-	10.4	-	18.4	26.4	50.4	24.0	40.0
	S	-	10.4	-	18.4	27.2	52.0	24.8	41.6
	M	-	10.4	-	18.4	26.4	35.2	8.8	24.8
Day 5									
Right	FLAT	-	11.2	-	19.2	-	-	-	-
	FLAT	-	12.4	-	19.2	-	-	-	-
	P	-	12.0	-	17.6	28.0	78.4	50.4	66.4
	P	-	11.2	-	18.4	28.0	55.2	27.2	44.0
	FLAT	9.6	11.2	-	18.8	-	-	-	-
Left	FLAT	-	11.2	-	19.2	27.2	-	-	-
	FLAT	9.6	11.2	12.8	18.8	26.4	-	-	-
	S	-	10.4	-	16.8	20.0	124	104	113.6
	S	-	10.4	-	16.8	20.8	123	102.2	112.6
Day 7									
Right	A	-	10.8	12.8	18.8	18.0	28.8	10.8	18.0
	A	-	10.8	-	17.2	18.0	30.4	12.4	19.6
	A	-	10.4	-	16.8	17.6	31.2	13.6	20.8
	A	-	11.2	-	16.8	16.8	30.4	13.6	19.2
Left	P	-	10.8	-	19.6	24.8	32.8	8.0	22.0
	P	-	10.4	-	18.4	19.6	32.0	12.4	21.6
	P	-	10.4	-	16.8	24.0	31.2	7.2	20.8
	P	-	10.4	-	16.0	16.8	33.6	16.8	23.2
Day 9									
Right	P	9.2	10.4	-	16.8	16.8	28.4	11.6	18.0
	P	-	10.0	-	16.8	16.8	27.6	10.8	17.6
	P	8.8	10.0	-	17.6	16.8	27.6	10.8	17.6
Left	P	9.6	10.8	-	16.0	26.0	41.2	15.2	30.4
	P	-	10.8	-	15.6	26.4	39.6	13.2	28.8
	P	10.4	12.0	-	17.6	26.4	37.6	11.2	25.6
INFANT 16									
Day 3									
Right	P	11.2	12.4	-	20.4	20.4	26.0	5.6	13.6
	P	-	11.2	12.0	16.8	19.2	25.2	6.0	14.0
	M	10.8	12.4	13.6	19.6	19.6	30.0	10.4	17.6
	M	-	14.0	-	-	19.2	26.8	7.6	12.8
Left	P	-	12.0	12.8	19.6	19.2	28.8	9.6	16.8
	P	10.8	12.4	13.6	20.0	22.0	29.2	7.2	16.8
	A	11.6	12.4	-	20.0	20.0	28.8	8.8	16.4
	A	10.8	12.0	14.4	20.0	20.4	32.0	11.6	20.0
	M	-	12.0	14.0	20.0	20.0	30.8	10.8	17.2

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 5									
Right	P	10.0	11.6	-	18.4	18.0	33.6	15.6	22.0
	P	10.4	11.6	11.6	18.8	18.4	31.6	13.2	20.0
	P	10.0	11.6	-	18.8	17.6	31.2	13.6	19.6
Left	P	10.4	11.6	13.6	18.8	18.0	30.4	12.4	18.8
	A	10.0	12.0	13.2	19.2	20.0	30.4	10.4	18.4
	A	10.4	11.6	-	18.8	19.2	32.4	13.2	20.8
Day 7									
Right	M	10.8	11.6	12.8	18.0	20.8	28.8	8.0	17.2
	M	11.2	12.4	-	18.8	19.2	29.6	10.4	17.2
	M	10.4	12.0	13.6	19.2	19.2	30.4	11.2	18.4
Left	P	-	11.2	12.4	18.8	20.4	30.4	10.0	19.2
	P	-	12.0	14.0	18.4	18.8	30.4	11.6	18.4
	A	10.8	12.4	-	17.2	18.4	31.6	13.2	19.2
Day 9									
Right	A	-	11.6	13.2	18.0	42.4	62.4	20.0	50.8
	A	-	11.6	-	18.0	40.8	58.0	17.2	46.4
	A	10.4	11.6	-	17.2	41.6	56.8	15.2	45.2
Left	A	-	12.0	-	19.2	18.4	31.2	12.8	19.2
	A	10.4	12.0	-	18.4	17.6	29.2	11.6	17.2
	A	9.6	12.0	14.0	16.8	16.8	30.0	13.2	18.0
Day 12									
Right	M	-	11.6	14.8	18.4	18.4	25.6	7.2	14.0
	M	-	12.0	-	19.6	18.4	26.0	7.6	14.0
	M	-	11.6	-	16.8	17.6	25.6	8.0	14.0
Left	A/P	-	11.6	-	18.4	18.8	28.0	9.2	16.4
	A	10.0	11.6	-	17.6	18.0	28.4	10.4	16.8
	P	10.0	11.6	-	18.0	16.8	30.4	13.4	18.8
INFANT 17									
Day 2									
Right	FLAT	9.2	10.8	-	18.0	-	-	-	-
	FLAT	-	10.0	13.6	19.6	-	-	-	-
	FLAT	-	11.2	12.8	-	-	-	-	-
Left	FLAT	9.2	10.0	12.0	17.2	-	-	-	-
	FLAT	-	10.4	12.4	20.0	-	-	-	-
	FLAT	-	10.4	-	-	-	-	-	-

Day 4 NICARDIPINE
Study performed Right and left. Data lost. Recorded as Cervical potentials within normal limits with no cortical potentials evoked.

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
INFANT 18									
Day 3									
Right	A	9.2	11.2	14.0	17.2	17.6	28.0	10.4	16.8
	P	9.2	10.8	13.2	17.6	19.6	24.4	4.8	13.6
	A	8.4	10.8	14.8	18.0	16.8	28.4	11.6	17.6
Left	A	*	*	*	*	19.6	27.2	7.6	*
	A	*	*	*	*	20.0	28.8	8.8	*
* Potentials exceded gain on recording channel therefore no latency available.									
Day 5									
Right	A	9.2	10.8	-	17.6	16.4	26.0	9.6	15.2
	A	10.0	10.8	-	18.8	17.6	28.4	10.8	17.6
1Hz 256 Stim	A	9.6	10.8	-	16.8	15.2	29.6	14.4	18.8
Left	A	10.4	11.6	-	18.8	18.4	28.4	10.0	16.8
	A	9.6	11.2	12.4	18.0	17.6	27.6	10.0	16.4
	A	9.6	11.6	15.6	18.8	18.4	28.4	10.0	16.8
INFANT 19									
Day 1									
Right	P	9.6	10.8	-	19.6	18.8	30.0	11.2	19.2
	P	8.8	10.0	-	18.4	19.6	28.8	9.2	18.8
	P	9.2	10.4	11.6	20.0	17.6	30.0	12.4	19.6
Left	P	8.8	10.8	-	16.8	18.4	30.8	12.4	20.0
	P	10.0	10.8	-	18.0	16.4	31.6	15.2	20.8
1Hz 256 Stim	P	-	10.4	-	16.4	17.2	27.6	10.4	17.2
1Hz 256 Stim	P	9.2	10.4	13.6	18.0	17.6	30.0	12.4	19.6
Day 3									
Right	P	9.2	10.8	-	19.6	18.4	30.8	12.4	20.0
	P	9.6	10.8	12.4	18.0	18.8	30.0	11.2	19.2
	P	9.2	10.4	-	18.8	19.2	30.8	11.6	20.4
Left	P	-	10.8	12.4	18.0	21.6	32.4	11.6	21.6
	P	9.6	10.8	-	16.8	18.8	32.0	13.2	21.2
	P	9.2	10.4	13.6	16.8	20.0	31.2	11.2	20.8
Day 6									
Right	P	9.6	10.8	-	18.0	18.4	30.0	11.6	19.2
	P	9.2	10.8	-	18.0	17.6	29.2	11.6	18.4
	P	10.4	11.2	12.4	17.2	17.2	33.2	16.0	22.0
Left	P	9.6	10.8	12.4	18.8	16.0	34.0	18.0	23.2
	P	-	10.8	14.0	18.0	17.6	32.0	14.4	21.2
	P	-	10.4	-	16.8	17.2	30.0	12.8	19.6

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
INFANT 20									
Day 2									
Right	FLAT	-	10.8	11.6	20.0	-	-	-	-
	S	-	10.8	12.0	18.8	34.0	50.0	16.0	39.2
	S	10.4	11.6	-	19.6	31.6	59.2	27.6	47.6
Left	FLAT	8.8	11.2	-	22.0	18.8	-	-	-
	FLAT	10.4	12.4	-	17.2	-	-	-	-
	FLAT	10.8	11.6	12.8	23.2	-	-	-	-
Day 4									
Right	P	10.0	11.2	12.4	18.0	31.2	49.6	18.4	38.4
	P	-	11.2	12.8	18.0	30.8	43.6	12.8	32.4
	P	10.0	11.2	-	18.4	22.4	43.2	20.8	32.0
Left	FLAT	9.6	11.2	-	18.4	-	-	-	-
	FLAT	-	11.2	-	19.6	-	-	-	-
	FLAT	-	11.2	12.4	20.0	-	-	-	-
	FLAT	-	11.2	-	19.2	-	-	-	-
Day 7									
Right	A	-	10.8	15.2	19.6	19.6	36.8	17.2	26.0
	P	10.0	11.2	16.4	20.43	24.8	35.2	10.4	24.0
Left	FLAT	10.0	11.2	-	19.6	18.8	-	-	-
	FLAT	10.0	11.2	-	17.2	19.2	-	-	-
	S	9.6	11.2	-	17.6	19.2	44.0	24.8	32.8
Day 17									
Right	A/P	9.2	10.4	14.0	18.4	18.4	28.4	10.0	18.0
	P	9.2	10.4	14.8	18.0	17.6	31.2	13.6	20.8
	P	9.2	10.4	-	17.2	17.6	30.8	13.2	20.4
Left	FLAT	9.2	10.4	13.0	18.0	-	-	-	-
	FLAT	9.2	10.4	14.0	18.4	-	-	-	-
	FLAT	9.2	10.4	-	16.0	-	-	-	-
INFANT 21									
Day 1									
Right	FLAT	10.0	11.6	-	16.4	16.8	-	-	-
	FLAT	9.6	11.2	13.2	17.2	17.6	-	-	-
	S	-	12.0	-	15.2	16.0	49.6	33.6	37.6
1Hz 256 Stim	S	9.6	11.2	-	18.4	18.4	48.0	29.6	36.8
1Hz 256 Stim	FLAT	10.4	11.6	12.8	16.8	-	-	-	-
Left	FLAT	-	9.6	-	-	-	-	-	-
	FLAT	-	11.2	12.4	-	-	-	-	-
	FLAT	-	12.0	15.2	16.8	-	-	-	-

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 3									
Right	S	10.4	11.2	13.6	18.8	17.6	44.4	26.8	33.2
	S	-	10.8	13.2	23.6	19.2	43.6	24.4	32.8
	P	-	11.2	-	18.4	18.4	36.8	18.4	25.6
1Hz 256 Stim	P	10.0	11.2	12.8	18.4	22.4	32.8	10.4	21.6
1Hz 256 Stim	S	10.8	11.6	13.6	19.6	20.0	38.4	18.4	26.8
Left	FLAT	9.6	11.2	13.6	19.2	22.0	-	-	-
	FLAT	9.6	11.2	13.6	24.4	24.0	-	-	-
	FLAT	-	12.0	-	19.2	20.8	-	-	-
1Hz 256 Stim	FLAT	-	10.8	12.8	19.2	18.4	-	-	-
Day 6									
Right	FLAT	-	10.0	12.0	14.8	21.2	-	-	-
	FLAT	9.2	10.4	-	14.8	20.0	-	-	-
1Hz 256 Stim	FLAT	9.2	10.4	12.4	15.6	-	-	-	-
	P	8.8	10.8	-	18.0	19.6	29.6	10.0	18.8
	FLAT	8.4	9.6	11.6	15.2	27.6	-	-	-
Left	FLAT	9.6	11.2	-	19.6	19.6	-	-	-
	FLAT	-	10.0	13.6	20.4	-	-	-	-
	FLAT	-	9.6	12.0	16.0	-	-	-	-
1Hz 256 Stim	FLAT	9.2	10.4	-	14.8	-	-	-	-
Day 8									
Right	FLAT	-	10.0	11.2	14.8	18.8	-	-	-
	FLAT	-	10.4	-	18.0	-	-	-	-
	FLAT	-	10.4	-	17.6	-	-	-	-
1Hz 256 Stim	FLAT	-	9.2	10.8	16.8	-	-	-	-
Left	FLAT	9.2	10.8	-	17.2	-	-	-	-
	FLAT	-	10.8	-	17.6	-	-	-	-
	FLAT	-	10.4	-	16.8	-	-	-	-
1Hz 256 Stim	S	-	10.8	12.4	22.4	22.8	56.0	33.2	45.2

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 12									
Right	S	9.2	10.4	11.6	19.6	18.4	38.0	19.6	27.6
	S	8.8	10.8	12.4	17.6	16.8	34.8	18.0	24.0
	S	9.2	10.8	12.4	19.2	18.0	36.8	18.8	26.0
Left	FLAT	9.2	10.4	-	18.4	19.6	-	-	-
	S	-	10.0	11.2	18.0	18.4	43.2	24.8	33.2
1Hz 256 Stim	S	-	9.2	10.8	18.8	17.2	41.6	24.4	32.4
1Hz 256 Stim	S	9.6	10.8	-	18.8	18.4	41.6	23.2	30.8
Day 15									
Right	A	-	10.4	12.4	17.6	19.2	31.6	12.4	21.2
	A	-	10.8	-	17.6	18.0	32.0	14.0	21.2
	A	9.2	10.4	14.0	19.2	17.2	32.0	14.8	21.6
Left	A	9.6	11.6	14.0	18.0	17.2	37.6	20.4	26.0
	A	9.2	11.2	-	19.6	18.0	38.0	20.0	26.8
	P	9.6	10.8	12.0	18.4	17.6	34.0	16.4	23.2
INFANT 22									
Day 1									
Right	A	-	9.2	10.8	18.8	17.6	35.6	18.0	26.4
	A	8.8	10.0	12.4	15.6	16.0	27.6	11.6	17.6
	A	8.4	10.0	11.2	18.8	21.2	31.6	10.4	21.6
Left	FLAT	8.8	10.0	12.8	16.0	14.8	-	-	-
	FLAT	-	8.4	10.0	15.6	-	-	-	-
	FLAT	-	9.6	-	19.0	-	-	-	-
Day 3									
Right	FLAT	8.2	9.6	12.0	18.0	-	-	-	-
	FLAT	-	9.2	13.2	16.8	-	-	-	-
	FLAT	-	8.8	-	16.0	-	-	-	-
1Hz 256 Stim	FLAT	-	9.2	12.0	16.8	-	-	-	-
Left	FLAT	8.4	9.6	-	15.6	-	-	-	-
	FLAT	8.4	9.2	-	15.6	-	-	-	-
	FLAT	-	9.6	-	13.6	-	-	-	-
1Hz 256 Stim	FLAT	8.0	9.2	-	17.2	-	-	-	-

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 5									
Right	FLAT	9.2	10.4	-	16.8	-	-	-	-
	FLAT	8.8	10.0	12.0	18.0	18.0	-	-	-
	FLAT	-	9.6	-	15.2	-	-	-	-
1Hz 256 Stim	FLAT	8.8	10.0	-	16.8	-	-	-	-
Left	FLAT	8.8	10.4	-	17.2	-	-	-	-
	FLAT	9.2	10.4	-	18.0	-	-	-	-
	FLAT	-	10.4	-	16.0	-	-	-	-
1Hz 256 Stim	FLAT	8.8	10.4	-	16.4	-	-	-	-
Day 7									
Right	S	8.0	9.6	-	18.0	15.2	32.4	17.2	22.8
	FLAT	-	9.6	-	18.0	-	-	-	-
1Hz 256 Stim	S	-	9.6	-	14.8	19.2	42.4	23.2	32.8
1Hz 256 Stim	S	-	8.4	10.8	17.2	17.2	39.6	22.4	31.2
1Hz 256 Stim	S	-	8.0	10.4	16.0	15.6	38.4	22.8	30.4
Left	FLAT	8.8	9.6	-	17.6	-	-	-	-
	FLAT	8.8	10.0	-	17.6	-	-	-	-
	FLAT	-	9.6	-	20.0	-	-	-	-
1Hz 256 Stim	S	8.8	10.0	-	15.6	16.4	43.2	26.8	33.2
1Hz 256 Stim	FLAT	8.8	10.0	-	19.2	-	-	-	-
Day 11									
Right	S	8.8	10.0	-	16.0	16.4	37.2	20.8	27.2
	S	8.8	10.0	11.6	16.8	16.8	36.4	19.6	26.4
	S	8.8	9.6	-	15.6	15.6	37.2	21.6	27.6
Left	FLAT	8.8	10.0	14.8	16.8	20.0	-	-	-
	S	8.4	10.0	-	18.0	15.6	39.2	23.6	29.2
1Hz 256 Stim	S	-	9.2	-	17.2	16.8	42.4	25.6	33.2
	S	-	9.2	10.4	16.8	15.6	50.0	34.4	40.8

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 14									
Right	P	8.4	9.2	13.6	18.4	21.2	28.4	7.2	19.2
	S	-	9.6	12.0	18.4	23.2	37.6	14.4	28.0
1Hz 256 Stim	A	-	8.8	-	12.4	18.8	35.6	16.8	26.8
1Hz 256 Stim	A	-	8.4	10.8	18.0	20.0	36.0	16.0	27.6
Left	P	8.4	9.6	11.6	16.8	17.2	35.6	18.4	26.0
	P	8.4	10.0	11.6	16.0	16.0	38.4	22.4	28.4
1Hz 256 Stim	S	-	8.4	-	15.2	14.8	48.0	33.2	39.6
1Hz 256 Stim	S	8.0	9.2	10.8	15.6	24.4	55.2	30.8	46.0
INFANT 23									
Day 1									
Right	FLAT	-	11.2	-	-	-	-	-	-
	FLAT	8.0	9.6	12.0	16.8	-	-	-	-
	FLAT	8.0	10.4	-	16.0	-	-	-	-
Left	FLAT	-	-	-	-	-	-	-	-
	FLAT	8.0	10.4	-	-	-	-	-	-
	FLAT	-	12.4	13.6	20.4	-	-	-	-
Day 2									
Right	FLAT	9.6	11.2	12.4	22.0	-	-	-	-
	FLAT	8.8	10.8	12.8	19.2	-	-	-	-
	FLAT	-	11.2	-	18.4	-	-	-	-
Left	FLAT	7.2	11.2	-	14.4	-	-	-	-
	FLAT	-	-	-	-	-	-	-	-
	FLAT	-	12.0	-	24.8	-	-	-	-
Day 4 NICARDIPINE									
Right	FLAT	10.8	12.0	-	18.0	-	-	-	-
	FLAT	-	11.6	-	-	-	-	-	-
	FLAT	-	12.0	-	-	-	-	-	-

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 6									
Right	FLAT	-	11.6	-	19.2	-	-	-	-
	FLAT	-	12.0	-	17.6	-	-	-	-
	FLAT	-	12.0	-	17.6	-	-	-	-
1Hz 256 Stim	FLAT	-	10.8	12.0	21.2	-	-	-	-
Left 1Hz 256 Stim	FLAT	10.8	11.6	13.6	19.6	-	-	-	-
	FLAT	-	11.6	12.4	22.0	-	-	-	-
	FLAT	10.8	12.0	13.2	22.4	-	-	-	-
	FLAT	-	12.0	-	22.4	-	-	-	-
Day 8									
Right	FLAT	-	10.8	-	18.8	-	-	-	-
	FLAT	-	10.8	14.4	19.2	-	-	-	-
	FLAT	-	11.2	-	25.6	-	-	-	-
1Hz 256 Stim	FLAT	-	10.4	11.6	16.4	-	-	-	-
Left 1Hz 256 Stim	FLAT	10.0	10.8	14.0	17.6	-	-	-	-
	FLAT	10.4	11.2	-	19.6	-	-	-	-
	FLAT	-	11.2	-	16.4	-	-	-	-
	FLAT	-	11.2	-	18.4	-	-	-	-
INFANT 24									
Day 1									
Right	P	8.8	10.0	11.6	17.2	19.2	25.6	6.4	15.6
	P	6.0	8.0	10.0	18.0	16.8	27.2	10.4	19.2
	A	-	8.4	10.4	16.8	15.2	24.8	9.6	16.4
Left	P	-	8.8	10.0	14.0	14.0	24.8	10.8	16.0
	P	7.2	9.2	-	14.4	20.0	26.8	6.8	17.6
Day 3									
Right	P	-	9.6	-	17.2	16.8	25.2	8.4	15.6
	P	8.4	10.0	-	16.4	16.4	28.0	11.6	18.0
	P	8.4	9.6	-	18.0	16.4	25.6	9.2	16.0
Left	FLAT	9.6	10.8	-	16.0	-	-	-	-
1Hz 512 Stim	P	-	10.0	-	16.8	17.6	28.8	11.2	18.8
1Hz 512 Stim	A/P	-	9.6	12.0	17.2	18.0	27.2	9.2	17.6

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 7									
Right	P	8.8	10.0	14.0	18.0	17.6	25.6	8.0	15.6
	P	8.4	9.2	-	17.2	16.0	28.8	12.8	19.6
	P	9.2	10.0	11.2	14.8	14.4	23.6	9.2	13.6
1Hz 256 Stim	M	-	9.6	12.4	15.2	16.8	24.0	7.2	14.4
Left	P	8.4	9.6	-	16.0	16.0	24.8	8.8	15.2
	M	-	9.6	-	16.0	14.4	23.6	9.2	14.0
	M	-	8.8	-	16.0	16.0	25.2	9.2	16.4
INFANT 25									
Day 1									
Right	FLAT	10.4	12.0	-	16.8	-	-	-	-
	P	-	11.6	12.8	18.4	-	33.2	-	-
	P	-	12.0	-	20.8	20.8	29.6	8.8	17.6
1Hz 512 Stim	P	-	11.2	12.4	18.8	20.0	31.6	11.6	20.4
Left	FLAT	10.4	12.4	-	18.4	-	-	-	-
	FLAT	-	12.4	-	16.4	-	-	-	-
	FLAT	-	12.0	13.6	19.2	-	-	-	-
1Hz 512 Stim	A	10.8	13.2	-	21.2	18.8	35.2	16.4	22.0
Day 2									
Right	FLAT	9.6	12.0	13.6	17.2	-	-	-	-
	P	-	12.4	-	21.2	22.0	37.6	15.6	24.8
	S	-	12.8	-	19.2	22.4	52.0	29.6	39.2
1Hz 512 Stim	P	9.6	12.8	-	18.4	30.0	40.0	10.0	27.2
Left	P	-	12.4	-	18.4	18.8	32.0	13.2	19.6
	P	9.2	11.6	-	17.2	18.8	27.2	8.4	15.6
	P	-	12.0	-	19.2	20.8	30.4	9.6	18.4
1Hz 512 Stim	P	9.6	11.6	-	16.8	19.2	30.0	10.8	18.4

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 4									
Right	FLAT	-	11.6	-	18.4	-	-	-	-
	P	10.8	12.0	-	17.6	19.2	31.6	12.4	19.6
1Hz 256 Stim	S	10.8	12.0	-	18.4	20.8	58.4	37.6	46.4
	P	10.4	12.0	-	17.2	19.2	34.8	15.6	22.8
Left	FLAT	10.0	11.6	13.2	15.6	-	-	-	-
	FLAT	-	11.6	-	16.4	18.8	-	-	-
1Hz 512 Stim	P	10.0	11.6	-	-	21.2	38.4	17.2	26.8
1Hz 512 Stim	P	-	11.6	-	18.4	18.0	33.6	15.6	22.0
Day 25									
Right	P	10.0	10.8	14.4	19.2	18.8	27.6	8.8	16.8
	P	-	10.8	12.8	18.0	16.8	28.0	11.2	17.2
	P	9.6	10.4	14.4	16.8	16.4	26.4	10.0	16.0
Left	A	9.6	10.8	14.8	17.2	17.6	27.6	10.0	16.8
	P	10.0	11.2	-	19.2	18.8	27.2	8.4	16.0
	P	10.0	10.8	-	20.8	20.4	28.0	7.6	17.2
INFANT 26									
Day 1									
Right	M	8.8	10.0	11.6	15.6	17.2	34.4	17.2	24.4
	M	9.2	10.4	-	18.0	17.2	32.8	15.6	22.4
1Hz 512 Stim	A	-	10.0	12.0	16.4	18.0	37.2	19.2	27.2
Left	S	-	9.6	12.0	18.8	19.2	45.6	26.4	36.0
	P	-	9.6	12.4	16.4	17.6	28.4	10.8	18.8
1Hz 512 Stim	P	-	9.6	12.0	17.2	15.2	30.0	14.8	20.4
Day 4									
Right	P	8.4	9.6	-	13.2	16.4	26.0	9.6	16.4
	P	-	9.6	-	17.6	17.6	32.8	15.2	23.2
	P	8.8	10.0	-	15.6	15.6	30.4	14.8	20.4
Left	P	8.8	9.6	-	20.4	20.0	25.2	5.2	15.6
	P	8.8	10.0	15.2	18.4	18.0	30.0	12.0	20.0
	P	8.4	9.2	12.0	18.0	15.2	28.4	13.2	19.2

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
INFANT 27									
Day 1									
Right	A	-	11.2	14.0	17.6	17.2	33.2	16.0	22.0
	A	-	10.4	13.2	19.6	20.8	38.4	17.6	28.0
	A	9.2	11.2	-	17.2	20.4	38.0	17.6	26.8
Left	S	9.6	11.2	13.2	18.0	24.8	39.2	14.4	28.0
	S	10.4	11.6	-	16.8	16.8	43.6	26.8	32.0
	S	10.4	11.2	-	19.2	32.2	45.6	22.4	34.4
Day 3									
Right	S	11.2	13.2	-	19.2	18.8	36.4	17.6	23.2
	S	-	11.2	14.8	19.2	21.2	35.6	14.4	24.4
	S	-	12.4	-	20.4	23.2	40.0	16.8	27.6
Left	S	11.6	12.8	16.4	22.4	19.2	42.4	23.2	29.6
	S	-	12.0	14.8	24.4	31.2	42.8	11.6	30.8
	S	8.0	12.4	14.4	25.6	24.4	46.8	22.4	34.4
Day 5									
Right	A	-	11.6	-	20.4	24.4	36.0	11.6	24.4
	A	8.4	11.6	-	18.0	19.2	38.0	18.8	26.4
	A	-	11.6	-	20.4	21.6	39.2	17.6	27.6
Left	S	-	12.0	-	18.4	18.4	46.8	28.4	34.8
	S	-	12.0	-	20.4	23.6	46.0	22.4	34.0
	S	9.2	11.6	-	20.4	19.2	43.6	24.4	32.0
INFANT 28									
Day 3									
Right	FLAT	-	11.6	-	16.0	-	-	-	-
	FLAT	-	11.2	12.4	17.6	17.6	-	-	-
	FLAT	-	12.0	-	16.8	17.6	-	-	-
1Hz 512 Stim	FLAT	-	11.2	12.8	19.2	-	-	-	-
Left	FLAT	10.4	13.2	16.8	20.4	-	-	-	-
	FLAT	12.4	13.6	14.4	22.8	-	-	-	-
	FLAT	-	13.6	-	-	-	-	-	-
Day 5									
Right	FLAT	10.4	12.8	-	-	-	-	-	-
	FLAT	-	13.2	-	-	-	-	-	-
	FLAT					-	-	-	-
1Hz 512 Stim	FLAT	11.2	12.4	-	17.6	-	-	-	-
Left	FLAT	10.4	11.6	-	19.2	-	-	-	-
	FLAT	-	11.6	13.6	15.2	-	-	-	-
	FLAT	-	12.0	15.2	-	-	-	-	-
1Hz 512 Stim	FLAT	10.4	11.6	15.6	21.2	-	-	-	-

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 8									
Right	FLAT	-	10.8	12.4	19.2	-	-	-	-
	FLAT	9.6	11.2	-	18.4	-	-	-	-
	FLAT	-	11.2	-	18.4	18.4	-	-	-
1Hz 512 Stim	FLAT	-	10.8	14.0	19.2	-	-	-	-
Left	FLAT	10.0	11.2	-	16.0	-	-	-	-
	FLAT	-	11.2	12.8	17.6	-	-	-	-
	FLAT	-	11.2	-	18.4	-	-	-	-
1Hz 512 Stim	FLAT	-	11.2	-	18.0	-	-	-	-
Day 10									
Right	FLAT	11.2	12.8	15.2	18.4	-	-	-	-
	FLAT	9.2	11.2	-	20.8	-	-	-	-
	FLAT	-	12.8	-	16.0	-	-	-	-
1Hz 512 Stim	FLAT	-	11.2	12.4	20.4	-	-	-	-
Left	FLAT	-	10.8	12.0	19.6	-	-	-	-
	FLAT	-	11.6	13.2	20.0	-	-	-	-
	FLAT	-	12.8	-	-	-	-	-	-
1Hz 512 Stim	FLAT	-	12.8	14.0	16.4	-	-	-	-
Day 12									
Study could not be performed owing to insurmountable 50 Hz interference.									
Day 16									
Right	FLAT	8.8	10.8	15.2	21.6	-	-	-	-
	S	-	10.4	-	18.4	58.4	84.8	26.4	74.4
	S	8.0	10.4	-	20.8	59.2	110	50.8	102
	S	-	10.4	-	21.6	44.0	89.6	45.6	79.2
Left	S	-	9.6	-	14.4	93.6	112	18.4	102.4
	S	8.8	11.2	-	17.6	76.8	119	43.2	107.8
	S	8.4	10.0	11.6	15.6	51.6	86.0	34.4	76.0
1Hz 512 Stim	M	-	10.4	19.2	24.0	16.8	32.0	15.2	21.6

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 19									
Right	FLAT	9.2	11.2	-	16.4	-	-	-	-
	FLAT	9.2	11.6	-	19.6	-	-	-	-
	FLAT	-	9.6	-	-	-	-	-	-
1Hz 512 Stim	S	-	10.4	-	16.8	21.6	51.2	30.0	40.8
Left	FLAT	8.8	10.8	-	18.8	19.6	-	-	-
	FLAT	8.0	10.4	-	18.0	23.6	-	-	-
	FLAT	8.8	10.4	-	18.4	-	-	-	-
1Hz 512 Stim	FLAT	7.6	10.4	-	16.4	-	-	-	-
Day 24									
Right	S	8.8	10.0	-	16.0	19.2	50.4	31.2	40.4
	S	-	10.4	13.6	22.8	34.4	74.8	40.4	64.4
	S	-	10.4	-	16.8	27.2	76.8	49.6	66.4
	S	-	10.4	-	15.2	19.2	49.6	30.4	39.2
1Hz 512 Stim	P	8.4	10.4	11.6	18.4	21.6	45.2	23.6	34.8
Left	FLAT	-	10.4	-	16.4	-	-	-	-
	FLAT	8.4	10.4	-	16.0	-	-	-	-
	S	-	10.4	-	17.6	38.4	74.4	36.0	64.0
1Hz 512 Stim	S	9.2	10.4	12.0	15.2	36.8	49.2	12.4	38.8
Day 30									
Right	P	8.4	9.6	11.2	17.2	18.0	55.2	37.2	45.6
	P	8.8	10.0	13.6	16.0	16.0	29.6	13.6	19.6
	P	-	9.6	-	17.6	18.4	48.8	30.4	39.2
1Hz 512 Stim	P	8.4	9.6	-	15.6	18.4	40.8	22.4	31.2
Left	P	8.4	10.0	-	15.6	18.4	38.8	20.4	28.8
	S	8.4	10.0	-	16.4	18.0	?	?	?
	S	-	10.4	-	18.4	17.6	52.8	35.2	42.4
1Hz 512 Stim	P	-	10.0	-	16.4	18.0	30.8	12.8	20.8

Day 37
Infant too irritable to study

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
INFANT 29									
Day 2									
Right	A	9.2	10.8	15.2	19.6	20.4	32.0	11.6	21.2
	A	9.6	10.8	-	19.2	20.8	37.2	16.4	26.4
1Hz 512 Stim	A	9.6	11.2	-	17.2	18.4	38.4	20.0	27.2
	P	9.6	11.2	-	18.4	19.2	32.8	13.6	21.6
Left	P	-	9.6	12.4	17.6	30.8	50.4	19.6	40.8
	S	9.2	10.8	-	15.6	24.4	44.8	20.4	34.0
	P	-	11.2	-	20.0	26.4	44.0	17.6	32.8
1Hz 512 Stim	S	-	10.4	13.2	18.8	63.2	97.6	34.4	87.2
Day 4									
Right	A	10.4	12.0	13.6	17.6	16.0	29.2	13.2	17.2
	A	10.0	11.6	13.6	18.4	18.8	31.2	12.4	19.6
	A	10.0	11.6	12.8	19.6	20.0	31.2	11.2	19.6
Left	M	-	11.6	13.2	18.0	18.8	29.2	10.4	17.6
	M	10.4	11.6	13.6	19.6	17.2	29.6	12.4	18.0
	M	-	11.6	13.6	19.2	18.0	28.4	10.4	16.8
INFANT 30									
Day 2									
Right	FLAT	-	11.2	13.2	20.4	-	-	-	-
	FLAT	-	12.0	13.2	16.0	-	-	-	-
	FLAT	-	11.2	-	17.6	-	-	-	-
1Hz 512 Stim	FLAT	-	10.8	-	17.2	-	-	-	-
Left	FLAT	-	12.0	14.0	18.0	-	-	-	-
	FLAT	-	12.4	15.2	19.2	-	-	-	-
	FLAT	-	11.2	12.8	21.6	-	-	-	-
1Hz 512 Stim	FLAT	-	11.2	12.8	17.6	-	-	-	-

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 4									
Right	FLAT	-	11.6	-	18.4	-	-	-	-
	FLAT	-	10.8	13.6	16.0	-	-	-	-
	FLAT	-	10.4	-	32.8	-	-	-	-
1Hz 512 Stim	FLAT	-	12.0	13.2	16.8	-	-	-	-
Left	FLAT	8.8	12.0	-	18.4	-	-	-	-
	FLAT	-	9.6	11.6	16.8	-	-	-	-
	FLAT	-	10.4	-	16.0	-	-	-	-
1Hz 360 Stim	M	8.8	11.2	-	17.6	27.6	36.8	9.2	25.6
1Hz 512 Stim	M	9.6	11.2	13.2	18.8	28.0	33.6	5.6	22.4
Day 9									
Right	M	-	11.2	12.4	22.0	22.0	32.8	10.8	21.6
	M	-	11.2	12.8	18.8	18.0	35.2	17.2	24.0
1Hz 256 Stim	M	10.4	12.0	-	22.0	19.2	34.4	15.2	22.4
	M	-	11.2	12.4	23.2	19.6	36.0	16.4	24.8
Left	A	-	12.4	-	22.8	20.8	38.0	17.2	25.6
	A	-	11.2	12.4	21.2	21.6	38.8	17.2	27.6
	A	-	12.8	-	24.0	29.6	37.6	8.0	24.8
1Hz 256 Stim	M	-	10.4	12.0	20.0	19.6	34.0	14.4	23.6
1Hz 256 Stim	M	10.0	11.2	-	20.8	20.4	33.6	13.2	22.4
Day 12									
Right	A	-	12.0	12.8	22.0	20.8	32.4	11.6	20.4
	A	-	11.2	12.4	21.2	21.2	33.6	12.4	22.4
	A	10.8	12.0	13.6	20.0	19.6	34.0	14.4	22.0
Left	A	9.2	11.2	14.8	20.0	47.2	65.6	18.4	54.4
	A	-	11.2	13.6	18.8	49.2	68.4	19.2	57.2
	A	-	11.2	12.8	20.4	49.2	75.2	26.0	64.0
Day 16									
Right	M	-	8.8	13.6	20.8	16.8	32.4	15.6	23.6
	M	9.2	10.8	13.2	16.4	17.2	32.8	15.6	22.0
	M	-	10.8	-	16.4	21.2	32.4	11.2	21.6
Left	M	-	10.4	12.0	18.8	20.8	34.4	13.6	24.0
	A	8.8	10.4	-	19.2	18.0	34.8	16.8	24.4
	A	9.6	10.8	12.0	17.6	18.8	35.2	16.4	24.4

Side	Form	C1	C2	C3	Cp	P0	N1	P0-N1	CCT
Day 23									
Right	M	10.0	11.2	-	18.4	18.4	32.8	14.4	21.6
	M	10.0	11.2	12.8	18.0	18.0	33.2	15.2	22.0
	M	10.0	11.2	12.8	18.0	18.4	32.4	14.0	21.2
Left	A	-	11.2	-	19.6	19.6	32.4	12.8	21.2
	M	9.6	12.0	15.6	18.8	18.8	32.8	14.0	20.8
	M	9.6	11.2	-.	18.4	25.2	32.8	7.6	21.6

Equipment for Griffiths Developmental Assessment

1. A small coloured plastic ball that rattles.
2. A small rubber ball
3. A brightly coloured ring with coloured cord.
4. The bell ring.
5. A pair of red embroidery rings.
6. A small handbell.
7. A torch.
8. A tuning fork.
9. A plastic cup and saucer.
10. A plastic spoon.
11. A pair of plastic beakers.
12. A small wooden toy on wheels with attached cord.
13. A car to be pushed along.
14. A car to be wound up.
15. A doll whose eyes 'go to sleep' and has hair.
16. A mirror.
17. A board picture book.
18. A small plastic box.
19. A tiny wooden box.
20. Box with 12 miniture toys - chair, doll, ball, horse, dog, cat, cup, spoon, button, car, brick and penny.
21. Four form boards of differing shapes and complexity.
22. Four yellow cubes.
23. A packet of paper tissues.
24. Three boxes of bricks.
25. A set of 20 coloured pictures.
26. A piece of coloured felt.
27. A screw toy.
28. The case.

Pencil and paper.

Appendix 5

Papers published from this work are bound in the following pages.

Gibson N.A., Brezinova V., Levene M.I.
Somatosensory Evoked Potentials in the Normal Newborn.
Electroencephalography and Clinical Neurophysiology (1992) 84: 26-31.

Gibson N.A., Graham M., Levene M.I.
Somatosensory evoked potentials and outcome in perinatal asphyxia.
Arch. Dis. Child. (1992) 67: 393-398.

Levene M.I., Gibson N.A., Fenton A.C., Papathoma E., Barnett D.
The use of a calcium channel blocker, Nicardipine, in the asphyxiated newborn.
Dev. Med. Child. Neurol. (1990) 32: 567-574.

Electroencephalography and clinical Neurophysiology, 84 (1992) 26–31

EVOPOT 90635

Somatosensory evoked potentials in the term newborn

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Summary Median nerve somatosensory evoked potentials (SEPs) were recorded from surface electrodes in 40 healthy term infants (range 36.5–43 weeks postmenstrual age). Electrical stimulation at 5 Hz was used, averaging the response to several runs of 1024 stimuli to each median nerve, bandpass 10–3000 Hz, sweeptime 100 msec. Identifiable potentials were collected over the cervical cord on all runs in all 40 infants and from the cortex in at least some runs in 39 out of 40 infants.

The cervical response showed little variation and consisted of a clear negative wave with up to 3 peaks, mean latency of the largest 10.2 ± 0.7 msec, followed by a positive deflection. The cortical response was very variable in form and latency between infants and to a lesser degree within infants. Four types of cortical wave form were found, symmetrical, asymmetrical, plateau and M shaped, of increasing complexity. In 11% of trials the response was absent or indistinct but could usually be uncovered by alteration in stimulus frequency or intensity. In the whole group, the mean latency for N1 was 30.0 ± 6.8 msec and for the central conduction time 19.8 ± 6.5 msec. Significant differences were found between the 4 cortical wave forms in the main variables measured, which gave support for form S being the most primitive and form M the most mature response.

Key words: Somatosensory evoked potentials; Newborn

It is known from neuropathological (Yakolev and Lecours 1967) and neurophysiological (Koh et al. 1988) studies that there are major changes in myelination and function of long pathways in late fetal and early infant life. Recent interest is focussing on SEP as a means of assessment in neonatal cerebral damage associated with perinatal asphyxia (Hrbek et al. 1977; Willis et al. 1987) and periventricular haemorrhage (Klimach and Cooke 1988b; Willis et al. 1989). It is therefore important to have accurate knowledge of the range of normal response in the early neonatal period.

The existing literature on the normal somatosensory response of healthy term newborn babies is mostly composed of data on small numbers of infants as part of attempts to give a normal range over a much broader age group. As such, the data are patchy and difficult to use. Existing reports give little or no information on cervical cord potentials nor on the cortical wave form and tend to concentrate on the latency of the first negative wave of the cortical response, the N1.

Before attempting to use SEP in the evaluation of the acutely sick newborn it will be necessary to have more detailed information on the range of response in normal infants. The major pathologies in the newborn are intracranial but the stressed neonate may have suffered traction injury at birth and so the cervical and cortical responses are important so that the central conduction time (CCT) (Hume and Cant 1978) can be used to assess the intracranial part of the pathway.

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Subjects and methods

Forty newborn infants were recruited from the postnatal wards of Leicester Royal Infirmary after full explanation of the procedure to the mother and subsequent consent. Ethical approval had been gained from the local ethical committee. The infants were selected on the basis of term delivery, normal antenatal features, a normal delivery or elective caesarean section, good condition at birth and normal general and neurological examination. Infants showing any signs of perinatal asphyxia or birth insult were therefore excluded. Most of the infants had had early ultrasound scanning as part of the routine antenatal care and gestation was estimated from ultrasound measurements or from the mother's dates. The value of postmenstrual age, which is gestational age plus postnatal age, was used.

The infants were studied immediately after a feed and all studies were completed within 2 h of a feed. The infants were not given any sedation. All studies took place in a warm nursery room with a room temperature in excess of 20 °C. The infants were lightly

dressed and wrapped loosely in blankets. A visual estimate of sleep state changes was made. The head was measured and Ag/AgCl electrodes placed over the second cervical vertebra (Cv2) and over C″3 and C″4, i.e., 2 cm behind C3 and C4 on the international 10–20 system (Jasper 1957). A reference electrode was placed at Fpz and an earth electrode on the upper arm. Scalp elecrodes were fixed with collodion and others with adhesive tape with the application of conductive jelly to keep all impedances below 2 kΩ. Three channels of information could therefore be measured, i.e., the cervical cord potentials and left and right scalp potentials.

Electrical pulses of 0.1 msec duration delivered at 5 Hz were given unilaterally to the median nerve, stimulating at the wrist with a hand-held device. The current, normally of 5–15 mA, was sufficient to cause a thumb twitch. The response to 1024 stimuli was averaged and we aimed to record 2 or 3 runs from each median nerve in each subject. In 8 infants, in addition, the responses were measured after 512 stimuli delivered at 3 Hz and 256 stimuli at 1 Hz. These responses were fed to a Medelec Sensor evoked potential system for amplification, filtering using a 10–3000 bandpass, averaging and display. A sweep time of 100 msec was used. The traces were stored on an Apple IIe microcomputer for later analysis. The procedure was well tolerated by the infants.

The traces obtained were analysed separately by two of us (N.A.G. and V.B.) with respect to wave form and the latency of defined points on the response curve. Wave form was decided by simple visual inspection of the trace and mean latencies for defined points were calculated for right and left median nerve stimulation in each individual. Conflicting interpretations of wave form were resolved by discussion.

For statistical analysis of the data parametric methods (such as *t* test) were employed when only the SEP measurements were involved (e.g., latencies of a SEP peak in different wave forms). Non-parametric methods (chi-squared, Spearman's rank correlation) were used for comparison of the SEP measures with the postmenstrual age. In addition, the main SEP differences were rechecked non-parametrically (Mann–Whitney test, Kruskal–Wallis test) to exclude effect of different sample size or variance.

Results

Data from right median nerve are available in all 40 subjects and data from the left in 37 subjects giving results for 77 somatosensory pathways. In all 40 infants responses to the given stimulus were obtained on at least some stimulus runs. Data are displayed in Table I.

TABLE I

SEP variables measured in 40 neonates. Two or three runs are averaged for each subject. All right–left differences are non-significant in *t* test for paired observation.

Parameter	No. of observations	Range (msec)	Mean (msec)	S.D. (msec)
Right C1	38	7.8–10.8	8.9	0.7
Left C1	35	7.8–11.0	8.9	0.7
Right C2	40	9.0–12.6	10.1	0.7
Left C2	37	9.0–12.6	10.2	0.7
Right C3	30	10.4–14.8	12.1	1.0
Left C3	23	10.6–14.4	12.2	1.0
Right Cp	40	14.4–19.0	16.5	1.0
Left Cp	37	14.4–19.6	16.8	1.0
Right P0	39	13.8–19.2	16.8	1.2
Left P0	37	15.4–29.4	17.5	2.7
Right N1	39	22.8–58.8	30.1	6.8
Left N1	37	22.8–51.0	30.1	6.8
Right CCT	39	13.0–47.8	19.2	6.3
Left CCT	37	13.4–39.8	19.9	6.5

Cervical potentials

These were obtained in every instance. The early and reproducible portion consisted of a large negative wave with up to 3 peaks within it followed by a deep positive deflection. The highest peak was named C2 as it was most commonly the second peak. Any preceding peak was named C1 and any following was called C3. The deep positive deflection was named Cp. Examples of cervical traces with superimposition to show reproducibility are shown in Figs. 1–4. The mean values for each parameter and their frequency are shown in Table I. There were no significant differences between right and left median nerve stimulation in any of the cervical response parameters.

The subsequent record from the cervically placed electrode showed more variation in character and was not subjected to detailed analysis.

Cortical potentials

The following variables were considered: latency of the small positivity preceding the first negative wave (P0); latency of the first negative wave at its peak (N1); rise time of the N1 peak (N1 latency – P0 latency); amplitude of N1 (amplitude difference N1 – P0) and latency of the first positive peak after N1, called P1. The central conduction time was calculated from the difference betwen C2 and N1. Table I shows the mean data for the right and left median nerve. All right–left differences were not statistically significant. The latencies for Cp and P0 are not significantly different suggesting that they may both represent the same electrical event.

There was striking variation in the response measured by the scalp electrodes as shown by the large standard deviation of the mean latencies. The main

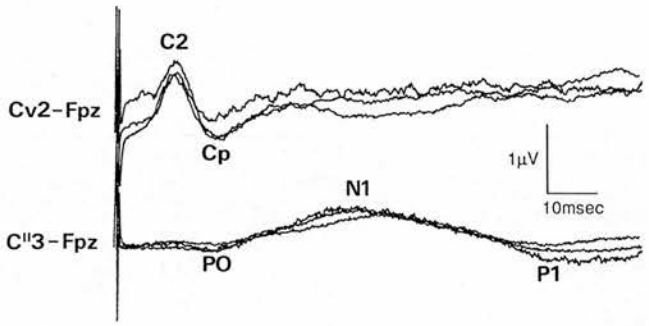

Fig. 1. Superimposed traces for 37 weeks PMA infant wave form S. In all figures negativity of the active electrode registers an upward deflection and each trace is obtained from right median nerve stimulation.

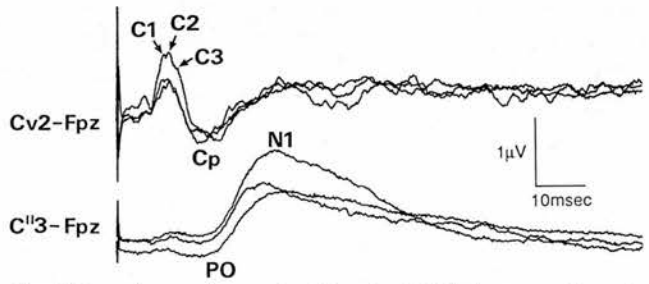

Fig. 2. Superimposed traces for 41 weeks PMA infant wave form A.

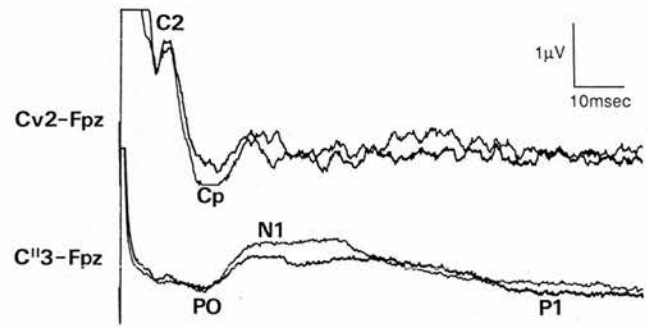

Fig. 3. Superimposed traces for 40 weeks PMA infant wave form P.

explanation for this was in the marked variation in wave form encountered. We identified 4 main wave forms, examples of which are shown in Figs. 1–4. Wave form S (symmetrical Fig. 1) was a broad negative wave, often of low voltage, which was symmetrical with both slow rise from and return to the baseline. Wave form A (asymmetrical Fig. 2) consisted of one broad asymmetrical negative wave with a shorter rise time and prolonged fall back to the baseline or below into positivity. Its maximum amplitude was more easily defined and lay at the peak of the upstroke. This form was normally of larger amplitude than form S. Wave form P (plateau Fig. 3) was characterised by a sharp rise to a plateau without a clearly defined pinnacle. The descending part was also steeper than in forms S and A and might drop into positivity. The plateau was seldom ruler-flat and could undulate. Wave form M (M shaped, Fig. 4), which was the most complex, took the form of a sharp rise to a clear negative peak followed by a fall which might reach positivity before a second rising wave to a less well defined peak and shallower descent towards positivity. Form M resembles the wave form encountered in recordings from older infants and children. The N1 was defined as the peak of the wave in form S, the peak of the upstroke in forms A and P and as the first negative peak in form M.

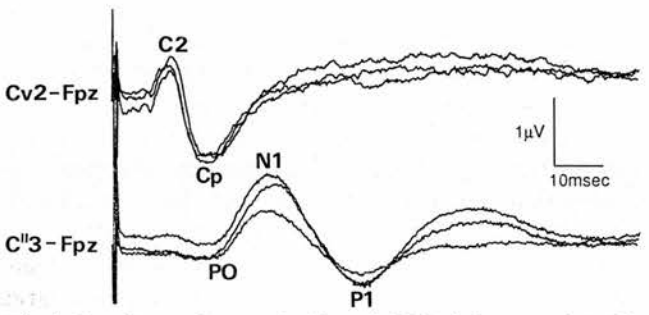

Fig. 4. Superimposed traces for 40 weeks PMA infant wave form M.

Of the 215 SEPs recorded from 40 subjects (111 from right median nerve, 104 from left median nerve) no recognisable peaks were found on 11 occasions (5%) in 5 infants. A response was present but poorly formed and not clearly fitting the above descriptions on 13 occasions (6%). There were 17 responses (8%) in form S, 18 (8%) in form A, 78 (36%) in form P and 78 (36%) in form M. In no subject was there bilateral absence of response but in 1 infant of 37.5 weeks postmenstrual age there was no demonstrable response on 3 runs of right median nerve stimulation at 5 Hz. Different stimulus rates were not tried in that infant. The infants with runs of stimulation not resulting in recognisable response were, in general, the least mature infants studied and this finding may be partly explained by stimulus intensity and frequency (see below). The runs which resulted in cortical response in these immature infants tended to yield forms S and A.

TABLE II

SEP variables measured in subjects with different cortical wave forms. Mean and standard deviation of each variable in msec for each wave form. Data from identical wave forms are averaged in each subject. N = number of subjects.

Variable	S (n = 6) (mean ±S.D.)	A (n = 7) (mean ±S.D.)	P (n = 26) (mean ±S.D.)	M (n = 26) (mean ±S.D.)
C2	11.0± 0.7	10.3±0.5	10.1±0.6	9.9±0.7
P0	21.0± 4.0	18.3±3.1	17.1±1.2	16.9±1.1
N1	44.9± 7.9	32.6±5.3	28.1±2.6	26.7±2.2
P0-N1	27.4± 6.0	14.8±3.3	10.9±1.7	10.0±1.9
CCT	37.2±10.0	22.4±4.9	18.0±2.4	16.9±1.8
P1	81.8±10.7	58.5±9.8	56.6±9.4	37.5±5.0
N1 amplitude (μV)	1.0± 0.2	1.6±0.6	1.3±0.5	1.3±0.3

TABLE III

Comparison of cortical peak latencies in subjects with different cortical wave forms. Data from identical wave forms are averaged in each subject. For each parameter, prominent differences (in t test) between wave forms are shown with their P values. As 6 comparisons are made for each variable a P value smaller than 0.008 (0.05/6) indicates an overall significance of the differences for the variable (Dunn-Bonferroni). Significant differences, confirmed in a non-parametric test (Mann-Whitney), are denoted by an asterix.

Variable	M-P	M-A	M-S	P-A	P-S	A-S
C2 latency			0.01		0.05	
N1 latency			0.001 *		0.001 *	0.01
N1 amplitude			0.01		0.02	
P0-N1 rise time		0.05	0.001 *		0.001 *	0.001 *
CCT			0.001 *		0.001 *	0.02
P1 latency	0.001 *	0.001 *	0.001 *	0.01	0.001 *	

No clear pattern with changes in sleep state was noted. It was found that the wave form was not constant within a particular infant. Wave form S was seen, on at least some occasions, in 6 infants, wave form A in 7 infants, form P in 26 infants and form M in 26 infants. The number of different wave forms seen in an infant's study was 3 in 1 infant, 2 different wave forms in 24 infants and in 15 infants the wave form was consistent in all runs. The most common combination was of type P with type M (18 infants). There was good agreement for wave form encountered on stimulation of right and left median nerve within infants.

Table II shows the results for the main variables in each of the 4 cortical wave forms. A systematic shift of latency was found from the longest values in form S to the shortest latencies in form M. This was true also for the cervical peak C2 associated with each of the cortical wave forms. Significant differences between the groups are shown in Table III. The SEPs with wave form M differed significantly from those with form S in most variables, as did those of wave form P. Differences between forms A and S were less prominent, as were differences between forms A and M. The overall distribution of data among the 4 types of wave form were tested for the latencies of N1 and P1 peaks, P0-N1 rise time and central conduction time, and found significant in all instances ($P < 0.00001$ in Kruskal-Wallis test). Where more than one wave form was found in one particular infant there were no significant differences in N1 latency within that infant.

Factors influencing the cortical wave form

The mean intensity of stimulus used was 11.2 ± 2.7 mA. No significant overall relationship was found between the intensity of the stimulus and the response wave form, the latency of N1 or the N1 amplitude. However, in individual cases an absent or indistinct SEP was replaced by a definite form when the stimulus intensity was increased.

It was found that in 4 of the 8 infants in whom different stimulus frequencies were employed, a reduction in the stimulus frequency changed the wave form to a more complex one. In 3 infants a cortical wave form was uncovered. No child had absent cortical response with a 1 Hz stimulus. Reduction in stimulus frequency significantly increased the peak amplitude of N1 ($P < 0.01$) but did not significantly alter the latency.

The mean postmenstrual age for the infants was 40.2 ± 1.5 weeks (range 36.5–43 weeks). Distribution of the cortical SEP wave forms in relation to age is shown in Table IV. An accumulation of absent responses and forms S and A were seen in the least mature infants. Wave forms P and M predominate in older infants with P commonest between 38.5 and 40.5 weeks and M between 40.5 and 43 weeks. The contingency distribution was significant in chi-squared test ($P < 0.001$). Rank correlation of age with the main SEP variables was undertaken. There was a significant negative correlation with postmenstrual age for C2, P0, N1 and P1 latencies, N1 rise time and central conduction time. Amplitude of the N1 peak did not significantly correlate with age.

TABLE IV

Distribution of cortical wave forms across the postmenstrual age range. Chi-squared value (for 2×2 table, 36–40 weeks combined) is 24.4, $P < 0.001$.

Age (weeks)	Absent, S or A	P or M
36.5–38	29	0
38.5–40	21	74
40.5–43	9	82

Discussion

Normal SEPs to upper limb stimulation in the newborn have been reported by a number of authors (Hrbek et al. 1968, 1969, 1973; Desmedt and Manil 1970; Blair 1971; Cullity et al. 1976; Desmedt et al. 1976; Pratt et al. 1981; Laget 1982; Willis et al. 1984; Gorke 1986; Zhu et al. 1987; Klimach and Cooke 1988a; Laureau et al. 1988). Methods of stimulation have varied as have stimulus rates. Early workers were sceptical about the possible uses of the technique in

the newborn as they could only recognise reproducible potentials in 10% (Pratt et al. 1981), 50% (Blair 1971) and 80% (Cullity et al. 1976) respectively. Willis (1984) reported that in one-third of newborns no reproducible potentials could be measured at Erb's point or over the cortex (for reasons of immaturity). All authors agree that the response is immature at term and even more so in preterm infants (Hrbek et al. 1973; Klimach and Cooke 1988a). We measured an identifiable cortical response on at least some runs in 39 of our 40 subjects (97.5%).

The mean latencies of the major cervical peak and of the early cortical potentials found in our study are generally longer than that of smaller series of infants previously reported (Willis et al. 1984; Zhu et al. 1987). Although part of the variation may be explained on the basis of method the main reason would appear to be the scatter of postmenstrual age and the inclusion of less mature SEP in our study. If we only included the SEP with cortical wave form M our results would be in good agreement with previous studies. However, this report represents the study of 40 consecutive normal term infants and we wish to draw attention to the variability which is not reported in the literature. The large percentage of absent SEPs in the study of Willis et al. (1984) may be accounted for by rejection of less mature wave forms. Laureau et al. (1988) in their study of SEP in early infancy noted that there were more marked changes in the cortical response than in the Erb's point and cervical potentials. Our study demonstrates that even in the range of postmenstrual age defined as full term there are marked changes in cortical SEP.

There are a number of factors known to affect EPs that might have accounted for some of the variability found in this study. Hypoglycaemia has been shown to affect the auditory evoked potentials of neonates by causing lengthening of latencies and even abolition of response (Koh et al. 1988). We did not measure blood glucose during this study but by studying our infants within 2 h of a feed hypoglycaemia was unlikely to have been a factor (Aynsley Green and Soltesz 1985). Sleep state is known to affect SEP but can only reliably be determined by full polygraphic recording of the infant and this was not performed in this study. Several studies (Hrbek et al. 1969; Desmedt and Manil 1970; Willis 1986) have shown that sleep state changes can affect SEP in infancy. It was noted in this study that wave form could change in infants without apparent change in sleep state as assessed by visual inspection. Sleep state changes may have had some effects on the results but our method does not allow systematic analysis of this variable. Temperature has a major effect on conduction in nerve pathways but the effect does not have a linear relationship. It has been shown that over the range of 30–35 °C there is little change in sensory conduction velocity (Todnem et al. 1989). Our infants were studied wrapped in a cot in a warm hospital room and there was no clear trend in C2 latency with this value being remarkably constant within individuals ruling out important changes in conduction velocity due to temperature change. We also undertook to stimulate the median nerve above the motor threshold therefore ensuring recruitment of the largest fastest conducting fibres. It may be that the least mature infant's central pathway is not capable of response to a frequent stimulus as it was found that in some absent cortical potentials were replaced by recognisable forms when the stimulus frequency was reduced.

The differing wave form could also be accounted for by electrode position 'viewing' the dipole at the primary somatosensory cortex from differing position. The authors accept that the visual evaluation of wave forms has a strong subjective component, particularly in defining the transitional wave forms P and A. However, significant differences in most measured parameters were found between the form M and P on one side and the form S on the other side. There was also good agreement between the wave form on each side within infants and Table IV shows a clear trend of wave form with maturity. The absence of right–left latency differences also supports our view that these changes relate to maturity.

The statistically significant relationship between the complexity of the wave form and increasing postmenstrual age is in agreement with the known incomplete maturation of the intracerebral part of the somatosensory pathway, particularly the thalamocortical fibres (Yakolev and Lecours 1967). While the cervical potentials have the complexity and form of the adult response the cortical potentials are very variable particularly in their later components. Multiple generators are known to contribute to the formation of the short latency adult SEP (Desmedt and Cheron 1981; Deiber et al. 1986). The small number of recording channels employed in this study could not give information about the origin and homology of the differing components. It is interesting to speculate whether techniques such as brain mapping may allow us to determine if the increasing complexity of the wave form is due to increasing complexity of the response of the primary somatosensory cortex or to the slotting in of the effects of different generators into a basic primitive wave form.

An altered form of evoked potential is sometimes seen in pathological circumstances, although less important than abnormal latency or loss of response (Jones 1982). The change of form may be accounted for by abnormal dispersion of conduction velocities in the relevant pathway and/or fall out of some conducting fibres. In the human neonate it has been observed that regression to a more primitive pattern can be

observed in spontaneous brain activity in pathological states (Ellingson 1980). It is therefore very important to have a knowledge of the range of normal wave form and latencies in the healthy newborn in order to make valid interpretation of the SEP in neurologically sick infants.

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Somatosensory evoked potentials and outcome in perinatal asphyxia

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Abstract

Somatosensory evoked potentials (SEP) can be measured in the term newborn infant and given an index of function in the areas of the brain most likely to be damaged in perinatal asphyxia. We studied the median nerve SEP in 30 asphyxiated term infants over the course of their encephalopathy and until discharge from the neonatal unit. Three types of response were noted: normal waveform, abnormal waveform, or absence of cortical response.

Follow up of the survivors was undertaken at a mean age of 12 months by means of a Griffiths' assessment and neurological examination. Nine infants died of their asphyxial illness and one of spinal muscular atrophy. Of the 20 survivors, three have cerebral palsy, four have minor abnormalities, and 13 are neurodevelopmentally normal.

There was a close correlation between outcome and SEP. All 13 infants with normal outcome had normal SEP by 4 days of age, whereas those with abnormal or absent responses beyond 4 days had abnormalities at follow up.

Perinatal asphyxia remains the single most important cause of neurodevelopmental handicap in the term newborn infant. The prognosis of the surviving infant is of importance both to the paediatrician deciding on follow up and physiotherapy and to the parents. The literature contains many reports of attempts to assess the prognosis using clinical examination, biochemical measurements, Doppler ultrasound assessment of cerebral blood flow velocity, electroencephalography (EEG), and computed tomography.[1–7] Each of these techniques is subject to inaccuracy. Two previous papers have discussed the use of somatosensory evoked potentials (SEP) in perinatal asphyxia on small numbers of infants.[8 9]

We undertook to investigate the use of SEP in the prognostic assessment of a group of asphyxiated term infants. The parts of the brain most vulnerable to damage in this condition are the cortex, the immediate subcortical white matter, and the periventicular white matter.[10] The somatosensory pathway traverses these areas and it seems reasonable to suppose that damage to these areas may be reflected in abnormalities of SEP.

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Patients and methods

Between May 1987 and December 1988 term infants were recruited from the neonatal unit of Leicester Royal Infirmary after a full explanation to the parents. Ethical approval had been obtained from the local ethical committee. The infants were selected on the basis of term delivery; the presence of adverse perinatal factors consistent with an asphyxial insult, such as an abnormal cardiotocograph, low scalp pH, cord prolapse or uterine rupture; and the presence of abnormal neurological findings in the neonatal period consistent with an asphyxial insult. The hypoxic-ischaemic encephalopathy was graded according to the description by Levene *et al*[11] modified from the Sarnat scheme.[2]

Thirty term infants with a mean gestational age of 39·5 weeks were recruited. Five were very small for dates (<3rd centile). All had clinical evidence of perinatal asphyxia and, in addition, one was subsequently shown to have spinal muscular atrophy and two had group B β-haemolytic streptococcal septicaemia, one of whom also had meningitis. Eight of the infants had mild encephalopathy and were neurologically normal by 3 days of age; six of the infants were moderately encephalopathic with more noticeable abnormalities of tone and seizures; the remaining 16 infants were severely asphyxiated. In addition, during the time of the study, there were two other infants fulfilling the enrolment criteria who did not take part. One infant died at 3 hours of age before he could be studied and the parents of one infant did not give consent for the study.

Median nerve SEP were recorded as soon as possible after admission to the neonatal unit and until resolution of the encephalopathy or death. Planned intervals between studies were every two days in the first week and twice a week thereafter. A hand held stimulator device delivering 1024 electrical impulses of 0·1 ms duration over the median nerve at a frequency of 5 Hz was employed. Normally three runs on each median nerve would be recorded. The response in the first 100 ms (sweep time) after each stimulus was recorded from silver/silver chloride skin surface electrodes over the cervical cord (Cv2) and the contralateral cortex (C″3 and C″4) with a reference electrode in a midline frontal position (Fpz). An earth electrode was placed on the forearm. When this arrangement failed to evoke measurable potentials, the stimulus was delivered at 1 Hz for 256 or 512 stimuli and the sweep time increased to 200 ms. The signals were fed to a Medelec Sensor evoked potential system for amplification, filtering using a 10–3000 Hz bandpass, averaging, and display. Sleep state could not be accurately assessed and would have been

distorted in many of the infants by the use of anticonvulsants, but a visual inspection of behaviour was made. The acutely ill infants had regular estimations of blood glucose performed by reagent strips (BM-Test 1–44, BM Diagnostics) to exclude hypoglycaemia which may effect evoked potentials.[12] Oxygen monitoring by transcutaneous electrodes ensured that recordings were not done in the presence of hypoxia.

The SEP traces obtained were stored on an Apple IIe microcomputer for later analysis. The features assessed in the SEP were the shape of the cervical and cortical waveforms, and the latency of the cervical C2 potential (the major cervical potential) and cortical N1 (thought to be the first response of the primary somatosensory cortex). The comparative normal values were taken from our own study of 40 normal term infants.[13]

All the surviving infants were followed up and assessed at one year of age. This assessment was done by an investigator (MG) unaware of the SEP results or the extent of the encephalopathy. One infant was assessed by his local paediatrician. The other 19 infants were seen in their own homes and had a Griffiths' assessment[14] and a neurological examination performed. The data available, therefore, were the Griffiths' subscale scores the Griffiths' quotient (GQ) and the neurological findings.

DEFINITIONS

In our study of normal term infants[13] we showed that there was marked variation in both waveform and latency within the range of postmenstrual age 37 to 43 weeks. A strong positive correlation was found between increasing complexity of waveform with shortening of latencies and increasing postmenstrual age. The mean (SD) cervical potentials showed little variability with C2 latency 10·1 (0·7) ms. The N1 for the whole group was 30·1 (6·8) but much less widely scattered data were obtained within each of the four waveforms encountered. It was decided to base a decision of abnormality on the appropriateness for the infant's postmenstrual age of the measured waveform and the latency of the measured N1 for that waveform. The upper limit of normal latency was taken as the mean plus 3 SD because the control data on normal infants were slightly skewed to the left. We found on repeated runs that normal immature infants may initially have absent cortical potentials that are uncovered by an increase in stimulus intensity or decrease in stimulus frequency and hence the manoeuvres described above were employed to attempt to uncover a waveform when the initial runs showed no potentials.

In the present study of asphyxiated infants the results obtained from cortical electrodes in each individual recording session could then be split into three main groups. (1) *Normal*: responses appropriate in both latency and waveform for the infant's postmenstrual age. (2) *Abnormal*: measurable response with either delayed N1 (>+3 SD from mean) for the encountered (appropriate) waveform or inappropriately immature waveform with normal N1 latency for that form. (3) *Flat*: complete absence of identifiable response—that is, flat traces on repeated runs.

Results

SEP

A total of 111 studies were performed on the 30 infants giving a mean of 3·7 and a mode of three studies. Three infants had only one study before death and the largest number in any one infant was 10 studies. Eighteen infants were studied on day 1, seven were first studied on day 2, four first studied on day 3, and one on day 7. Cervical SEP were easily measured in all but one infant who was studied only a few hours before death, revealing no measurable potentials. In the other 29 infants cervical potentials were always normal even in those infants who had suffered shoulder dystocia during delivery (two infants).

The usual pattern over the course of the encephalopathy was for a progression of results from abnormality to normality. Asymmetry of response did occur but was seldom marked except in infant 20 (see below). Eleven infants had persistently normal SEP throughout their encephalopathy (pattern A). In addition, a further two infants had abnormal SEP with delayed latency of N1 in the first two days but normal SEP results thereafter (pattern B). Nine infants had initial potentials which were absent or severely abnormal and then the potentials were abnormal or absent for a variable length of

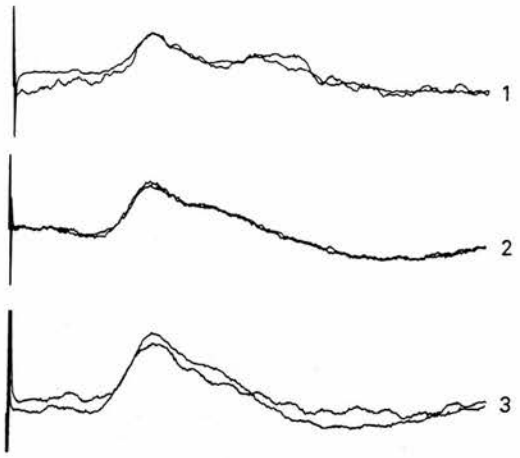

Figure 1 Infant 4 (41 weeks' gestation). Superimposed traces of response to left median nerve stimulation measured at C"4-Fpz on days 1, 2, and 3: pattern A.

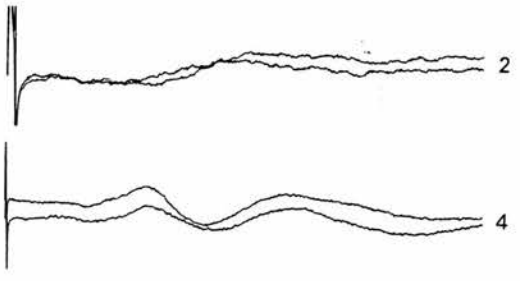

Figure 2 Infant 29 (42 weeks' gestation). Superimposed traces of response to left median nerve stimulation measured at C"4-Fpz on days 2 and 4: pattern B.

time before returning in an immature fashion in which they persisted or normalised (pattern C). In the other eight infants, all of whom had severe encephalopathy, the findings were of persistently flat traces with no cortical response measured at any time (pattern D). Examples of patterns A, B, C, and D are shown in figs 1–4.

OUTCOME

Ten of the infants in the study died. All of these infants had a pattern of neurological abnormality consistent with severe hypoxic-ischaemic encephalopathy. They died between 2 and 70 days but mostly in the first week of life.

The surviving infants were followed up to assess their outcome. One infant was seen by his local paediatrician and thought to be neurodevelopmentally normal. The results of the Griffiths' assessment subscales and GQ scores are available for 19 infants who were seen at a mean age of 12 months (range 9·5 to 14·5 months). They showed a wide range of results from 64 to 123. On neurological examination there were three infants with cerebral palsy, two of whom had spastic quadiplegia and were developmentally delayed (GQ 64 and 72) and one with a left hemiplegia (GQ 110). There were four other infants with low GQ scores (72, 85, 87, and 90) and questionable neurological findings who are best described as 'dystonic.' There are therefore three outcome groups among the survivors: unequivocal normality with normal neurology and high Griffiths' score, dystonic infants with questionable neurological findings and GQ scores in the lower part of the normal range, and those with clear abnormality manifest as cerebral palsy.

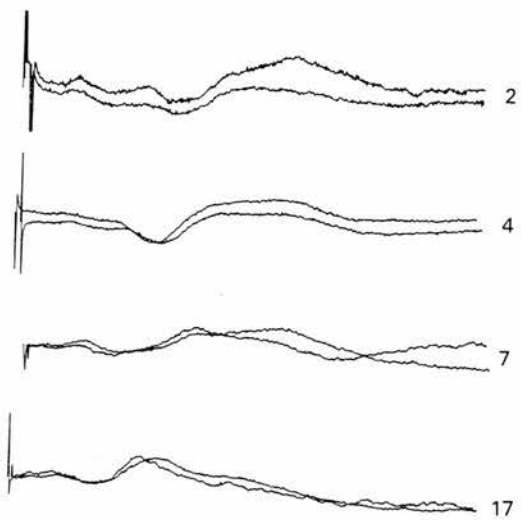

Figure 3 Infant 20 (39 weeks' gestation). Superimposed traces of response to right median nerve stimulation measured at C"3-Fpz on days 2, 4, 7, and 17: pattern C.

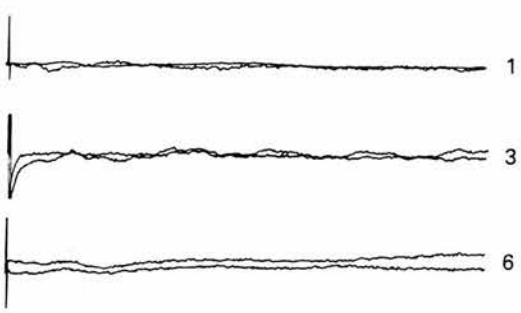

Figure 4 Infant 14 (40·5 weeks' gestation). Superimposed traces of response to right median nerve stimulation measured at C"3-Fpz on days 1, 3, and 6: pattern D.

CORRELATION OF SEP WITH OUTCOME

The relationship of outcome to encephalopathy grade is shown in table 1 and is comparable with other studies reported in the literature. Table 2 shows the relationship of outcome to SEP pattern. The infants' outcome results were divided into normal outcome (13 infants), which was unequivocal neurological normality with normal GQ score, and abnormal outcome (seven infants) which includes the three infants with cerebral palsy and four in the dystonic group. The serial SEP results of those whose SEP changed over the course of their encephalopathy are shown in table 3. Those that had a normal outcome had reached normal SEP results by 4 days of age. All seven of the infants in the abnormal outcome group had abnormal SEP studies persisting beyond 4 days. There was no clear difference between those with cerebral palsy and the dystonic infants in terms of length of persistence of SEP abnormality nor of its pattern.

Of the 10 infants who died, eight had absent cortical SEP on all occasions. The infant who died of spinal muscular atrophy had normal cortical potentials. The other infant who died of cardiovascular complications of his asphyxia (infant 15) had bilaterally abnormal potentials at day 5 and then persisting asymmetry thereafter. Therefore no infant dying of asphyxia had normal potentials by 4 days.

Discussion

From the literature there are a number of investigations which can assign a good prognosis to an asphyxiated infant. These are the presence of only grade one hypoxic-ischaemic encephalopathy,[2 15] a normal EEG[2] or a normal computed tomogram in the second week of life.[7] It is

Table 1 Relationship of encephalopathy grade to outcome

Encephalopathy	*Outcome*				*Total*
	Normal	*Dystonic*	*Cerebral palsy*	*Died*	
Mild	8	0	0	0	8
Moderate	4	1	1	0	6
Severe	1	3	2	10	16

Table 2 Relationship of SEP pattern to outcome

SEP	*Outcome*				*Total*
	Normal	*Dystonic*	*Cerebral palsy*	*Died*	
A	10	0	0	1*	11
B	2	0	0	0	2
C	1	4	3	1	9
D	0	0	0	8	8

See text for definition of patterns
*Child with spinal muscular atrophy.

Table 3 SEP results over the first 10 days related to those whose SEP changed (patterns B and C). Right (R) and left (L) refer to the median nerve stimulated (N1 measured in ms)

	Days								*Comments*	*Outcome*
	1	*2*	*3*	*4*	*5*	*7*	*9*	*10*		
Infant 7										
R	Absent		Absent		Absent	Immature form N1 52·4		Immature form N1 57·0	Persistent delayed or immature SEP at 6 weeks	Doubtful neurology GQ 85
L	Absent		Absent		Absent	Immature form N1 46·6		Immature form N1 39·8		
Infant 8										
R	Imature form N1 34·3		Absent		Absent	Immature form N1 34·8			Normal response at 7 weeks	Doubtful neurology GQ 88
L	Imature form N1 37·1		Absent		Absent	Immature form N1 36·2				
Infant 15										
R		Normal form N1 29·4		Delayed N1 66·8		Immature form N1 30·2	Normal form N1 27·8			Died
L		Imature form N1 44·0		Delayed N1 123·0		Normal N1 32·4	Delayed N1 38·6			
Infant 20										
R		Absent/immature N1 54·6		Delayed N1 45·4		Delayed N1 36·8			At 17 days right normal and left absent	Left hemiplegia GQ 110
L		Absent		Absent		Absent				
Infant 21										
R	Absent		Immature form N1 39·2		Absent	Absent			Response still immature at 14 days	Spastic quadriplegia GQ 72
L	Absent		Absent		Absent	Absent				
Infant 22										
R	Normal N1 31·6		Absent		Absent	Immature form N1 38·2			Normal on right, immature on left at 14 days	Spastic quadriplegia GQ 64
L	Absent		Absent		Absent	Absent				
Infant 25										
R	Absent	Delayed N1 43·2	Normal N1 33·2						Normal response when next tested at 25 days	Normal neurology, developmentally normal
L	Absent	Normal N1 29·9	Delayed N1 36·0							
Infant 26										
R	Delayed* N1 34·8			Normal N1 29·7						Normal GQ 13
L	Normal N1 34·6			Normal N1 27·8						
Infant 28										
R		Absent		Absent		Absent	Absent		Still immature/delayed at 30 days	Doubtful neurology GQ 90
L		Absent		Absent		Absent	Absent			
Infant 29										
R		Normal N1 35·1		Normal N1 30·6						Normal GQ 123
L		Delayed N1 59·2		Normal N1 29·0						
Infant 30										
R		Absent		Absent		Delayed* N1 34·6*			Still delayed at 23 days	Dystonic GQ 72
L		Absent		Delayed N1 35·2		Delayed N1 36·4				

*Mature waveform present which has mean +3 SD for N1 of 32·9.

almost as clearcut to pick out those infants at extremely high risk of abnormal neurodevelopmental outcome on the basis of an isoelectric EEG,[5] extensive hypodensity on computed tomography,[6] severe brain energy depletion shown by ^{31}P nuclear magnetic resonance spectroscopy,[16] marked abnormality of Doppler signals from assessment of cerebral blood flow velocity,[4] or profound and persisting neurological abnormality.[1] However, these investigations all leave a grey area of infants with the same test result and differing outcome. The attraction of SEP is the ability to measure an index of function in the areas of the brain most severely affected in perinatal asphyxia.

There have been two previous studies of SEP in perinatal asphyxia. Hrbek *et al* described the use of SEP and visual evoked potentials in 57 infants.[8] Their study is very difficult to assess as they do not state the gestational age of their patients, the method is not described, and there is no data on follow up. However, they developed a scoring system of SEP abnormality and reported those with the highest score (most abnormal SEP) to have the worst asphyxia. A more complete study by Willis and colleagues looked at 10 term asphyxiated infants followed up to a mean of 20 months.[9] These authors aimed to perform SEP at 2, 4, and 6 months and defined abnormality as N1 absent or more than 3 SD above the mean. Persistently normal SEP predicted normal outcome and persistently abnormal SEP predicted severe disability at follow up. Those with abnormal SEP at 2 months which improved had only moderate or mild disability at follow up. Both of these studies are supported by our data. We also found that those with the most abnormal SEP had suffered the greatest asphyxial insult but, in addition, we found that SEP can be predictive in the neonatal period.

We included data on the cervical response as the presence of a cervical response of normal form and latency shows that any abnomality of cortical response occurs as a result of dysfunction in the central part of the pathway and is not due to peripheral damage as might occur in shoulder dystocia. We did not have access to the technique of electromagnetic stimulation of the motor cortex.[17] It is motor function that is most often impaired in infants who have sustained asphyxial damage and this technique might have allowed a more specific look at the effects of perinatal asphyxia on the motor pathways during the encephalopathy. However, our hypothesis that abnormality of sensory pathway function might reflect damage in motor areas would seem reasonable.

The effects of sleep state and of drugs must be considered. The first line anticonvulsant used during our study was phenobarbitone and it has been shown to have no effect on SEP.[18 19] Sleep state is known to alter the waveform and amplitude of the short latency SEP[20 21] but not signficantly to affect the latency, which was the major characteristic we assessed. Sleep state is also altered in encephalopathic infants and any test used has to be employed in the circumstances that present.

We have previously shown that there is a wide range of normal latency for N1 in the term newborn infant.[13] We described different waveforms which became increasingly complex with increasing maturity. The abnormalities shown in the asphyxiated infants in this study are mostly profound. Criticism could be levelled at the category of abnormality relating to the inappropriateness of the form or latency for the infant's postmenstrual age. Most of the variation in N1 latency for the whole group of normal infants (SD 6·8 ms) related to a wide range of N1 in the immature waveforms (immature infants), whereas in the mature forms the SD of N1 is only 2·2 ms. It was therefore thought important to relate results to maturity of the infant as this was the main variable found in normal infants. It is of note that in the more severely asphyxiated infants when the SEP first returned it was in a form which we found associated with the least mature infants and therefore abnormal for that infant's postmenstrual age. This is consistent with findings of the recovery of EEG in sick neonates.[22] Studies in older children with coma[23–25] have shown that SEP may be lost early on but rapid recovery of SEP is associated with good outcome and sustained abnormality of SEP correlates with poor outcome. We have shown that this is also the case in perinatal asphyxia.

The only infant (number 20) with appreciable asymmetry of SEP had persisting absence of cortical response on stimulation of the left median nerve until discharge from the unit at 17 days. There was improvement over time from abnormal to normal on right median nerve stimulation. This is demonstrated in fig 3. Unfortunately he was not subsequently studied. Computed tomography in the neonatal period showed the appearances of neonatal stroke of the right hemisphere and on follow up he had a left hemiplegia.[26 27]

The timing of any neurodevelopmental assessment in a cohort of sick neonates will always have a potential effect on the results. At one year it is relatively easy to pick out those with unequivocally normal outcome and those with cerebral palsy but a grey area will inevitably remain. Later assessment allows more and more scope for profound influences from upbringing and other illness factors. Piper *et al*, using the Griffiths' assessment, in a cohort of preterm infants examined at 6, 12, and 24 months, showed that at one year 25% were neurodevelopmentally suspect but only 12% at two years.[28] Much of this change was accounted for by movement from the suspect group to frank abnormality. It is likely that some infants in our doubtful group will prove to have clearer abnormalities on later testing.

Prediction of outcome in the perinatally asphyxiated term infant can be difficult but our results suggest that SEP may have a part to play. We were able to confirm that infants with mild encephalopathy all had the same SEP results and a good outcome but that, in addition, a group of infants with moderate encephalopathy and one infant with severe encephalopathy also had the same SEP results and had a normal outcome. In our study the infants with normal potentials by 4 days of age were all neuro-

developmentally normal on follow up at 1 year of age. None of the infants with abnormal SEP beyond this time had a normal outcome.

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THE USE OF A CALCIUM-CHANNEL BLOCKER, NICARDIPINE, FOR SEVERELY ASPHYXIATED NEWBORN INFANTS

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The concept of cerebral protection by pharmacological agents following global cerebral injury is now widely accepted as a promising method for the clinical management of this condition. Calcium-channel blockers have been singled out for evaluation by a number of research groups, using various animal models (Takenaka and Handa 1979; Harper *et al.* 1981; Harris *et al.* 1982; White *et al.* 1982; Haws and Heistad 1983; Hossmann *et al.* 1983; Kägström *et al.* 1983; Smith *et al.* 1983; Steen *et al.* 1983, 1984, 1985; White *et al.* 1983*a, b*; Winegar *et al.* 1983; Berger *et al.* 1984; Dean *et al.* 1984; McCalden *et al.* 1984; Mohamed *et al.* 1984, 1985; Newberg *et al.* 1984, 1986; Vaagenes *et al.* 1984; Edmonds *et al.* 1985; Forsman *et al.* 1986; Mabe *et al.* 1986; Sakabe *et al.* 1986; Fleischer *et al.* 1987). This group of drugs has at least three potentially important actions: protection of the neuron from the effect of calcium ion (Ca++) entry; prevention of post-ischaemic cerebral arteriolar vasoconstriction; and improvement of myocardial function (White *et al.* 1983*a, b*).

Calcium ion entry into the compromised cell triggers a cascade of biochemical events which can cripple or kill the cell. Phospholipase A_2 is activated (Siesjö 1981), which leads to accumulation of arachidonic acid within the cell. Following reperfusion, the arachidonic acid is metabolised to vasoactive prostaglandins (Aveldaño and Bazán 1975, Moncada and Vane 1978), leading to platelet activation and arteriolar vasoconstriction. Liberation of superoxide radicals during reperfusion may also cause cellular injury (Siesjö 1981). These mechanisms best explain the repeatedly observed phenomenon of secondary cerebral hypoperfusion following hypoxic-ischaemic injury. Several research groups have shown experimentally that calcium-channel blocking drugs prevent or modify secondary cerebral hypoperfusion when given after severe global hypoxic-ischaemic insult (White *et al.* 1982, 1983*a, b*: Steen *et al.* 1984; Newberg *et al.* 1986; Sakabe *et al.* 1986; Thiringer *et al.* 1987).

Birth asphyxia is an important and common complication of delivery. We have reported previously that six per 1000 fullterm infants develop post-asphyxial encephalopathy (Levene *et al.* 1985), while the incidence of death or severe neurological disability in fullterm infants due to birth asphyxia is one per 1000 (Levene *et al.* 1986). This condition has many similarities to severe, global, hypoxic-ischaemic injury sustained by adults following cardiac arrest.

To date there are few data on the cerebral protective effects of calcium-channel blocking drugs in the asphyxiated

perinatal animal. In one study the calcium antagonist lidoflazine, when used together with oxygen free radical scavengers, prevented post-asphyxial hypoperfusion in newborn lambs (Thiringer *et al.* 1987). Immature rats suffered less severe structural brain-damage if pretreated with flunarizine (Silverstein *et al.* 1986), but no improvement in cerebral blood-flow was found with nimodipine in an asphyxiated newborn beagle model (Ment *et al.* 1987).

To date there are no reports of the use of calcium-channel blocking drugs in human newborn infants. We have reported previously that Doppler ultrasound will detect a group of severely asphyxiated infants with a very poor prognosis (Archer *et al.* 1986), and we justified the use of a water-soluble, non-light sensitive calcium-channel blocker, nicardipine, for those infants with the most severe form of birth asphyxia, for whom the prognosis was very poor. We report here the effects of nicardipine on cerebral blood-flow velocity, mean arterial blood pressure and cortical electrical activity.

Method

Infants with severe post-asphyxial encephalopathy (Levene *et al.* 1985) and abnormal Doppler studies were considered potentially suitable for inclusion in this study. These babies were comatose, required ventilatory support and had multiple convulsions. Routine care involved establishing arterial access (either an umbilical artery catheter with its tip in the mid-aorta or a radial artery cannula) for blood gas estimates and continuous estimation of mean arterial blood pressure (MAP). Continuous assessment of EEG function was performed with a Cerebral Function Monitor 870 (Critikon, USA), and somatosensory evoked potentials (SEP) were also recorded regularly throughout the course of the infant's illness. SEP were recorded using a Medelec Sensor system and by averaging the responses to 1024 electrical stimuli delivered at a motor threshold over the median nerve at 5Hz, using a 10 to 3000Hz bandpass filter. Potentials were collected from surface electrodes over the second cervical vertebra and both cerebral cortices and referred to a midline frontal electrode.

Infants with severe asphyxia were initially examined every four to six hours with duplex Doppler ultrasonography, and 30 consecutive cardiac impulses from the anterior cerebral artery were recorded onto audiotape and analysed off-line by the method described by Prytherch and Evans (1985). The Pourcelot Resistance Index (PRI) and mean cerebral blood-flow velocity were also recorded. On the first occasion that the PRI was found to be low ($<0{\cdot}55$), and if the infant was still comatose, the parents were interviewed and asked for signed consent to administer nicardipine. The parents were seen together, and pains were taken to ensure that they understood the likely poor prognosis as the result of the asphyxia, as well as the potential hypotensive effect of the drug. The protocol stated that the drug infusion would be terminated if there was a drop in MAP of more than 15 per cent from the pre-infusion level. The study had been approved by the Leicestershire District Ethical Committee.

Before infusion of nicardipine, the baseline Doppler assessment from the anterior cerebral artery and SEP were recorded. The continuous systemic blood pressure chart and Cerebral Function Monitor (CFM) paper strip were marked to note the start of infusion. Approximately hourly Doppler assessments were made and SEP measurements were repeated every two to three hours. During the infusion, blood was drawn every two to three hours for measurement of nicardipine levels. The plasma was separated and frozen at $-40°C$ for subsequent assay by Syntex Ltd. After the infusion had finished, blood was drawn at three, six, 12 and 24 hours for further determination of serum levels. Regular Doppler recordings, MAP and CFM were continued for 24 hours after infusion of nicardipine.

Nicardipine was started at a dose of 5 to 10μg/kg/hr by continuous intravenous infusion. This was increased by 5 to 10μg/kg/hr every 60 to 90 minutes, up to a dose of 20μg/kg/hr. Further increases of 10μg/kg/hr were made at hourly intervals, up to a total of 40μg/kg/hr. The

TABLE I
Clinical details

Case	Gest. age (wks)	Birthweight (g)	Apgar scores (mins) 1	5	10	Age at death (days)
1	39	2860	0	1	2	1·5
2	40	4080	0	2	5	9
3	38	3610	10	*		15
4	38	3420	0	0	6	70

*This infant collapsed at age 19 hours.

TABLE II
Changes in heart rate and mean arterial blood pressure

	Heart rate (bpm) Pre-infusion	Increase (%)		Mean arterial blood pressure (mmHg) Pre-infusion	Lowest	Change (%)	
1	130	114	(88)	55	45	−10	(−18)
2	146	29	(20)	51	59	+9	(+17)
3	158	52	(33)	53	49	−4	(−8)
4	184	34	(18)	52	27	−25	(−48)

TABLE III
Details of nicardipine infusion

Case	Infusion Age at start (hrs)	Duration (hrs)	Max. dose (mg/kg/hr)	Max. serum level (ng/mL)	Dose at max. serum level
1	9·5	4	20	27·6	20
2	9	4	40	9·3	20
3	30	11	40	37·1	40
4	14	3	20	25·8	20

total duration of infusion did not exceed 12 hours.

Results

Four fullterm infants were studied and their details are shown in Table I. Three had suffered severe intrapartum asphyxia and the fourth (case 3) was found collapsed at 19 hours after birth on the postnatal ward. No cause was found for the sudden collapse, but following resuscitation he showed clinical signs of severe PAE. All had low PRI measurements before infusion of nicardipine. Nicardipine was started within 12 hours of delivery in three cases and in the fourth (case 3) it was started four hours after resuscitation on the postnatal ward.

All four infants had a normal MAP (>50mmHg) before starting nicardipine. One infant's blood pressure increased during the infusion, but blood pressure decreased in the other three (Table II). All infants showed an increase in heart rate during the infusion, ranging from 18 to 88 per cent (Table II).

All four infants showed abnormal CFM activity before starting nicardipine, with long periods of discontinuous voltage interspersed with seizure activity. There was no change in the trace, either during or after nicardipine infusion. Evoked potentials of normal latency were measured from cervical electrodes in all the babies, but later cortical responses were not seen before, during or after nicardipine infusion in any infant.

At least three measurements of nicardipine in serum were made during and after the course of each infusion. The

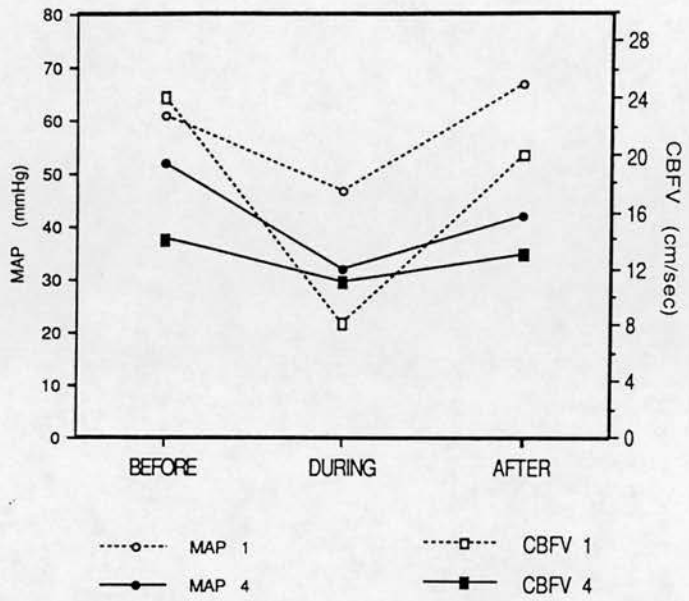

Fig. 1. Changes in mean arterial blood pressure (MAP) and cerebral blood-flow velocity (CBFV) before, during and after nicardipine infusion for infants 1 and 4.

highest serum level in any infant was 37·1ng/mL, while the infant was receiving 40μg/kg/hr (Table III). In all cases serum levels fell to values <5ng/mL by 12 hours after nicardipine withdrawal.

Cases 1 and 4 showed an identical and dramatic change in their condition about three hours after the infusion had begun. Both were receiving 20μg/kg/hr when their MAP suddenly fell, and they became intensely mottled and grey. The infusion was immediately stopped and their skin perfusion gradually improved over the next two hours. The MAP, which had fallen acutely by 18 per cent and 48 per cent coincidentally with their deterioration, improved rapidly after nicardipine withdrawal. Figure 1 shows the relationship between MAP and CBFV in these two infants, recorded before, during and after the nicardipine infusion. The CBFV fell at the time of the hypotensive episode and recovered with improvement of systemic blood pressure.

Discussion

This is the first study of the use of calcium-channel blockers in human infants. We have shown previously that there is a delay before the development of abnormal cerebral haemodynamics as diagnosed by Doppler ultrasound (Archer *et al.* 1986), and we questioned whether this might represent a potentially treatable refractory period during which neuroprotective drugs might be of benefit. We had planned to study six severely asphyxiated babies before evaluating the feasibility of using nicardipine in a controlled study. Because of the dramatic effect on blood pressure and skin perfusion seen in two babies, we felt we could not justify continuing this study.

The most effective calcium-channel blocker in the management of global hypoxic-ischaemic cerebral insult is not obvious. Various drugs have been evaluated in animal models, including nimodipine (Kägström *et al.* 1983; Smith *et al.* 1983; Steen *et al.* 1983, 1984, 1985; Mabe *et al.* 1986; Newberg *et al.* 1986; Ment *et al.* 1987); lidoflazine (Winegar *et al.* 1983, Vaagenes *et al.* 1984, Dean *et al.* 1984, Fleischer *et al.* 1987, Thiringer *et al.* 1987); flunarizine (White *et al.* 1982, Hossmann *et al.* 1983, Newberg *et al.* 1984, Edmonds *et al.* 1985, Silverstein *et al.* 1986); verapamil (White *et al.* 1983*a, b;* Berger *et al.* 1984) and nicardipine (Sakabe *et al.* 1986).

When considering the newborn infant, it is necessary to be able to dilute the drug to small dosages, based on birthweights of 2·5 to 3·5kg. Nicardipine was the only water-soluble calcium-channel blocker with vascular sensitivity available to us.

Unlike some other calcium-channel blocking agents, it has the additional advantage of being resistant to photodegradation. Nicardipine has a relatively greater vasodilating effect on constricted cerebral arteries compared with systemic vessels (Yamamoto *et al.* 1983). In a study on adult dogs after a 10-minute period of complete cerebral ischaemia, nicardipine prevented secondary cerebral hypoperfusion compared with an untreated control group (Sakabe *et al.* 1986).

For two of our infants, the use of nicardipine was closely associated with the development of severe hypotension and circulatory collapse. Serum levels confirmed that the dosage was appropriate, so apparently this reaction was not due to toxic levels. Healthy adult volunteers have sustained serum levels of nicardipine of about 100ng/mL, with no adverse effect (Debbas *et al.* 1985). All calcium-channel blocking agents reduce systemic resistance and cause a fall in blood pressure (Hof 1983). Three of the infants in this study showed a fall in MAP. There is dispute as to the effects of calcium-channel blockers on myocardial contractility (Stone *et al.* 1980). Some drugs, such as nifedipine, appear to have a negative inotropic effect (Walsh *et al.* 1981), while others are reported to have a positive effect. There is also some evidence that the effect on myocardial contraction may be dose-related (Nakaya *et al.* 1983).

The reason for the collapse of our two infants must remain speculative. It is possible that a negative inotropic effect, together with peripheral vasodilatation, caused sudden failure of peripheral blood-flow. Infants suffering from severe birth asphyxia may have compromised myocardial function (Cabal *et al.* 1980), and this may be an additional factor in the acute failure of cardiac output in the presence of drug–induced vasodilatation. Unfortunately we were unable to measure cardiac output during this study and clarification must await further studies. It is not clear whether this is an idiosyncratic reaction to nicardipine or a risk in the use of all such agents, but we must caution against the further use of calcium-channel blockers in severely asphyxiated newborn infants.

The selection of the infants for this study might be criticised. We decided to study infants with the most severe form of post-asphyxial encephalopathy, for whom death or severe disability was a high probability (Levene *et al.* 1986). We felt that for this group we could justify the use of a drug, the actions of which in the newborn period have not been evaluated. We further required that the babies had abnormal Doppler findings also suggestive of a very high risk of adverse outcome (Archer *et al.* 1986). It was unlikely that any drug would have a dramatically beneficial effect on these infants, and we anticipated that a calcium-channel blocker might cause some degree of hypotension. These facts were explained to the babies' parents and their informed consent was obtained to observe the effects of nicardipine on the circulation of their infants. Although all four infants later died, we are quite certain that the cause of death was related to the pre-existing asphyxia and not to the drug.

Hypotension appears to be common in reports of calcium-channel blockers being evaluated for their rôle in neuroprotection (Takenaka and Handa 1979, Harper *et al.* 1981, Harris *et al.* 1982, Hossmann *et al.* 1983, Haws and Heistad 1983, Smith *et al.* 1983, McCalden *et al.* 1984, Mohamed *et al.* 1984, Forsman *et al.* 1986, Sakabe *et al.* 1986). In the newborn animal, the plateau over which autoregulation of cerebral blood-flow normally occurs is probably narrow and shifted to the left compared with more mature animals (Hernandez *et al.* 1980). For this reason, any drug that causes a significant lowering of blood pressure in the newborn may also cause a reduction in cerebral blood-flow. Although it is not yet proven, it is very likely that human infants who have been severely asphyxiated fail to autoregulate their cerebral blood-flow. If this is the case, any reduction in systemic arterial pressure will cause further cerebral hypoperfusion. In the two infants in this study who developed severe hypotension during the course of nicardipine infusion, measurement of CBFV before, during and after administration of the drug showed that CBFV fell as MAP fell, and as blood pressure rose again so did

the velocity in the anterior cerebral artery.

Although this is not proof, it does support the suggestion that cerebral blood-flow in these infants was pressure-passive. The combination of absent cerebral autoregulation and induced hypotension may be critically important in exacerbating cerebral injury in patients with pre-existing compromise and possibly impaired cerebral perfusion. For this reason we believe that the further use of calcium-channel blocking agents for asphyxiated human newborns must be undertaken only with great caution.

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SUMMARY
A continuous infusion of nicardipine was given to four severely asphyxiated fullterm infants who were at high risk for adverse outcome and had abnormal cerebral Doppler haemodynamic studies. The heart rate increased in all four infants and mean arterial blood pressure (MAP) fell in three. Two infants had a sudden and marked fall in MAP, together with severe impairment of skin blood-flow and a concurrent fall in cerebral blood-flow velocity. The serum level of nicardipine was <40ng/mL in all cases. The use of nicardipine, and possibly other calcium-channel blockers, may be associated with marked hypotension, and if there is no cerebral autoregulation, may cause further cerebral hypoperfusion, so use of these drugs in asphyxiated newborn infants should only be attempted if blood pressure is carefully monitored.

RÉSUMÉ
La nicardipine chez les nouveaux-nés présentant une asphyxie sévère
Une perfusion continue de nicardipine a été administrée chez quatre nouveaux-nés à terme avec asphyxie sévère qui présentaient un risque élevé de devenir pathologique et avaient présenté des résultats anormaux aux études hémodynamiques cérébrales avec doppler. Le rythme cardiaque s'accrût chez les quatres nouveaux-nés et la pression artérielle moyenne (MAP) diminua dans trois cas. Deux nourrissons avaient présenté une chute soudaine et marquée de la MAP, ainsi qu'une altération grave de la circulation sanguine cutanée et une chute simultanée de la vitesse de circulation sanguine cérébrale. Le taux sérique de nicardipine était <40ng/mL dans tous les cas. L'utilisation de nicardipine et éventuellement d'autres bloqueurs des canaux calciques peut être associée avec une hypotension marquée et s'il n'y a pas d'auto-régulation cérébrale, cela peut créer une hypo-perfusion ultérieure; aussi l'utilisation de ces médications ne doit être tentée que si la pression sanguine est soigneusement contrôlée.

ZUSAMMENFASSUNG
Nicardipin bei Kindern mit schwerer Asphyxie
Vier reife Kinder mit schwerer Asphyxie, die hinsichtlich ihrer Entwicklung hochgradig gefährdet waren und die abnorme cerebrale hämodynamische Doppler-Untersuchungen aufwiesen, bekamen Nicardipin-Infusionen. Die Herzfrequenz stieg bei allen vier Patienten an und der mittlere arterielle Druck (MAP) fiel bei drei Patienten ab. Zwei Kinder hatten einen plötzlichen, starken Abfall des MAP, einhergehend mit schweren Hautdurchblutungsstörungen und einem Abfall der cerebralen Strömungsgeschwindigkeit. Der Serumspiegel des Nicardipin betrug in allen Fällen 40ng/mL. Die Anwendung von Nicardipin, und vielleicht auch anderer Kalziumantagonisten, kann eine schwere Hypotonie zur Folge haben, und wenn keine cerebrale Autoregulation eintritt, resultiert daraus eine verstärkte cerebrale Mangeldurchblutung. Die Gabe dieser Medikamente sollte bei Neugeborenen mit Asphyxie daher nur erwogen werden, wenn der Blutdruck sorgfältig überprüft werden kann.

RESUMEN
Nicardipina en recién nacidos con asfixia grave
Un gota a gota continuo de Nicardipina se administró a cuatro recién nacidos a término con una asfixia grave, que tenian un alto riesgo de un curso adverso y que tenian unos estudios hemodinámicos cerebrales con Doppler anormales. La frecuencia cardiaca aumentó en los cuatro niños y la presión arterial media (PAM) descendió en tres. Dos niños tuvieron una súbita y marcada caída de la PAM, junto con una alteración grave del flujo sanguíneo cutáneo y una caída concurrente en la velocidad del flujo sanguíneo cerebral. El nivel sérico de Nicardipina fue de menos de 40ng/mL en todos los casos. El uso de Nicardipina y posiblemente de otros bloqueantes del calcio puede ir asociado con una hipotensión marcada. Si no hay una autoregulacion cerebral ello puede causar una hipoperfusión cerebral. Por ello el uso de tales fármacos en lactantes recién nacidos con asfixia sólo deberia ensayarse si la presiòn sanguínea es cuidadosamente vigilada.

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