A Study of Periventricular Leucomalacia and Intraventricular Haemorrhage in the Preterm Neonate

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To

Robert and Eleanor

"Whenever God Prepares Evil For A Man, He First Damages His Mind."

Anonymous scholiast on Sophocles' "*Antigone*", 440 B.C.

Abstract

A STUDY OF PERIVENTRICULAR LEUCOMALACIA AND INTRAVENTRICULAR HAEMORRHAGE IN THE PRETERM NEONATE

J. Q. Trounce

In a prospective ultrasound study of 200 very low birthweight infants periventricular leucomalacia (PVL) was identified in 27 babies, 19 of whom developed cysts and eight at the echodense phase. Periventricular echodensity of more than two weeks duration but without cystic degeneration (prolonged flare) was found in a further 25 babies. Intraventricular haemorrhage (IVH) was detected in 107 babies. Only eight of these babies had parenchymal "extension" and of these five had associated abnormality of the contralateral hemisphere (four PVL, one prolonged flare). Twenty-one of the babies with smaller haemorrhages also developed PVL and a further ten had an associated prolonged flare. Sixty-nine infants (34.5% of the total) had no ultrasound abnormality.

Autopsy was performed on 30 of the 42 babies who died (60 hemispheres). The accuracy of ultrasound diagnosis for periventricular haemorrhage was 88% with sensitivity of 91% and specificity 85%. The corresponding figures for PVL were 88%, 81% and 92% respectively. Three hemispheres which had shown prolonged flare on ultrasound were macroscopically normal but on microscopy showed extensive spongiosis and microcalcification of the periventricular white matter.

Periventricular haemorrhage showed a sharp decline in frequency after 30 weeks of gestation; there was no such clear-cut relationship to birthweight. Other significant risk factors for haemorrhage were vaginal delivery, acidosis, hypercapnia, positive pressure ventilation, coagulation disorder, arrythmia, number of blood transfusions, tolazoline therapy, treatment with alkali, surgery and systolic blood pressure above 55 mmHg. A reduced risk with poor intrauterine growth and anaemia probably reflect a relatively greater gestation and a healthier infant respectively. Significant for PVL were a lower gestation, acidosis, hypercapnia, positive pressure ventilation, pneumothorax, coagulation disorder, hyperbilirubinaemia, number of blood transfusions and surgery; again anaemia showed a reduced risk. Pneumothorax, hyperbilirubinaemia and negative correlation with anaemia strongly predicted both PVL (cystic and echodense) and prolonged flare adding further evidence that the latter appearance is part of the PVL spectrum albeit at the milder end.

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It goes without saying that this study was dependent upon the agreement and cooperation of all the parents (and babies). Nobody refused to be included and they all showed great willing and interest at a time when they were under considerable stress. To them all I am deeply indebted.

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Contents

Chapter 1

Introduction

Rapid advances in both obstetric and neonatal care have led to a progressive fall in the perinatal mortality rate to 8.0 per thousand for England and Wales in 1991. Nevertheless morbidity has not shown a parallel decline and a significant proportion of the survivors are left with variable degrees of handicap. Although sequelae may affect various organs, to the parents it is "brain damage" which remains the major and understandable cause for concern. Two groups of infants are particularly vulnerable to suffering neurological sequelae - the severely asphyxiated term infant and the preterm neonate (especially if compromised in any way before, at or after birth). It is to the latter group that I turn my attention and some idea of the extent of the problem is given by an article by Levene and Dubowitz (1982). They reviewed the outcome of a total of 1249 infants of birthweight 1500 grams or less collected from ten different centres and published between 1976 and 1982. They found that 229 of the babies suffered significant neurological handicap, an overall incidence of 18%. Developmental delay (developmental quotient <80) was found in 14.6% and cerebral palsy in 10.6%.

With regard to the preterm infant the advent of cranial ultrasound offered a non-invasive and safe way to sequentially study the brain and any associated complicatons. The commonest pattern of insult, intraventricular haemorrhage (IVH), had been recognised by the pathologists for over one hundred years and had subsequently been identified on computerised tomography (CT) scanning. Not surprisingly this was the first lesion that the ultrasonographers latched onto. Improvements in the quality of the equipment and hence the definition of the scans allowed even the smallest haemorrhage to be identified. Studies ensued to examine the frequency,

predisposing factors and sequelae to IVH. It was during the course of this work that the sonographers recognised a pattern of discrete echo-free lesions in a periventricular distribution. This correlated with another well-recognised pathological entity, cystic periventricular leucomalacia (PVL).

The early reports concerning PVL consisted largely of small numbers of case reports. These showed the condition to be much more frequent in premature babies and suggested a high incidence of subsequent handicap. However, a lot of unanswered questions remained such as the overall incidence of the lesion and the ability of ultrasound scanning to identify it. Clearly a prospective study of a large number of preterm infants was needed to clarify these issues. The purpose of the study which commenced in November 1983 and which is to form the major part of this thesis, was to answer the following questions:

a) what is the incidence of periventricular leucomalacia in the very low birthweight infant?

b) is there any association between periventricular haemorrhage (PVH), and especially those with parenchymal extension, and periventricular leucomalacia?

c) in babies who die, how accurate is the scan diagnosis in relation to the autopsy findings? If ultrasound imaging is to be effective in predicting prognosis then clearly an accurate differentation of the pathological entities must be possible on scanning.

d) which clinical events show statistical significance as risk factors for subsequent development of periventricular leucomalacia?

e) how do ultrasound scan abnormalities correlate with subsequent problems of neurodevelopment including vision and hearing? The neurological outcome of the infants will be briefly discussed but was never intended as a major part of the thesis.

As the pathogenesis of PVL and PVH are closely linked, it is impossible to treat these two lesions as unrelated (and, indeed, they are often both present in the same brain). The thesis will, therefore, discuss the various aspects of both patterns of insult.

Chapter 2

A Historical Review Of The Pathology And Diagnostic Imaging Of Periventricular Leucomalacia

i)Pathology of PVL.

The Work of Virchow.

More than a century has passed since an interest was first shown in the condition which we now call periventricular leucomalacia. In 1867 Virchow, the father of neuropathology, described a distinct pattern of abnormality affecting the brain in a "considerable number of babies dying before birth and a not inconsiderable proportion dying soon after birth" (Virchow 1867). Although he noted softening of the brain in the affected areas the specific changes were only occasionally seen with the naked eye as yellowish flecks but were readily recognised on microscopy albeit using comparitively unrefined equipment. The striking abnormality was a swelling of the neuroglial cells and their filling with black granules, which Virchow recognised as fat, to the point when eventually all normal appearances were lost in the affected area and all that remained was a mass of fat granules. Virchow observed the changes far more often in the white matter than the grey matter and both the cerebral hemispheres and the spinal cord were affected. The swelling of the neuroglial cells resembled the changes of acute inflammation and in addition there was often hyperaemia of the affected area. Indeed he termed the condition "Congenitale Encephalitis und Myelitis". Because he first identified the abnormality during a smallpox epidemic in Berlin in the 1850's he attributed the changes to the infant being born to an infected mother (although the child showed no cutaneous manifestations). He had previously observed fatty change in the neuroglial cells in congenital syphilis and thus he added this as a possible aetiological factor and also

acknowledged that there might be other causes e.g. maternal eclampsia or infants dying postnatally of severe diarrhoea. The final point that Virchow made was that the condition was unlikely to be universally fatal and might well account for some cases of childhood idiocy and paralysis. A year later he added that, although the fatty change was the most important finding, he had recognised an associated abnormality within the softened area of brain (Virchow 1868). This was the appearance of spindle-shaped bodies consisting of altered axon cylinders containing myelin-enclosed strands.

Are The Changes Pathological?

Controversy ensued with other workers as to the cause of the fatty change. Jastrowitz suggested that it was a physiological process, a feature of normal myelination (Jastrowitz 1872). Hayem found the abnormality to a varying degree in every neonatal brain he examined (a point disputed by Virchow in the above-mentioned paper) and he proposed nutritional deficiency rather than inflammation as the cause (Hayem 1868). As we shall see more than fifty years was to pass before Rydberg resolved this issue (see *The Work of Rydberg*).

The Work of Parrot.

In 1868 Parrot also demonstrated fatty deposition within the neuroglia of the brain and spinal cord (Parrot 1868). Usually this was a purely histological finding but occasionally accumulations formed hard white plaques. The changes were maximal in the corpus callosum becoming scantier as one moved away from this structure and the cortex was unaffected. Similar fatty changes were found in the lung, liver, kidneys and heart. He too considered a lack of adequate nutrition to be the underlying cause and provided experimental evidence as additional support - young animals deprived of sufficient nutrition showed identical changes. Five years later Parrot expanded on his findings (Parrot 1873). The fatty change, even if found in older infants, took its origin from the perinatal period and he clearly pointed out that antenatal events might play a role. In this paper he observed that the changes may be widespread and even reach the surface of the brain. He distinguished the steatosis or "white softening" due to fatty change from the "red softening" of haemorrhage and infarction (although he recognised that the two may coexist in the same brain). Parrot reported two important associated findings within the CNS at autopsy -

firstly, a secondary atrophy of the nervous tissue below the site of fatty change e.g. within the medulla and secondly the presence of ventricular enlargement. Clinical hydrocephalus was apparent in one case but in the others he was uncertain whether it related to an accumulation of CSF or to a loss of cerebral tissue i.e. atrophy or "anencephalic hydrocephalus" as Cruvheilier called it (Cruveilhier in Parrot 1873) [a debate which has been rekindled with the advent of ultrasound more than 100 years later]. Although Parrot again claimed that nutritional deficiency was the primary problem he added that it may cause damage through an effect on the vascular supply to the brain i.e. arterial insufficiency or venous congestion may occur as a sequel and it is in fact this which then induces the fatty change and softening. He pointed out that the preterm infant is especially vulnerable.

The Work of Rydberg.

Interest in this condition then appeared to wane until Rydberg reported a series of 75 neonatal autopsies and observed focal necrotic changes in the white matter in eight cases, six of whom had associated haemorrhage either intraventricular or meningeal (Rydberg 1932). He also used the term softening to describe the changes within the brain substance and noted that "malacic disintegration" might occur without bleeding. He found the changes to be "rather frequent" in premature foetuses. Rydberg proposed that the intracerebral changes were the sequel to mechanical factors, especially head compression during labour, and that this might act in one of two ways:

1) the rise in intracranial pressure during a contraction leads to a rise in blood pressure (Cushing effect) and then following the contraction when the intracranial pressure returns to normal the increase in venous pressure causes a haemorrhage;

2) an insufficient rise in blood pressure consequent upon the raised intracranial pressure could lead to areas of hypoperfusion and localised ischaemia into which secondary haemorrhage might occur as a sequel.

Rydberg also clarified the situation concerning the fat deposition and both schools of thought might claim victory. Fat is indeed seen physiologically from about 28 weeks of gestation until 8 months postnatal age i.e. the time of maximal myelination and especially in the white matter and corpus callosum. In this case the fat is extracellular i.e. outside the glial cells and

the brain tissue is otherwise normal. On the contrary, fat within the glial cells, a situation associated with decomposition and degeneration of brain tissue, is always pathological.

Schwartz's "Lower Pressure Principle".

Schwartz too felt that mechanical factors were important in the aetiology of the areas of cerebral "softening" as he called them (Schwartz 1956). He proposed a different mechanism - following rupture of the membranes the atmosphere provides a strong negative pressure, a suction effect which may be important for the normal birth process. However, when the head lies in the cervix exposed to the lower pressure a uterine contraction imparts a much higher pressure to the foetal body and as a result blood passes to the head causing venous engorgement (sinuses, vein of Galen) with secondary bleeding from the terminal vein and malacic changes within the periventricular white matter. Indeed Schwartz recognised abnormalities of the periventricular white matter in nearly every infant dying between the ages of one and thirty days (Schwartz 1958). This gradient of pressure differences was termed "the lower pressure principle".

Banker and Larroche - "The Border Zone Theory".

Arguably the most important paper on periventricular leucomalacia (PVL), as the authors named the condition, was published in 1962 by Banker and Larroche. They reported on 51 infants who were aged 6 hours to 13 months at the time of death and all of whom showed the changes of PVL at autopsy. By closely examining the brains of all infants dying under one month of age throughout the year of 1959 they were able to define an incidence of this abnormality at post-mortem and this was 18.8%. They described the macroscopic appearances including their characteristic sites and the sequence of histological changes timed as accurately as possible after a predisposing insult. They recognised an association with intraventricular haemorrhage (originating from the terminal vein) in five infants. They reviewed the clinical data in an attempt to identify risk factors and the most important were prematurity and respiratory problems. All the infants suffered at least one severe but non-terminal anoxic insult (usually severe apnoea or cardiac arrest) and all showed associated lung pathology especially aspiration or "pneumonitis", which is likely to represent the condition which we now term hyaline membrane disease.

Finally, they proposed the "border zone" theory i.e. the lesions occur due to hypoperfusion of the border zones between the territories of the anterior, middle and posterior cerebral arteries.

More Recent Pathological Contributions.

Several reports were published in the ensuing years quoting an incidence for the condition varying between 7% (Armstrong and Norman 1974) and 34% (Pape et al. 1976); the differences were partly a reflection of variations in the populations studied. Further attempts were made to identify clinical risk factors in much the same way as Banker and Larroche had done. Finally, it was the pathologists who first questioned the aetiology of parenchymal haemorrhage which remains a contentious and unresolved issue. In 1974 Armstrong and Norman studied 28 cases of periventricular leucomalacia at autopsy and demonstrated rebleeding into 7 of them. The controversy as to whether it represents extension of an intraventricular haemorrhage or rebleeding into an area of infarction will be further discussed in Chapter 6.

ii)Cerebral Circulation.

The Germinal Matrix.

The vascular bed of the germinal matrix is the most important region of the fetal cerebral circulation. The germinal matrix is the "factory" of the fetal and preterm brain from whence are produced the glial cells before they migrate to their functional site. The area receives a rich blood supply in accordance with this important function. The germinal matrix starts to form at about 10 weeks of gestation and may be seen from about 22 weeks. The arterial supply is derived from Heubner's artery (a branch of the anterior cerebral artery) and from branches of the lateral striate arteries and anterior choroidal artery (which are branches of the middle cerebral artery). The venous drainage is to the terminal vein (Hambleton and Wigglesworth 1976). The veins within this region are extremely thin walled (Gruenwald 1951) and histologically it is difficult to differentiate whether the small vessels are arterial, capillary or venous (Coen et al. 1970). Pape and Wigglesworth (1979) have shown an extensive capillary bed directly beneath the ependyma over the whole caudate region. The fine capillaries are interspersed with larger and more irregular vessels which are difficult to classify histologically into arteriole, capillary or venule.

Injected specimens using barium-gelatin sometimes show a very short channel between an arterial branch and one from the terminal vein. The vascular bed of the germinal matrix is the source of origin of more than 80% of intraventricular haemorrhages. The germinal matrix and its associated capillary bed involutes from about 32 weeks of gestation onwards and is usually no longer present at full term. Occasionally, however, germinal matrix haemorrhage can occur in such a mature infant.

The Major Cerebral Arteries and Their Branches.

The anterior, middle and posterior cerebral arteries appear at about 4 months of gestation. Subsequently they give two important types of branch arteries. These are the cortical branches which supply the cerebral cortex and the medullary branches which pass through the cortex, supply the subcortical white matter and end in the walls of the lateral ventricles. Using injection techniques with colloidal barium sulphate and radiography, de Reuck was able to delineate the precise vascular anatomy (de Reuck 1971). He showed that there were three patterns in which these arteries terminated in the periventricular region and two of these resulted in "watershed" areas between ventriculopetal branches passing towards the ventricle and ventriculofugal branches going in the opposite direction (Diagram - see "Diagram And Photographic Plates Of Scans And Pathological Specimens").

The Role of Arterial Watershed Areas in the Aetiology of PVL.

A year later de Reuck proposed that these areas were the sites vulnerable to PVL and hence the typical finding that the cysts were 3-10 mm. from the ventricular wall i.e. within the arterial end zones (de Reuck 1972). He pointed out that the cortex was spared at this gestation for two reasons. Firstly, there are numerous leptomeningeal anastamoses between the branches of the anterior, middle and posterior cerebral arteries. Secondly, the relatively higher metabolic rate of the white matter in the newborn makes this region more vulnerable to ischaemic insults. From 8 months of gestation onwards there is considerable development of the ventriculofugal branches of the lateral striate arteries resulting in an increasing protection of the periventricular area from ischaemic insults. Although PVL can occur in the term infant, subcortical cysts are more commonly seen and this lesion may also occur rarely in the preterm (Trounce and Levene 1985).

Takashima and Tanaka (1978) used barium sulphate suspension and benzidine stain to outline the cerebral vasculature at autopsy and the brain was then fixed for later examination. They showed that no vessels could be identified in the softened areas of PVL and concluded that the lesions were ischaemic in origin. Normally with advancing gestation the medullary arteries show a pattern of increasing branches but the arteries of the PVL patients appeared immature with either very short branches or none at all. Indeed they identified one group of premature infants who developed PVL despite having no neonatal complications but in whom the ventriculofugal arteries were very poorly developed and they proposed this as the major underlying aetiological basis.

Autoregulation of Cerebral Blood Flow.

Autoregulation refers to the capacity to maintain a constant cerebral blood flow in the face of an alteration in the arterial blood pressure over a physiological range. This myogenic mechanism is thought to be controlled by the autonomic nerve supply of the vessels. This is a normal function of the healthy term infant but may be lacking in the preterm and especially so if compromised by asphyxia or respiratory distress. Milligan studied five ventilated infants of between 25 and 31 weeks gestation (Milligan 1980). He measured the arterial blood pressure directly and the cerebral blood flow by jugular venous occlusion plethysmography. Following the administration of blood (transfusion in four, exchange transfusion in one) they all showed a rise in blood pressure, a corresponding rise in cerebral blood flow and four of them developed a fatal intraventricular haemorrhage within the next 12 hours. Milligan postulated that this change of blood flow was a very important factor in causing the haemorrhage and also speculated that the opposite effect might occur and induce ischaemic damage.

Does Loss of Autoregulation Predispose to PVL?

Lou studied 19 infants of whom 14 had a birthweight of < 2.5 kg. (Lou 1979a). He measured their cerebral blood flow using Xenon 133 and also monitored their blood pressure. He showed that in the normotensive neonate the cerebral blood flow (CBF) is about 40 mls./100 gm. of brain tissue/min. which is rather lower than the normal adult value (64 mls./100 gm./min.). More importantly a fall in systolic blood pressure below 45mmHg. resulted in a proportional decrease in CBF to < 20 mls./100

gm./min. The CBF appeared entirely dependent on the blood pressure i.e. it was a pressure passive system with loss of the normal autoregulation which is seen in the healthy term infant. Lou postulated that this effect of hypotension on CBF explained the predilection for ischaemia in the "watershed" regions and suggested that hypoxaemia will exacerbate the problem. PVL was subsequently demonstrated in four infants (3 at autopsy and one on CT scanning) and all 4 had been shown to have a CBF of 20 mls./100 gm./min. or less (Lou 1979b).

Is Venous Infarction Important?

Clearly arterial insufficiency particularly as a sequel to hypotension appears to be one important basis for the development of PVL. More recently venous infarction secondary to obstruction of the terminal vein by a large intraventricular haemorrhage has been reported and this may also be important in the pathogenesis (see Chapters 5 and 6).

iii)Imaging of PVL Lesions.

Early Ultrasound Work.

The first attempt to use ultrasound as a means of imaging was by Dussik who, in 1942, tried to visualise the cerebral ventricles in adults (Dussik 1942). The echoes from the skull, however, prevented this. Thirteen years later Leksell, using the A-mode technique, reported the demonstration of midline shift in a child with a large frontal haematoma (Leksell 1955). In a perinatal context the earliest use of ultrasound was for recognition of pregnancy and its complications (multiple fetuses, hydramnios) and early measurements of the biparietal diameter (Donald 1958). With B-mode scanning a two-dimensional image was formed on the screen and Garrett et al. were amongst the first to take advantage of this and they reported the diagnosis of hydrocephalus in infants in 1975 (Garrett et al. 1975).

First Report of Ultrasound to Examine the Preterm Brain.

A team of workers at University College Hospital, London were the first to report the potential value of ultrasound imaging in demonstrating intracranial complications of the preterm infant which had previously been so well demonstrated at autopsy (Pape et al. 1979). They identified germinal matrix or intraventricular haemorrhage in five of the 31 preterm

infants of 32 weeks gestation or below whom they examined. They used ultrasound measurements as a guide to lumbar puncture therapy in one infant with post-haemorrhagic ventricular dilatation. Perhaps of most interest in the context of this thesis was an infant of 31 weeks gestation who suffered a pneumothorax and cardiac arrest on the second day of life. Aged 34 days an irregularity of the periventricular area was seen on the scan and subsequently ventricular enlargement which was diagnosed as cerebral atrophy. Pape and her colleagues attributed the changes to periventricular infarction but as the child survived they were unable to confirm or refute this suggestion.

Ultrasound Imaging of Intraventricular Haemorrhage.

The early 1980s saw a deluge of papers dealing with all aspects of intraventricular haemorrhage - the ultrasound diagnosis, incidence, clinical risk factors and the neurodevelopmental outcome. To the surprise of many workers this turned out to be a relatively common complication of the premature infant. However, with some relief it was shown that most of the infants suffered no sequelae and it later became apparent that periventricular leucomalacia was much more worrying in terms of prognosis.

Ultrasound Imaging of Periventricular Leucomalacia.

Hill et al. (1982) were the first to report correlation between scan findings and haemorrhagic PVL at autopsy in a single case report of a 33 week gestation infant who suffered mild hyaline membrane disease, necrotising enterocolitis and thrombocytopaenia. The echogenic areas seen bilaterally in the periventricular white matter corresponded exactly to areas of haemorrhagic infarction, the histology of which showed lipid-laden macrophages and reactive astrocytes. A year later Levene and colleagues reported the ultrasound appearances of the evolution of the haemorrhagic infarction into cystic cavities (Levene et al. 1983a) and then in 1984 Nwaesei and her coworkers showed that gliosis without haemorrhage could produce a similar echodense appearance on an ultrasound scan (Nwaesei et al. 1984). Three early reports of the incidence of PVL diagnosed by ultrasound scanning give figures varying between 5 and 16.8% of preterm infants (Bozynski 1985; Levene 1983a; Fawer 1985a) although each of these studies has had a major drawback being either retrospective or including comparatively few babies. Three studies reported predisposing

risk factors to PVL (Sinha 1985; Weindling 1985a; Calvert 1987) and these will be discussed in more detail in Chapter 7.

The Role of Computerised Tomography.

I have concentrated exclusively on the development of ultrasound imaging for two reasons. Firstly, this was the technique which I used and secondly because it is generally accepted as the current method of choice for examining the neonatal brain and for PVL in particular. Computerised tomography (CT) will accurately detect the presence of intracranial haemorrhage (Krishnamoorthy 1977; Papile 1978). CT, however, has proved disappointing in its ability to diagnose hypoxic-ischaemic lesions in the premature neonate (Estrada et al. 1980; Flodmark et al. 1980) and compares poorly with real-time ultrasound. Estrada and colleagues (1980) studied 63 neonates and concluded that low attenuation in the periventricular region on the CT scan is not a marker of hypoxic-ischaemic insult as in the term infant but is a normal finding probably related to immaturity of myelination. Flodmark and coworkers performed a CT/autopsy correlation study in 90 infants of whom 60 were 1500 grams birthweight or less (Flodmark et al. 1980). Hypodense areas on the scan were universal in the preterm infants - a normal finding, they concluded, and related to the increased water content of the brain and immature myelination. Chow compared ultrasound with CT scanning in five preterm babies and one term infant (Chow 1985). He showed that echodensity on the ultrasound scan could correspond to either haemorrhagic areas or those of hypodensity on CT, confirming the difficulty in differentiating haemorrhagic from non-haemorrhagic infarction on ultrasound. He also noted the insensitivity of CT scans for demonstrating cysts which were readily seen on ultrasound and Chow proposed serial ultrasound as the diagnostic tool of choice. Slovis and Shankaran also noted the inability of CT to demonstrate cysts (Slovis and Shankaran 1984) and Martin and colleagues failed to identify cysts on the CT scan of an infant in whom they had previously diagnosed definite cystic changes on ultrasound scanning (Martin et al. 1983).

The Role of Nuclear Magnetic Resonance.

The newest of the imaging techniques nuclear magnetic resonance (NMR) has been used to show abnormal myelination patterns in children who had been shown to have PVL in the neonatal period (Dubowitz et al.

1985). Wilson and Steiner have extended this work and studied 12 infants who were shown to have PVL on ultrasound (Wilson and Steiner 1986). NMR was performed at various ages between 4 weeks and 26 months and they observed the following changes:

a) focal areas of decreased signal intensity within the white matter which were thought to represent cysts;

b) dilatation of the lateral ventricles;

c) a degree of brain atrophy;

d) delayed myelination.

They observed that extensive cystic change or delay in myelination correlated with an adverse neurodevelopmental outcome. Ultrasound cannot detect the delay in myelination and NMR may be of value for selected cases or in future studies to look more specifically for this abnormality.

Chapter 3

The Neurodevelopmental Outcome

At first sight it may seem a little strange to look at the neurodevelopmental outcome before all other aspects of the condition. However, I feel that a review of its sequelae emphasises the importance of periventricular leucomalacia as a pattern of neonatal cerebral insult. Indeed it was the early evidence that it might cause significant handicap which prompted the study that will form the major part of this thesis. As intraventricular haemorrhage and periventricular leucomalacia are so closely related, I shall briefly cover haemorrhage in the first instance.

Neurodevelopmental Sequelae to Intraventricular Haemorrhage.

When cranial ultrasound was introduced into neonatology the initial findings surprised and, perhaps, even worried the clinicians a little - intracranial haemorrhage was a common finding in preterm infants and surely, therefore, this might be associated with a high handicap rate. Fortunately, follow up studies have not borne out this anxiety and most babies, especially those with smaller grades of haemorrhage, have a normal developmental outcome.

Shankaran and colleagues (1982) scanned 242 infants of whom 114 were of birthweight less than 1500gm. All five with mild haemorrhage (i.e. without ventricular distension) were normal at follow up. Nine of the 17 with moderate haemorrhage (ventricular distension) showed subsequent neurological abnormality but in three infants this amounted to no more than a mild increase in lower limb tone. The worst outcome was in the seven survivors with parenchymal extension of whom five developed cerebral

palsy. Shankaran states that degree of haemorrhage was the most important factor in the outcome although it is of note that all seven infants with parenchymal extension underwent ventricular shunting.

Stewart and coworkers (1983) reported on 109 surviving preterm infants who had a Griffiths assessment at a corrected age of 18 months. The 25 babies with uncomplicated periventricular haemorrhage (PVH), i.e. no ventricular distension nor atrophy suffered the same frequency of abnormalities (8%) at follow up as the 62 babies with normal scans. Two factors appeared particularly important in prognosis - all 9 babies with evidence of atrophy on the scan suffered handicap (major in 6) and all four babies with grade 4 haemorrhage developed major handicap. Although not identified on the scans, Stewart postulated that PVL might account for the handicap in some infants. Her final statement is that "...cerebral ischaemia and infarction were almost certainly responsible for more developmental sequelae at follow up than PVH."

Papile et al. (1983) followed up 198 infants of birthweight 1500 grams or less and also found an identical incidence of handicap (10%) in those with grade 1 and 2 haemorrhages to the babies with normal scans. This rose to 36% in those with grade 3 haemorrhage (i.e. intraventricular with distension) and 76% with grade 4 (i.e. intraventricular with parenchymal extension). Post haemorrhagic ventricular dilatation did not increase the risk of major handicap - 57% in this group compared to 59% of infants with a similar grade of haemorrhage but without dilatation.

Palmer and colleagues (1982), however, suggested that ventricular dilatation was important in prognosis. Comparing 14 babies with IVH alone with 11 infants with IVH plus ventricular dilatation they reported that the latter group had a significantly worse outcome. Although they suggested that the size of the haemorrhage was less important than the presence of ventricular dilatation it is of note that the group with dilatation had significantly worse bleeds. Twelve of the 14 with IVH alone had grade 1 haemorrhage compared to one of the 11 with associated dilatation and there were 2 with parenchymal involvement in the former group but five in the latter. Indeed, in a separate paper this same Hammersmith group reported that all 6 babies with parenchymal involvement on the ultrasound

scan were abnormal when assessed at one year of age (Dubowitz et al. 1984).

The overall conclusion is that small and uncomplicated bleeds, which of course will account for the majority, carry an excellent neurodevelopmental prognosis. Those with larger bleeds and particularly those with "intraparenchymal extension" are less fortunate. I have already discussed the continuing controversy concerning the aetiology of parenchymal haemorrhage (see also Chapters 5 and 6) but perhaps this was the first evidence that there was an alternative and more ominous pattern of ultrasound abnormality which involved the cerebral parenchyma - i.e. periventricular leucomalacia.

Note: In this section I have used the original authors' nomenclature of either PVH or IVH. The former term was introduced to cover the whole spectrum from isolated germinal matrix haemorrhage through intraventricular rupture and finally to parenchymal extension. However, in the context of these reports the differentiation of the terms is more a matter of semantics than any important ultrasonographic features.

Neurodevelopmental Sequelae to Periventricular Leucomalacia.

Several studies have now reported on the outcome of children with this condition and without exception they indicate that it carries a bad prognosis. I shall now describe these studies in more detail.

Perhaps the first "word of warning" was a brief letter to the Lancet in the summer of 1983 from Levene and colleagues (Levene et al. 1983b). They described 13 infants with cystic PVL (6 of whom had no evidence of IVH). Eleven survived and of these 8 (73%) showed severe handicap and only two were normal.

Bowerman et al. (1984) the following year reported six survivors of gestations ranging between 28 and 36 weeks who showed ultrasound evidence of PVL and who were neurodevelopmentally assessed between 3 and 24 months of uncorrected age. All had shown parenchymal echodensity on early scans but only three demonstrated cystic change. All showed abnormal tone (spastic diplegia being the commonest pattern and

affecting 4 infants). Four suffered developmental delay, 3 had seizures, 2 had visual impairment and 2 hearing loss.

Also in 1984 McMenamin and coworkers reported on the findings in 460 infants of birthweight <2.25 kg. (McMenamin et al. 1984). One hundred and seventy seven (38%) had IVH of whom 64 had associated parenchymal echodensity. They differentiated large echodensities (33 infants) which led to porencephaly in the 8 long term survivors and may well have represented parenchymal extension. Of the eight, five developed severe sequelae and three moderate handicap when assessed at ages ranging between 7 and 23 months uncorrected. The other 31 infants had "small intraparenchymal echodensities" extending a few millimetres into the white matter and bilateral in half of the cases. Cystic degeneration occurred in 3 survivors and in the other 19 there was complete resolution over a mean of 18 days. Interestingly one infant at postmortem showed astrocytic gliosis similar to the findings we demonstrated in a child with prolonged flare (see Chapter 6). I suspect this group includes a spectrum of the conditions we now recognise as transient flare, prolonged flare and cystic PVL (see Chapter 4). At follow up 14 were normal, 6 had mild defects and 2 moderate handicap but none showed severe sequelae. They make no comment concerning the patterns of handicap and also don't differentiate the three children with cystic change.

Weindling and colleagues (1985b) reported 8 preterm infants with PVL who were assessed between 12 and 18 months of chronlogical age. All showed cerebral palsy (spastic quadriplegia in 5 and diplegia in 3) and all showed varying degrees of neurodevelopmental delay including speech problems. One suffered infantile spasms and 6 showed visual impairment; all had normal hearing.

Bozynski and colleagues from Ann Arbor diagnosed cystic PVL in 5 out of 138 babies of birthweight 1200 grams or less (Bozynski et al. 1985). One subsequently died from cot death at the age of one month and the four survivors were assessed between 8 and 25 months of corrected age. All developed cerebral palsy (3 spastic diplegia and one quadriplegia) and developmental delay.

This group have just reported the outcome in 116 infants of birthweight 1200 grams or less (Bozynski et al. 1988). In this study they looked specifically for features of cerebral palsy when assessing the infants at a corrected age of 12-18 months. Bozynski and colleagues found the sonogram at "term" to be the best predictor of handicap, especially the presence of PVL or ventriculomegaly at that time. Of the 85 whose scans were normal at "term" three developed cerebral palsy compared to nine of the 31 with abnormal scans. They only had three babies with PVL and it is possible that with larger numbers this finding might have proved an accurate predictor of handicap. Their statement that cystic cavities are invariably associated with sequelae is, perhaps, a bit too dogmatic as both we and other groups have seen a normal outcome following cystic degeneration.

Rushton and coworkers in Birmingham studied 216 infants of birthweight less than 2Kg. and an additional 67 larger babies with neurological abnormality (usually convulsions) [Rushton et al. 1985]. They identified PVL in 18 of the 283 babies (17 of low birthweight and one of the larger group). Eight died (3 cystic, 5 echo dense) and they report the outcome in the 10 survivors, all of whom showed cysts. Apart from the two children who escaped handicap, the group do not state the age at which neurodevelopmental assessment was performed. Eight developed cerebral palsy (of whom 5 showed spastic quadriplegia) and 5 suffered developmental delay which was severe in three. One needed a shunt for hydrocephalus. They made the important observation, as Levene had originally done, that two of the 10 were entirely normal at follow up - one at eighteen months and the other at two years.

De Vries and colleagues (1985) contrasted the outcome in 18 babies with severe haemorrhage (parenchymal in 5) with 5 infants who survived after showing cystic PVL. They were between nine and eighteen months of uncorrected age when last reviewed. In the former group 9 were completely normal, 4 showed minor handicap, 3 moderate handicap and only two suffered severe sequelae and both of these had associated ischaemic lesions. Two of the five with parenchymal extension showed no evidence of cerebral palsy at follow up. All five with cystic PVL have cerebral palsy (3 diplegic, 2 quadriplegic), four have convulsions, all have a DQ <65 and four are cortically blind. Three are over two years old and

cannot sit unsupported. Clearly the outlook for cystic PVL appears significantly worse than that for haemorrhage even in its most extensive forms.

In the same year the Hammersmith group gave a detailed account of three children with PVL, two cystic and one with persisting echodensity, who were assessed at 18 months of uncorrected age (Dubowitz et al. 1985). All three showed spastic quadriplegia and severe developmental delay with DQ <60. This makes the important point that even in the absence of cystic degeneration a persistent echodensity (or prolonged flare as we named it) may auger badly for subsequent neurodevelopment.

Fawer and colleagues initially reported their follow up findings in 1985 describing 11 preterm infants with PVL who were assessed at 12 months of corrected age (Fawer et al. 1985b). One child had PVL and parenchymal haemorrhage and showed extreme handicap - spastic quadriplegia, DQ of 15, visual and hearing impairment and a shunt for hydrocephalus. Of the other 10, four showed cerebral palsy, two developmental delay and one visual impairment; five, however, were normal. They noted that small cysts (2-3 mm. diameter) carried a good prognosis whereas multiple and more diffuse cystic change correlated with a higher risk of handicap.

Two years later this group expanded on their findings. They reported on twenty four survivors of 34 weeks gestation or less who all showed ultrasound evidence of PVL (Fawer et al. 1987). The infants were assessed at a corrected age of eighteen months. In twelve there was the characteristic appearance of echodensity giving way to echolucent cysts, seven showed small cysts with no preceding echodensity and five had persistent echodensity (over two weeks) but no cystic change. Thirteen showed frontal PVL and had a good prognosis, all having a DQ >80. Of the six with fronto-parietal changes 3 were normal; the other three and all five with occipital cysts suffered major handicap. Of these eight, 5 developed cerebral palsy (2 spastic quadriplegia, 2 diplegia and one hemiplegia), 6 had DQ <80, 4 showed visual impairment and one suffered convulsions. Two needed shunting for hydrocephalus. They all had normal hearing. They demonstrated, therefore, that occipital cysts carry a particularly grim prognosis and also confirmed their previous finding that

larger cysts are more worrying. As Dubowitz had noted, two infants with echodensity but no cysts developed major handicap - one with spastic diplegia but a DQ of 93 and the other with spastic quadriplegia, DQ of 63 and visual impairment.

Calvert and colleagues (1986) reported the follow up data on fifteen infants with PVL. Assessment was between 5 months and 3 years and three months of corrected age and as five were less than 9 months old (corrected) the interpretation must be a little guarded. Fourteen showed cerebral palsy (7 spastic quadriplegia, 5 spastic diplegia and two hemiplegics). Of the ten who could be assessed eight were considered to show normal intelligence. Three had speech delay which was presumed to be the sequel to impaired oral motor function. One was blind and a further six showed strabismus. All had normal hearing and one of the fifteen appeared entirely normal.

Graziani et al. (1986) reported the neurodevelopmental outcome in 139 infants of 33 weeks gestation or less. The children were followed for periods varying between 12 and 48 months uncorrected age. Fifteen children developed cerebral palsy of which spastic diplegia was the commonest variant. In 10 of these the neonatal ultrasound scans had shown multiple, bilateral periventricular cysts of 3-7mm. diameter, 3 had shown small cysts (<3mm.) and subsequent asymmetrical ventricular enlargement and the other two showed porencephaly secondary to parenchymal extension. Although three babies with large periventricular cysts and some with small cysts did not develop cerebral palsy, Graziani comments that cystic PVL seems to be the best current predictor of cerebral palsy. It is interesting, and perhaps a little surprising in the light of other studies, that there was no significant difference in the mean Bayley mental score for the infants with and without cerebral palsy.

Stewart and coworkers attempted to identify ultrasound abnormalities associated with subsequent handicap in a study of 342 surviving infants of less than 33 weeks gestation (Stewart et al. 1987). The infants were reviewed every three months up to a year and underwent a Griffith's assessment at either 12 or 18 months with allowance made for prematurity. On the early scans i.e. at age one week parenchymal echodensity was the most important - all nine infants with this appearance

suffered handicap and in eight this was of a major degree. Although she states that cysts developed in all cases there is no differentiation between porencephaly and cystic PVL. On the discharge scan the high risk group, which comprised 8% of the children, consisted of hydrocephalus or cerebral atrophy - 94% of these developed handicap and in 61% it was major. The study is weakened on two accounts, the first being its largely retrospective nature. Secondly they do not differentiate PVL as a category in its own right but the cases appear to be distributed amongst the other groups as either dilatation or cerebral atrophy. The grouping of the early appearance of "parenchymal echodensity" as a single category is also no longer satisfactory as it is too non-specific.

Cooke (1987) has recently reported the outcome in 524 survivors of birthweight 1500 grams or less who were followed up for variable periods of between two and five years. In the light of other studies it is perhaps rather surprising that only 6 of the 34 with cystic PVL (17.6%) developed cerebral palsy as opposed to 22 of the 32 (68.8%) with porencephaly. Hemiplegia and quadriplegia were more common as sequelae than diplegia. Forty one per cent of those with cystic PVL and 53% with porencephaly showed subsequent developmental delay and he also comments on an association between parenchymal cysts and both cortical blindness and convulsions. Sixteen of the thirty four with cystic PVL (47%) and seven with porencephaly (21.9%) were normal at follow up. As Cooke points out, throughout this period the quality of equipment was improving - he only had a 7.5 MHz. transducer for the last eighteen months. In addition, and perhaps more importantly, the study is weakened as he had to review and reclassify some of the earlier ultrasound scan findings in the light of further developments in the field during this time.

In conclusion, PVL and especially the cystic variety appears to be the best neonatal ultrasound marker that we currently have for predicting handicap. Cerebral palsy is the most common sequel although there is also an association with developmental delay, cortical blindness, convulsions and ventricular dilatation. More specifically it appears to be larger, multiple and occipital cysts which carry a particularly high rate of handicap.

Chapter 4

Study Outline.
Patients And Methods

i) Patients.

Birthweight rather than gestation was chosen as the criterion for entry into the study as it offers a more clearcut figure. Gestation is less easily determined as values can be derived from the mother's date of her last menstrual period, ultrasound scan in early pregnancy or postnatal gestational assessment and these three figures can sometimes be widely discrepant. I elected to include all babies of 1500 grams birthweight or less. Starting on January 1st 1984 I planned to enrol 200 very low birthweight infants and took advantage of the proximity of two neonatal intensive care units, Leicester Royal Infirmary and Nottingham City Hospital, in order to achieve this number. Over the two year period 1982-84 126 infants of less than 1500 grams were admitted to the former centre and 216 to the latter and it was thus estimated that it would require about fifteen months to collect the 200 babies. It took a month longer than predicted with the final baby being enrolled on April 30th 1985. Babies born at other hospitals and transferred in to either centre were included with the exception of those arriving too late for a scan to be performed within the first three days of life. The only other babies to be excluded were those who died before a scan was performed. Because the information acquired was of clinical importance parental consent was not sought. In most cases, however, the parents were present during at least one scan session and the findings and significance were discussed with them. The study was approved by the ethical committee at both hospitals.

ii) Methods.

1. Ultrasound Scans.

The first two months of the study period (November and December 1983) were spent learning the technique of neonatal cranial ultrasonography including the normal cerebral appearances and identification of the important abnormalities.

In both centres an ATL Mk 300i real-time scanner fitted with a multifrequency (3.5, 5.0 and 7.5 MHz) scanhead was used. The lateral resolution at the focus range is 1.6 mm. with the 5.0 MHz frequency and 1.0 mm. with 7.5 MHz. (manufacturer's specifications). All infants were scanned at least twice per week during the first month of life and then at least once per week until discharge. In selected cases the infants were recalled for at least one further scan after discharge from hospital. The indication for further scans was the presence of an abnormality on the discharge scan which might not have reached its final stage of evolution. The three patterns of lesion thus included were haemorrhages which had not completely resolved at the time of discharge (or transfer back to the referral hospital), parenchymal lesions (echodensity, cysts or haemorrhage) or ventricular dilatation. The scans were performed through the anterior fontanelle in both coronal and parasagittal planes. A permanent record of every scan was made either on videotape or X-ray film and these were available for later review if necessary. I took advantage of Dr. Malcolm Levene's considerable experience of neonatal cranial ultrasonography and discussed with him any scans where interpretation was difficult.

Definition of Scan Abnormalities.

At the start of the study no agreed definitions were available for the ultrasound appearances of PVL. As a preliminary Dr. Levene and I clearly defined the ultrasound abnormalities that had been consistently recognised over the previous three years. These definitions were adhered to throughout the study and final diagnosis was made at discharge or death. The definitions were as follows:

Normal - no ultrasound abnormality detected at any time (Plate 2).

Small haemorrhage - echoes in and around the region of the germinal matrix and corresponding to the grade I haemorrhage of Levene et al. (1985) [Plates 3a and 3b].

Intraventricular haemorrhage - echoes within the lateral ventricles with distension or formation of an intraventricular clot. This corresponds to the grade II lesion of Levene (1985).

Parenchymal haemorrhage - an echodense area involving the ventricle and the parenchyma. The apex of the echoes lies near the midline with the base extending well into the parenchymal substance. There is complete loss of the outline of ventricular structures. In surviving infants a porencephalic cyst would develop with complete loss of the ependyma of the lateral part of the lateral ventricle. We refer to this lesion as representing "parenchymal haemorrhage" (Plates 4 and 5).

The term periventricular haemorrhage (PVH) has been used by some workers to describe haemorrhage arising from the germinal matrix which may have spread into the ventricle. The logic behind this is the failure of ultrasound to accurately identfy liquid blood in the ventricle, i.e. differentiating a ruptured from an unruptured germinal matrix haemorrhage may be impossible. For the purpose of this thesis I retain the differentiation of intraventricular haemorrhage from small haemorrhage dependent on whether intraventricular thrombus is seen.

Periventricular leucomalacia - we recognised three appearances which we believed to represent the spectrum of PVL:

(a) *Cystic* : an echodense triangle with its apex lying at the lateral border of the lateral ventricle. In many infants an intraventricular clot is seen within the ventricle and accompanies this parenchymal appearance. The triangular parenchymal appearance has been recently described by Rushton et al. (1985) and we refer to it as "PVL". In surviving infants the echodensity resolves to discrete echo-free cavities representing cyst formation. The ependyma of the lateral ventricles remains intact in most cases (Plates 6a and 6b, 7a and 7b).

(b) *Precystic* : some infants die in the precystic (echodense) phase and if the ultrasound appearances described above are present at death this is referred to as precystic PVL (Plates 8a and 8b, 9, 10).

(c) *Prolonged flare* : an appearance of relative increased echodensity in the periventricular region seen in both coronal and parasagittal views and persisting for at least two weeks but not undergoing cystic degeneration. Although subjective assessment of echodensity is difficult these lesions were less echogenic than those of parenchymal haemorrhage despite standardised gain and energy output settings (Plates 11a and 11b).

We used the term "transient flare" to describe the appearance of periventricular echodensity which resolved within a fortnight and was not followed by cystic degeneration. We did not consider this appearance represented a significant pathological abnormality and it will not be considered further in this thesis.

Ventricular dilatation - this was divided into:

(a) *Progressive* - ventricular index (VI) rapidly increasing to cross the 97th centile line. The ventricular index is defined as the distance from the midline to the most lateral extent of the lateral ventricle with the measuring calipers in the same horizontal plane at the level of the interventricular foramina (Levene 1981). If the dilatation was asymmetrical then the measurement of the larger ventricle was used except in those with porencephaly. This group usually required treatment with lumbar punctures or a ventricular shunt.

(b) *Persistent but non-progressive* - ventricular index increasing more slowly to cross centile lines above the 97th but then arresting and following a normal rate of growth.

Babies with VI greater than the 97th centile due to distension with echodense haemorrhage, and who subsequently and without any therapeutic manoeuvre return to normal VI measurements are not included in the ventricular dilatation group.

2. Clinical Data.

Extensive clinical data relating to antenatal, perinatal and postnatal events in the first four weeks of life or until the time of death if this occurred sooner were prospectively recorded. Appendix 1 shows the "fixed" data involving maternal and neonatal details - this information was collected on all 200 babies. In addition selected infants had regular blood gas and blood pressure measurements depending on the clinical indication; this I shall call the "continuous data". In one centre (LRI) blood pressure data were measured directly from arterial cannulae or catheters when these were in situ. In infants without arterial access indirect methods were used and only the systolic pressure was recorded. At the commencement of the study blood pressure was not routinely measured in the other centre. Subsequently this was adopted but blood pressure data are incomplete as some infants not requiring intensive care may never have had blood pressure recorded. When available this information was included for

analysis. No measurements nor blood tests were performed solely for the purpose of the study and the only information used was that which was needed clinically for the optimal management of the baby. The fixed data was coded for computerisation along with the scan findings and measurements of blood gases and blood pressure.

3. Autopsy Correlation.

In the babies who died an ultrasound diagnosis was made before autopsy in all cases where parental permission was granted for a post-mortem examination. The brain was removed complete at the time of the post-mortem examination and suspended in 10% formalin for at least one month to allow fixation before sectioning. Coronal cuts were made at 1 cm. intervals and the macroscopic appearances noted. Histological examination of the periventricular area was performed as an integral part of every autopsy in Nottingham (Dr. David Fagan). The lack of paediatric pathological expertise in Leicester at the time of the study meant that a selective policy was needed. Dr. Fagan kindly agreed to undertake histological examination in all cases where ultrasound studies and/or macroscopic pathological examination showed any abnormality of the periventricular area. For the purposes of analysis each hemisphere was considered separately. The number of true positive (TP), true negative (TN), false positive (FP) and false negative (FN) ultrasound diagnoses for each cerebral hemisphere was noted. The accuracy, sensitivity and specificity of ultrasound were measured using the equations shown in Appendix 2.

In order to demonstrate the spectrum of PVL lesions I have included five additional babies who were not in the above study. Three were born at Nottingham City at the same time as the study was underway of whom two (RM, MK) were excluded as there were no in vivo scans and the ultrasound examinations were performed soon after death. The third (NH) had scans during life because of severe respiratory complications but was excluded from the study on birthweight criteria. One infant (AC) was born in Leicester and was also excluded by his birthweight. The final infant (JM) was born at 29 weeks gestation, also in Leicester but shortly before the study commenced. She suffered severe arrythmias in the first twenty four hours of life related to hyperkalaemia. An ultrasound scan at the age of 17 days showed extensive bilateral cystic PVL involving temporal and

occipital regions and this was still present when she was last scanned at the age of 7 weeks. She died suddenly aged six months and thus illustrates the longer-term evolution of PVL. Details of these five babies are summarised in Table 1.

4. Definitions and Statistical Analysis.

Definitions.

Variables were considered as categorical (mainly dichotomous as shown in Appendix I), continuous or intermittent (Table 2). Continuous refers to an absolute value which varies from infant to infant, and intermittent to all recordings made at variable and non-standard times. The definitions (where not obvious) are listed below:

Pre-eclampsia - diastolic blood pressures above 90mmHg. together with proteinuria and/or oedema, or both.

Antepartum haemorrhage - vaginal bleeding after 20 weeks of gestation and prior to delivery of the infant. This includes retroplacental clot found at birth.

Fetal distress - type II dips detected on antenatal CTG monitoring and/or meconium staining of the liquor, or both.

Intrauterine growth - weight centile for gestational age derived from the charts of Gairdner and Pearson (1985) and Kitchen et al. (1981).

Recurrent apnoea - apnoeic episodes requiring stimulation and/or bradycardia with colour change and persisting for three days or more.

Persistent ductus arteriosus (PDA) - characteristic pan-systolic murmur together with full peripheral pulses.

Arrythmias - as determined by observation on an ECG monitor.

a) tachycardia > or = 200/minute for three minutes or more.

b) bradycardia < or = 80/minute for three minutes or more. Bradycardia associated with an acute insult such as pneumothorax was excluded as was bradycardia as a terminal event. Also bradycardia associated with recurrent apnoea was not included in this category.

c) other ECG abnormality suggesting conduction disorder but with a normal heart rate.

Necrotising enterocolitis (NEC) - defined according to the BAPP survey criteria (British Association for Perinatal Paediatrics 1983).

Coagulation disorders - platelets $<20 \times 10$ /mm and/or clotting time prolonged three times or more.

Pneumonia - radiological criteria.

Convulsions - clinically evident only and recognised by an experienced observer.

Intracranial pathology detected by ultrasound was coded as either PVH or PVL and these were further subdivided according to the definitions outlined above. The haemorrhage was classified as germinal matrix (small), intraventricular or parenchymal extension and the PVL as cystic, "precystic" or "prolonged flare". The fixed data were recorded as present or absent with the exception of pneumothorax for which the date of occurrence was noted. The timing of continuous data, pneumothorax and of scan changes was recorded as accurately as possible. This allowed us to distinguish between those factors antedating haemorrhage and PVL (and therefore presumed to be possible "predisposing factors") from those occurring subsequent to any scan changes ("associated factors"). All this data was coded and computerised using a VAX 8600 computer.

Stastical Methods.

I was grateful for the assistance of an experienced statistician (Mr. David Shaw) in analysing the data related to the predisposing risk factors. Two binary variables were created indicating whether the infant developed PVH and/or any evidence of PVL. Possible risk factors were analysed for PVH and PVL separately and in two stages. Initially multiple chi-square tests were performed on the categorical variables and Mann-Whitney U tests on the continuous and intermittent variables. The intermittent data was recorded together with the infant's age in hours to allow calculation of the proportion of time the infant was found to be above or below preset values. In the first analysis we used cut-off levels as previously reported in the literature - PaCO2 of 7KPa or more (Levene et al. 1982) and pH <7.2 (Skouteli et al. 1985). Subsequently the blood pressure and blood gas data were stratified by stepwise increments as shown in Table 2 and each increment was analysed separately as the proportion of time within the strata. The cut-off value which showed the most significant result was then used for further analysis. The second stage involved multivariate analyses by logistic regression using "GLIM" (acronym for generalised linear

modelling package) on all factors found to be significant at the 1% level to determine independently significant factors (Anderson et al. 1980). All factors significant at the 1% level are introduced into the GLIM analysis and the amount of variability of the outcome being assessed (IVH or PVL in this case) which is explained by each variable is analysed. The factor which most reduces the variability is the most significant independent variable. The process is repeated using the remaining variables to find the second and subsequent most significant independent factors until the point when the analysis shows that there is not a significant alteration of variability, i.e. this is not an independently significant risk factor. This form of logistic regression is termed a forward stepwise selection procedure.

Chapter 5

The Incidence Of Intraventricular Haemorrhage And Periventricular Leucomalacia

Haemorrhage in and around the lateral ventricles is a common lesion of the preterm brain with an incidence variously reported between 32% (Clark et al. 1981) and 90% (Bejar et al. 1980). Periventricular leucomalacia (PVL) has also been recognized to affect the infant's brain but to date its incidence has been largely derived from post-mortem studies and may not reflect its frequency in surviving infants. High resolution real-time ultrasound enables a diagnosis of PVL to be made in the living infant (Hill et al. 1982; Levene et al. 1983a; Fawer et al. 1985a; Bowerman et al. 1984; de Vries et al. 1985; Rushton et al. 1985; Nwaesei et al. 1984; Levene et al. 1985; Sinha et al. 1985) but there have been only three studies (Levene et al. 1983a; Fawer et al. 1985a; Sinha et al. 1985) reporting its overall incidence which ranges between 7.5% and 17.8% of low birthweight populations. This chapter compares the incidence of PVL with intraventricular haemorrhage in the study group.

Results.

There were 209 babies of appropriate birthweight for the study but two were excluded due to late transfer and a further seven died before a scan could be performed. The remaining 200 infants comprise the study population reported in this thesis.

The median birthweight was 1200gms (range 650-1500gms) and the median gestational age was 29 weeks (range 25-37). Fifty six infants were of 1000gms birthweight or less.

Normal - sixty nine infants (34.5%) had entirely normal scans.

Haemorrhage - haemorrhage was seen in 107 babies (53.5%) and in 37 this was small, i.e. in the region of the germinal matrix (grade I). Intraventricular haemorrhage (grade II) occurred in 62 babies and in a further eight there was parenchymal haemorrhage.

Parenchymal haemorrhage and PVL - of the eight babies with parenchymal haemorrhage on early scans, four subsequently developed echodensity in the contralateral periventricular region after a variable period (Plates 12a, 12b and 12c). In the two long-term survivors the former lesion resolved with the formation of a large porencephalic cyst and the latter into multiple discrete cysts. I believe this appearance represents parenchymal haemorrhage on one side with contralateral PVL. One infant had a persistent flare of the opposite side and in only three babies with parenchymal haemorrhage was there no associated contralateral parenchymal lesion.

PVL - fifty two babies (26%) showed parenchymal lesions thought not to be primarily haemorrhagic. Eight babies died in the precystic phase of PVL and in a further 19 infants cysts subsequently developed. In another 25 there was prolonged flare of periventricular echodensity.

A total of 123 infants had evidence of haemorrhage, cystic or precystic PVL or flare (Figures 3 and 4). Haemorrhage alone occurred in 71 infants and a further 36 had the appearances of PVL together with haemorrhage. Fifty five infants had parenchymal involvement (Figure 5) and only 3 of these showed the appearances of haemorrhage alone. Two others had PVL alone and 14 had a flare with no other abnormality. Thirty six of the 55 (65.5%) showed evidence of both haemorrhage and PVL.

Ventricular dilatation - twenty one babies (10.5%) developed ventricular dilatation; 9 were non-progressive and 12 required treatment. Twelve of the 21 (57%) had associated parenchymal involvement. Thirteen infants developed ventricular dilatation by 14 days and in all cases it had developed by the age of four weeks.

Deaths- forty two babies died (21%) and all deaths occurred before discharge from hospital. Twenty one of the babies who died weighed 1000gms or less at birth. Fourteen of the deaths involved babies of 26 weeks gestation or less. The time of death ranged from day 1-121 and 22 of the babies died before a week of age. Post-mortem information

was obtained in 30 of the 42 (71%) dead infants and is discussed in Chapter 6.

Timing - haemorrhage occurred within the first seven days of life in 83 of the 107 (78%) infants, but 17 infants (15%) showed the first ultrasound appearance of haemorrhage after 2 weeks of age. Eight of the 107 (7.5%) babies with haemorrhage did not show an abnormality until aged 31 days or more (Figure 6).

The echodense phase of PVL was first noted within three days from birth in 14 babies and by the age of a week in a further eleven. In the final two infants the change was observed by the tenth day.

Nineteen infants developed cysts. One was present at the first scan on the third day of life. In three cysts developed between 4 and 7 days and after 11 days in the rest. The median time for cysts to be first detected was 18 days of age. Only one infant developed an echofree cystic lesion after 30 days from birth (Figure 7).

Eleven of the 25 (44%) infants with prolonged flares were found to have this abnormality on the first scan (1 to 3 days). Eighteen (72%) developed flaring by the end of the first week. The flare was first noted after 20 days in only two infants (Figure 8).

Site - of the infants with cystic PVL the changes were bilateral in eight and unilateral in eleven. Twelve babies had cysts within the parietal area, nine in the occipital region and six in the frontal area. In eleven babies the cysts were confined to one zone and in eight there were changes in two sites. No baby had frontal, parietal and occipital involvement (Table 9).

Gestation - of the 107 babies with haemorrhage, 99 (93%) were of 30 weeks gestation or less. There was a marked decrease in the incidence of haemorrhage from 62% at 30 weeks to 19% at 31 weeks gestation (Figure 10). A similar pattern was seen in the babies with PVL and persistent flare - 25/27 in the former group and 22/25 in the latter were 30 weeks or less (Figure 11).

Birthweight - there was no such clearcut watershed for birthweight as for gestation. However, at a birthweight of 1100 grams or less 48 of the 75 babies (64%) suffered haemorrhage as opposed to 59 out of 125 babies (47.2%) of birthweight 1101 grams or more (Figure 12). Grouping all patterns of PVL together there was even less of a relationship to birthweight. At 1100 grams or less the incidence was 19 out of 75

babies (25.3%) whereas for birthweight 1101 grams or more it was 33 out of 125 babies (26.4%) [Figure 13].

Discussion.

Incidence of Periventricular Leucomalacia.

The incidence of the ultrasound appearances which we believe represent cystic and precystic PVL is 13.5% in a group of very low birthweight infants.

The first reported incidence of PVL based on ultrasound scanning was published in 1983 (Levene et al. 1983a). Retrospectively over a one year period Levene and colleagues studied 120 infants of birthweight 1500 grams or less. Fifty eight babies (48%) showed features of IVH of whom 12 suffered parenchymal extension. Nine (7.5%) had haemorrhagic PVL which they defined as "an area of increased echodensity in the periventricular region distinct from the site of PVH and seen in both coronal and parasagittal planes." Five of the nine had associated IVH. Two infants died the day after detection of echogenicity, one was lost to follow up and five developed cystic degeneration. The ninth survived and did not develop cysts - perhaps the first observation of the appearance that I have labelled as a persisting flare. This study also confirmed the weakness of CT scanning at detecting cysts which were clearly apparent on ultrasound.

Two years later Fawer et al. (1985a) reported their one year prospective study. They defined PVL as increased echogenicity in the periventricular white matter in a triangular shape with its apex to the ventricle and its base to the cortex. This should be reproducible in all scan planes and progress to areas of decreased echogenicity. They included all infants of 34 weeks gestation or less and those of greater maturity if they showed abnormal neurology. The former group contained 83 babies of whom 36 showed PVH and 13 had ultrasound evidence of PVL - an incidence of 16.8%. There were 36 infants of more than 34 weeks gestation and 3 (8.3%) showed PVL, all of whom were of full term. The Lausanne group propose a biphasic distribution of PVL affecting infants of less than 34 weeks and more than 37 weeks. Clearly the numbers are too small to be dogmatic but it behoves us to remember that PVL is not solely an affliction of the preterm neonate. Like other workers Fawer noted that cysts might occur without any preceding echogenicity. This applied to 6 of

her 16 cases despite frequent scanning and she suggested that the echogenic areas were too small to be detected.

Sinha and coworkers (1985) studied 219 infants of 32 weeks or less over a fourteen month period. They defined ischaemic lesions as "echo-dense areas within the cerebral parenchyma, distinct from and not contiguous with PVH and seen in both planes. They nearly all went on to cysts and transient bilateral flares were ignored". Thirty nine babies (17.8%) showed such appearances of whom 27 (69.2%) had an associated haemorrhage. Although the lesions were periventricular in 32 cases, they were diffuse in distribution in four and confined to the cortical area in the other three babies. They identified haemorrhage in 106 babies (48.4%) and 27 of these had associated ischaemic lesions.

Bozynski and colleagues (1985) enrolled 100 surviving infants of birthweight 1200 grams or less in a two year prospective study. They confined themselves to "cavitary" PVL and identified such changes in five babies, of whom three had associated IVH/PVH.

Calvert and colleagues (1986) also included only babies with cystic changes in their three year study. They scanned all babies of birthweight 1500 grams or less and those with a clinical indication. They observed cystic PVL in 15 babies of whom 10 were of very low birthweight so the incidence in the babies of <1500 grams was 2.3%. Eight of the fifteen suffered an associated IVH but it is interesting that only 9/15 showed echogenicity preceding the cysts. All 15 babies with cysts survived.

By restricting themselves only to the babies who survived and those with cystic changes neither Bozynski nor Calvert is giving an accurate figure for the overall incidence of PVL. In terms of morbidity these are important statistics and have been discussed in Chapter 3.

The only other published incidence of PVL derives from post-mortem studies and varies between 7% (Armstrong and Norman 1974) and 34% (Pape et al. 1976). The latter study looked only at a highly selected group of 106 infants of birthweight 1500gms or below all of whom were outborn.

The Different Patterns of Parenchymal Injury.

All areas of extensive echodensity within the parenchyma seen in association with intraventricular haemorrhage have until recently been assumed to represent parenchymal haemorrhage. Hill et al.(1982) were the first to recognise that parenchymal echodensity might be due to

haemorrhagic infarction and Levene and colleagues (1983a) later reported the evolution of "haemorrhagic" PVL to cystic degeneration. Nwaesei and coworkers (1984) have shown that echodensity may be due to gliosis without haemorrhage. Few would now disagree that multiple small echolucent areas in the periventricular white matter represents PVL. A characteristic triangular echodense region in the parenchyma precedes cystic degeneration and if seen in those infants who die before cysts develop then I have termed this the "precystic" phase of PVL. Rushton reports accurate pathological correlation of PVL in five infants with the "echodense" ultrasound appearance (Rushton et al. 1985). I believe this equates with my "precystic" appearance and we have confirmed this (see Chapter 6).

A prospective study by McMenamin and colleagues (1984) would appear to encompass all three patterns of parenchymal injury that I have recognised but they used only two subdivisions. Over 16 months they studied 460 infants of birthweight 2250 grams or less and 177 suffered IVH. Of these, 64 had associated intraparenchymal echodensity (IPE) which was first identified between days 1 and 15. Thirty three had a large IPE which they defined as globular and extending into a large part of the white matter of the frontal or parietal lobes or both. In 32 it was unilateral and nearly always on the same side as the maximal IVH. All the surviving infants developed porencephalic cysts at the corresponding site. These large intraparenchymal echodensities probably represent the lesions that I have defined as parenchymal haemorrhage and perhaps also some examples of precystic PVL. The other 31 babies had small IPE's defined as linear echodensities extending from the angles of the frontal horns of the lateral ventricles for a few millimetres into the white matter. In 15 cases the changes were bilateral. Of the 22 survivors 19 showed complete resolution over a mean of 18 days (range 4-56) and the other three developed small cysts at the corresponding site. It is likely that this group corresponds to my infants with cystic PVL and those with transient and persistent flares. The neurodevelopmental significance of these various lesions is discussed in Chapter 3. It is unfortunate that the St. Louis team confined themselves to parenchymal changes associated with haemorrhage for my experience would suggest that such a large collection of infants must have included some with isolated parenchymal lesions.

Parenchymal Haemorrhage.

The ultrasound appearance we refer to as "parenchymal haemorrhage" and the subsequent evolution to porencephaly is quite different to that which we recognise as PVL. We have seen four infants in whom the appearance of parenchymal haemorrhage preceded contralateral PVL and the two survivors developed porencephaly in one hemisphere and multiple cystic degeneration in the other. The timing also suggests that at least in some cases the massive parenchymal haemorrhage may induce secondary cerebral ischaemia with contralateral PVL. The delayed timing of the parenchymal echodensity following IVH might also suggest venous infarction as a possible cause and this will be discussed later. Only eight infants showed the appearance we believe to represent parenchymal haemorrhage.

Extension of Haemorrhage or Ischaemia with Rebleeding?

The most difficult and controversial area of the diagnosis of parenchymal lesions is the differentiation between extension of haemorrhage and PVL. Even at autopsy it may be impossible to distinguish primary haemorrhage from rebleeding into an ischaemic lesion or venous infarction. The presence of a plasminogen activator in the germinal layer tissue of infants up to 30 weeks gestation would increase fibrinolytic activity (Hambleton and Wigglesworth 1976). One might suspect that this would predispose to parenchymal extension from an intraventricular haemorrhage. However, Armstrong and Norman (1974) demonstrated rebleeding into an ischaemic periventricular area in 25% of their cases. Flodmark and colleagues (1980) reported that of 19 preterm babies thought to have parenchymal haemorrhage on CT scan, autopsy revealed rebleeding into an ischaemic area in 18 (95%). More recently Volpe and his team using positron emission tomography (PET) demonstrated extensive areas of diminished cerebral blood flow around an apparent primary parenchymal haemorrhage and suggested that the haemorrhage may have been secondary to ischaemia (Volpe et al. 1983). Towbin, in fact, had made a similar observation at autopsy - the area of necrosis is greater than the area of haemorrhage and he concluded that venous infarction was the primary lesion and the haemorrhage was secondary (Towbin 1968). These reports do not prove that ischaemia is the underlying cause of parenchymal haemorrhage in all cases (as suggested by Rushton and colleagues [1985]) but makes it likely that a number of such

lesions are primarily ischaemic. Further evidence for this is shown in Plates 13a and 13b which show a sequence of scans of the same baby. The initial appearance is of ischaemia showing a right-sided parenchymal echodensity with its apex at the lateral margin of the lateral ventricle. Three days later a large parenchymal haemorrhage is seen in the corresponding area. Clearly no conclusions can be drawn from a single case and further work is needed to clarify this issue which remains unresolved.

The Role of Arterial Insufficiency in the Aetiology of PVL.

The term PVL was originally coined by Banker and Larroche (1962) to describe a specific but subtle macroscopic appearance in infants dying following a complicated perinatal course. The most obvious lesions were "white spots". Since then the term PVL has been used more widely to describe a number of different macroscopic and microscopic appearances (Pape and Wigglesworth 1979; Lancet Editorial 1984). Shuman and Selednick (1980) offered further support for the border zone theory which was originally proposed by Banker and Larroche. In a series of one hundred perinatal autopsies (18 stillbirths and 82 postnatal deaths) they identified PVL in 17. They observed the two commonest sites for lesions to be the occipital radiation at the trigone (17 babies) and the white matter around the foramen of Monro (11 babies), i.e. the border zones of arterial supply. Further evidence that arterial insufficiency may be important is offered by animal studies. The adult cat has a cerebral circulation very similar to the human foetus towards the end of its gestation. If the basilar and carotid arteries are variously occluded or narrowed then lesions which are very similar to PVL in their location and histology will result (Abramowicz 1964). Indeed Abramowicz astutely suggested that there was a double vulnerability with immaturity of the arterial supply to the periventricular region in addition to the watershed offered by the border zones of supply.

Is Venous Infarction Important in the Aetiology of PVL?

Although PVL may be the sequel to border zone infarction, it is likely that more than one aetiological factor is involved. Leech and Alvord (1974) studied 25 brains affected by PVL and described three distinct patterns although they could co-exist. There were focal areas of necrosis which in their most extensive form could reach the subcortical region.

Secondly there were concentric lesions perpendicular to the deep penetrating arteries and the authors concluded that arterial insufficiency could account for these two types of lesion. The final pattern that they described was of radially arranged linear lesions parallel to the straight veins passing through the white matter and which they suggest could be the sequel to venous stasis-thrombosis. A few years previously Towbin had suggested that venous infarction was more important than arterial insufficiency (Towbin 1969; Towbin 1970). He proposed the scenario in which hypoxia (before or after birth) induced circulatory failure with congestion of the deep venous system such as the vein of Galen. This pressure would be transmitted upstream to the periventricular veins which would become engorged with subsequent thrombosis, infarction and haemorrhage. I believe that some cases may be due to venous infarction - eight babies in my series showed a pattern of thrombus distending a lateral ventricle associated with development of a triangular echogenic area in the ipsilateral parenchyma. Pape and Wigglesworth (1979) have described congestion of the branches of the terminal vein in cases of massive germinal matrix haemorrhage with associated venous infarction of the surrounding periventricular white matter. This would account for the frequency of PVL in infants with Grade II haemorrhage. The possible role of venous infarction will be further reviewed in the next chapter.

The Incidence of Haemorrhage.

The overall incidence of haemorrhage (53.5%) corresponds with previous studies in the very low birthweight infant (Levene et al. 1982; Sinha et al. 1985). Of the 107 babies with haemorrhage described here, parenchymal extension occurred in only 8 (7.5%), whereas previous workers have reported parenchymal involvement in about 20% of cases (Levene et al. 1982). I believe that many parenchymal lesions which we now recognise as PVL have been classified as parenchymal haemorrhages in the past and this would explain my lower frequency for the latter lesion.

The Incidence of Prolonged Periventricular Flare.

This is the first prospective study of the incidence of abnormal ultrasound appearances which have been carefully defined prior to starting data collection. The definition of cystic and precystic PVL was based on sound pathological correlation but I chose to use the term "flare" to avoid assuming pathological abnormality in all cases where this was persistent.

Some periventricular echodensity is very common, usually transient and of no pathological significance (Grant et al. 1983; Laub and Ingrisch 1986). I decided to include as abnormal only those in whom the echoes persisted for two weeks or more and could be consistently seen in two planes. Prolonged flare was seen in 12.5% of infants in this study and is clearly an important ultrasound finding but we must await follow-up data on the outcome of these infants before establishing its prognostic significance (see Chapter 3 and Graham et al. 1987 [*discussed in Chapter 8*]).

Timing of Lesions.

Previous studies have shown that the majority of IVH's occur within three days of birth (Levene et al. 1982; de Crespigny et al. 1982). In this study accurate timing of IVH was not possible but 78% of the haemorrhages were noted before the age of 7 days. Sinha noted all his haemorrhages by 4 days of age with a median time for first diagnosis of two days (Sinha et al. 1985). Eight of the 107 haemorrhages (7.5%) occurred at the age of one month or more. In one case the haemorrhage was first noted the day after a cardiac arrest but in the other eight there was no preceding insult. This group resembles the pattern of late haemorrhages as reported by Hecht et al. (1983) and like his cases the haemorrhages in my babies were small. The echodense phase of PVL was observed in the first three days of life in fourteen cases and in the other thirteen by 10 days of age. This corresponds to Fawer's finding that the increased echogenicity occurred early, usually by the tenth day (Fawer et al. 1985a), but shows a marked contrast to the Toronto group whose mean age for first noting the echodensity was 37 days (range 1-85) [Nwaesei et al. 1984]. The difference may be partly due to their selection criteria as the babies had to survive at least twenty days for inclusion in their retrospective study. The median time for initial observation of ischaemic changes in Sinha's study was 7 days with a range of 1-70 days (Sinha et al. 1985). The age at which cysts were first identified ranged from 5 days (Levene et al. 1983a; Fawer et al. 1985a) to as late as 10 weeks (Bozynski et al. 1985). I observed cysts in one infant at the first scan which was performed on the third day of life. In another infant, who is described in the next chapter, a well circumscribed cyst was present at autopsy following his death at age five days and must have taken its origin antenatally.

Site of Lesions.

All of the 15 babies with cystic PVL reported by Calvert and colleagues had bilateral changes (Calvert et al. 1986). In 10 the cysts were confined to the parietal area, in 4 there was parietal and frontal involvement and one child had bilateral parieto-temporal changes. Four of the babies reported by Bozynski also had bilateral cysts (Bozynski et al. 1985). In 2 these were parieto-occipital, in one fronto-occipital and in the final case the site was not specified. One infant had unilateral cystic change in the frontal region.

My results differ from those of Calvert and Bozynski in showing relatively more infants with unilateral change. These babies often showed a large ipsilateral IVH distending the ventricle and the characteristic parenchymal echodensity which would evolve into cystic degeneration if the child survived. I cannot explain why my study contained relatively more of these infants unless our inclusion criteria and/or definitions varied in some way. Like Bozynski my infants showed changes distributed across the three areas related to the periventricular region (frontal, parietal and occipital) and it seems surprising that Calvert had no infant with occipital cysts. Again, I cannot explain this discrepancy between our findings.

Chapter 6

Pathological Correlation

For the first one hundred years or so after its initial recognition the diagnosis of periventricular leucomalacia remained entirely in the hands of the pathologists. Indeed, the original term was applied to the small white spots seen macroscopically in the periventricular white matter around the lateral ventricles (Banker and Larroche 1962). This appears to be a later stage in the evolution of PVL which initially is seen as an area of infarction. The histological features have been equally well documented with the early coagulation necrosis giving way to axonal disintegration. A cellular reaction with lipid-filled microglial cells then develops followed by a reactive astrocytosis. Finally the central areas of the lesions liquefy, foamy macrophages appear and cavitation results (Pape and Wigglesworth 1979). The sequence of changes would evolve over approximately a two week period.

With the advent of imaging techniques came the ability to identify these lesions during life. Clearly it is important to ensure that one's interpretation of a scan accurately represents the underlying pathological lesion. Previous workers have reported accurate correlation between ultrasound demonstration of IVH and its finding on CT or at autopsy (Mack et al. 1981; Babcock et al. 1982; Levene et al. 1982; Thorburn et al. 1982a; Pape et al. 1983; Szymonowicz et al. 1984a). Pathological correlation for periventricular leucomalacia is less well documented and no studies have attempted to differentiate parenchymal lesions due to "extension of haemorrhage" from periventricular leucomalacia. This chapter is concerned with the accuracy of correlation of the in vivo (scan) diagnosis with that found at autopsy.

Results.

Forty two of the 200 study babies died and all deaths occurred before discharge from hospital. Post-mortem examination was performed in 31 of the 42 deaths but in one infant the brain was too soft to fix. The results of the correlation between autopsy and ultrasound is shown in Tables 14 and 15 for the 30 infants with complete post-mortem data. Histological examination was performed on 25 brains. Of the sixteen babies undergoing autopsy in Leicester five had no microscopic examination of whom two had small germinal layer haemorrhages and three were normal. None of them showed any parenchymal changes either on ultrasound scanning or in the macroscopic brain sections.

Haemorrhage - haemorrhage into the germinal matrix, ventricle or extension into the cerebral parenchyma was diagnosed both by ultrasound and subsequently at autopsy in 31 hemispheres. The results are summarised in Table 14. A false positive ultrasound diagnosis of haemorrhage was made in 4 hemispheres (3 infants) in which post-mortem examination subsequently showed a normal hemisphere. In three the ultrasound appearance was thought to be haemorrhage in the region of the germinal matrix and the other showed the appearances of more extensive clot in the lateral ventricles. A false negative diagnosis of haemorrhage was made in three hemispheres (two babies). For details see Table 15. All three hemispheres contained a small germinal matrix haemorrhage which had ruptured into the ventricles. The accuracy of ultrasound diagnosis of haemorrhage is 88%. The sensitivity of diagnosis is 91% and specificity is 85%.

Ischaemic lesions - echodensity in the periventricular white matter detected by ultrasound and thought not to be parenchymal extension of periventricular haemorrhage was seen in 20 hemispheres and PVL lesions were diagnosed at autopsy in 20 hemispheres (see Tables 14 and 15). The accuracy of the ultrasound diagnosis was 88%. A false positive ultrasound diagnosis of abnormal periventricular echodensity was made in 3 hemispheres (2 infants). One child was only scanned once and the other had 3 scans and mild bilateral flare was thought to be present on each occasion. A false negative ultrasound diagnosis of PVL was seen in 3 hemispheres (2 infants). In two hemispheres there was non-haemorrhagic PVL and in one hemisphere extensive haemorrhagic PVL was found and not previously detected by ultrasound. The infant whose ultrasound scan showed a flare but necropsy revealed a definite cyst in the corresponding

site has been included as a false negative diagnosis for the purposes of analysis. The sensitivity of ultrasound in the diagnosis of PVL is 81% and the specificity 92%.

Spectrum of PVL lesions - to demonstrate the variety of PVL lesions an additional five infants have been considered together with the study infants. The ultrasound appearances we have described as prolonged flare (see Chapter 4) occurred in two infants (three hemispheres) whose brains were examined at autopsy. The flares persisted for two weeks and three months respectively and were present on the last scan prior to death. No macroscopic abnormality was seen in either brain but on histological examination extensive spongiosis and microcalcification was present in the periventricular white matter corresponding to the areas of echodensity (Plates 14a and 14b).

One infant showed at autopsy the characteristic "white spots" described by Banker and Larroche (1962). On ultrasound examination persistent bilateral flare had been seen and it was thought that small echofree cavitations subsequently occurred shortly before death. The cysts were not confirmed at autopsy but the echofree areas may have corresponded to the macroscopic white spots of lipid accumulation.

Seven infants (eight hemispheres) showed the pathological appearance of haemorrhagic infarction at autopsy. These infants died between the ages of 5 hours and 13 days. In all cases the floor of the ventricle appeared intact. In six of these infants in whom an ultrasound diagnosis of pre-cystic PVL was made, the necropsy appearance was consistent with haemorrhagic infarction in the region of the echodensity.

Three infants were found to have periventricular cysts at autopsy. In all cases the initial ultrasound appearance was of a triangular shaped echodensity with its apex towards the angle of the lateral ventricle from which echofree cavities developed in two of the three cases. A unilateral periventricular cyst was not detected in one baby on scanning although a flare had been seen in the corresponding area. This infant was scanned only once during life.

One preterm infant who was not a member of the study population died aged six months of Sudden Infant Death Syndrome. At discharge from the neonatal unit an ultrasound scan showed extensive echofree cavitation in the periventricular white matter of both hemispheres. At autopsy there was irregular, ventricular dilatation but the posteriorly placed cysts

remained only as flattened cavities whilst the anterior cysts could no longer be seen at all.

Discussion.

Ultrasound and Autopsy Correlation for Haemorrhage.

Real-time ultrasound appears an extremely good method for diagnosing both PVH (accuracy 88%) and PVL (accuracy 88%) in this series of 30 brains. Previous studies have produced similar autopsy correlation with the ultrasound diagnosis of periventricular haemorrhage in the region of 90% accuracy (Babcock et al. 1982; Levene et al. 1982; Thorburn et al. 1982a; Pape et al. 1983; Szymonowicz et al. 1984a). In the two infants with a false negative diagnosis of haemorrhage there was an interval of a few hours between the last scan and death and the bleeding may have occurred during this time. A false positive diagnosis of haemorrhage was made in four hemispheres (three babies), all of whom died within 24 hours of birth. One baby had a massive contralateral parenchymal haemorrhage and it is possible that on scanning I detected spread of thrombus from this site with no actual focus of bleeding within the ventricle in question. Symonowicz and her colleagues (1984a) reported congestion of the germinal matrix region simulating germinal matrix haemorrhage but this was not present in the infants reported here.

Hope and colleagues (1988) have recently reported their pathological correlation in fifty infants of less than 33 weeks gestation. They confirmed the accuracy of ultrasound in identifying GLH and IVH but reported a high rate of false positive diagnosis using ultrasound in the most immature babies (26 weeks or less), confirming the observation of Symonowicz (1984a). This they ascribed to bulkiness of the germinal layer and choroid. Parenchymal haemorrhage was present in 11 hemispheres and correctly identified in nine. They proposed venous infarction secondary to IVH as a major cause of parenchymal haemorrhage and do not include it as a pattern of PVL as I have done.

Ultrasound and Autopsy Correlation for PVL.

Less information is available on the correlation between the ultrasound diagnosis of PVL and autopsy data. Nwaesei and colleagues (1984) studied 23 infants (46 hemispheres) whose mean gestational age was 28.8 weeks. They reported 78% accuracy between ultrasound

demonstration of increased echoes or cysts in the periventricular region and the finding of PVL at autopsy in the corresponding site. The study can be criticised on several points - it was retrospective and by the authors' own confession some of the scans were of poor quality. In addition the frequency of scanning was less than optimal; all six with false negative diagnoses had had no scan for at least 6 days before death and in two infants with false positive findings it was 128 and 140 days respectively between the last scan and death. Finally, Nwaesei only included infants if they survived for at least 20 days and thus restricted herself to a selected population for it is my experience that the development of PVL usually occurs at a much earlier age (see Chapter 5). This group do make one very important observation. They identified periventricular infarction in 12 infants (all bilateral) and in 4 cases this was haemorrhagic but in the other 8 it wasn't. They could not, however, be discriminated on scanning; both haemorrhagic and non-haemorrhagic infarction may produce identical changes on ultrasound. Hill et al. (1983) had made a similar observation previously in four full-term infants with lesions more typical of a neonatal stroke pattern. Ultrasound showed focal increase in echogenicity but CT scanning revealed low density changes in the corresponding site suggesting a non-haemorrhagic ischaemic injury. The authors suggested that local oedema might explain the echogenicity.

In the previous chapter I referred to Fawer's prospective study in which 16 infants were identified with the ultrasound appearances of PVL (Fawer et al. 1985a). Five of these died and they all underwent autopsy. Two infants showing cystic changes died at 15 and 73 days of age respectively and the cysts were confirmed at post-mortem. The other three babies died between the ages of 2 and 24 days with ultrasound appearances of increased echogenicity. At autopsy these changes corresponded to vascular congestion and microscopy showed the characteristic features of PVL - coagulation necrosis, lipid-laden macrophages and gliosis. Of the 103 infants who did not show ultrasound evidence of PVL twenty died and fourteen underwent autopsy. No macroscopic nor histological features of PVL were found in any of the brains.

The autopsy correlation with prolonged flares in three hemispheres revealed extensive gliosis and microcalcification. This agrees with the findings of Nwaesei in that haemorrhagic change is not a prerequisite for increased echogenicity on the ultrasound scan (Nwaesei et al. 1984). McMenamin and colleagues (1984) have described the autopsy findings in

two infants whom they classified as having small intraparenchymal echodensities. One infant died aged 21 days and brain histology revealed bilateral astrocytic gliosis compatible with PVL. In the other infant the ultrasound changes had resolved by day 38 and following his death at 63 days the brain appeared normal at autopsy. Overall the accuracy of ultrasound in diagnosing the spectrum of PVL lesions is reassuring and this supports the validity of the ultrasound definitions which I used (see Chapter 4).

Hope and colleagues, however, felt that the most important weakness of ultrasound was in identification of hypoxic ischaemic damage (Hope et al. 1988). This may partly reflect their criteria for diagnosing this insult. Of the 39 hemispheres affected only 10 showed macroscopic changes (and these were often minimal). In the remainder it was a histological diagnosis based on the presence of gliosis. The high rate of false negative diagnosis by ultrasound must be tempered with the fact that only one case of extensive PVL was missed. They correctly identified hypoxic ischaemic changes in 11 hemispheres but in addition made a false positive diagnosis in a further 10, some of whom showed marked echodensity on ultrasound but no abnormality at autopsy. It is interesting that despite their frequent finding of gliosis at post-mortem, the UCH team failed to recognise the pattern which I describe as a "prolonged flare" and which I have shown to correlate with gliosis (see above). Also, they did not observe the progression of hypoxic ischaemic changes into cystic PVL, a pattern which is uncommon in surviving infants at UCH. Again, this differs from my experience for of the nineteen babies with cystic PVL five died and fourteen survived to leave the neonatal unit. One of the latter group died after discharge at the age of fourteen months.

PVL was missed on ultrasound scanning in two babies (three hemispheres). In one hemisphere the changes were early and in the other two there were histological abnormalities only (spongiosis and reactive astrocytosis but no microcalcification). A discrete cyst was missed in one infant whose only scan was performed 48 hours before his death at age five days. The scan showed some flaring in the area where the cyst was subsequently observed at post mortem. The cyst undoubtedly would have been present at the time of the scan and I cannot explain why it was not detected. One possibility is that distortion may have occurred during fixation of the brain to give a cystic appearance larger than it had been in vivo.

Parenchymal Haemorrhage : Extension or Ischaemia With Secondary Bleeding?

Armstrong and Norman (1974) reported bleeding into the ischaemic area in 25% of their infants with periventricular leucomalacia and I found this in 6 of 34 (18%) hemispheres. There is, however, considerable controversy as to the differentiation between parenchymal extension of IVH and bleeding into a previously ischaemic lesion. Rushton and colleagues (1985) have recently reported eight infants with parenchymal abnormalities on ultrasound and at autopsy all showed PVL. These authors proposed that this is the underlying aetiology to all parenchymal haemorrhagic lesions. The evidence for this is still far from conclusive and it is beyond the scope of this study to resolve this question.

I have attempted to differentiate parenchymal extension of IVH from PVL by ultrasound scanning and the relative incidence of both is discussed in Chapter 5. The autopsy data reported here confirms that in all cases in whom "precystic" PVL was diagnosed by ultrasound this was subsequently found to be correct. No infant with parenchymal extension of intraventricular haemorrhage died in the acute stages and correlation in this group was not possible.

The Role of Venous Infarction in Parenchymal Lesions.

The term periventricular leucomalacia may, in fact, include lesions of different pathogenesis and amongst these is venous infarction. Twenty years ago Towbin studied whole brain histological sections of 120 preterm infants (Towbin 1968). In 63 there was congestion and possibly small IVH, in 34 moderate infarction and IVH and 23 showed extensive infarction. He suggested that hypoxia (ante-, peri- or postnatal) induced circulatory failure which in turn resulted in venous congestion. Congestion and thrombosis of the terminal vein would lead to infarction of the germinal matrix region and venous bleeding would ensue to give rise to intraventricular haemorrhage. He went on to suggest that a similar pathogenesis might give rise to lesions in the white matter. In its mildest form this would consist of small petechiae where the engorged veins broke down but more severe degrees of congestion and thrombosis could lead to white matter necrosis. Indeed he proposed that periventricular leucomalacia might result from focal microinfarcts in a satellite pattern around a large venous infarction (Towbin 1970). He found the peak incidence of infarction in infants of 28 weeks gestation. Recently Gould and colleagues from University College

Hospital have reported the autopsy findings in four babies of 24-27 weeks gestation who died before the age of four days (Gould et al. 1987). Macroscopically there was intraparenchymal haemorrhage and this appeared contiguous with intraventricular haemorrhage in three of the four. Microscopically, however, there were multiple perivascular haemorrhages in the white matter and the ependyma was intact in all four cases. Indeed, in two it bulged into the ventricle giving the appearance that it might rupture in that direction. There were no features of ischaemia but histology showed venous infarction. Normally the medullary veins in the periventricular white matter drain to the germinal layer veins and then to the terminal vein. Gould suggested completely the opposite sequence of events to Towbin, i.e. that the germinal layer haemorrhage leads to venous obstruction with a rise in pressure and then to venous infarction. Further support for this theory comes from the barium gelatin injection studies of Hambleton and Wigglesworth (1976). In most of the 19 brains that they examined where germinal layer haemorrhage was present this was of capillary origin and the terminal vein was intact. In three, however, there was venous congestion and rupture and this was thought to be due to obstruction by a more extensive haemorrhage.

Final Points Concerning Pathological Correlation.

I have had the opportunity of observing a variety of appearances in the immature brain which represent the spectrum of perinatal ischaemic injury. The histologic appearances of PVL have been described originally by Virchow (1867) and later by Banker and Larroche (1962). These appearances may be present without macroscopic abnormality and I have shown that ultrasound can demonstrate both gliosis and the "white spots" of Banker and Larroche. Haemorrhagic infarction and subsequent cavitation is also readily diagnosed by ultrasound imaging. Two cases have been reported of infants showing extensive cavitation on sequential ultrasound scans in whom the echo-free cystic lesions disappeared by 6 months (Bowerman et al. 1984; Dubowitz et al. 1985). The older infant whom I described offers pathological correlation to this sequence of scan findings. With collapse of the cystic cavities compensatory ventricular dilatation occurred due to cerebral atrophy. As far as I know this is the only such pathological correlation reported to date.

Chapter 7

Clinical Risk Factors For Intraventricular Haemorrhage And Periventricular Leucomalacia

Factors predisposing to germinal matrix haemorrhage in the preterm infant have been well documented by previous workers using autopsy (Moriette et al. 1977), computerised tomography (Clark et al. 1981) and ultrasound scan diagnosis (Cooke 1981; Levene et al. 1982; Thorburn et al. 1982b; Horbar et al. 1983; Szymonowicz et al. 1984b; McDonald et al. 1984a). It is agreed that periventricular haemorrhage (PVH) is a condition of prematurity related to rupture of capillaries within the germinal matrix. The presence of respiratory distress syndrome and its complications are important associated factors.

By contrast, the cause of periventricular leucomalacia (PVL) is uncertain. If PVL is to prove a significant cause of neurodevelopmental handicap then it behoves us to try and identify possible causal factors so that these may be prevented or treated as the case may be.

Results.

Categorical and continuous data were available for all 200 infants. Intermittent data in the form of blood gas recordings were made on 171 infants. Twenty nine had no respiratory distress and required no supplemental oxygen. Blood gases were not measured in this group. Systolic blood pressure data were available from 113 of the infants.

On univariate analysis fourteen risk factors reached statistical significance ($p < 0.01$) for prediction of development of PVH (Table 16) and ten factors were significantly associated ($p < 0.01$) with the development of PVL (Table 17). The results of the stratification analysis for the intermittent data is shown in Table 18. For PVH, pH <7.2, and

paCO2 > 7 were found to be the blood gas levels which were most strongly associated with haemorrhage. Infants who developed PVH spent a considerably longer proportion of time with blood pressure above 55 than those without haemorrhage ($p = 0.0007$). Infants with PVH had significantly higher growth centiles than those without haemorrhage ($p < 0.001$). It appears that there is a reduced risk of PVH in infants with less good intrauterine growth. When considering PVL, acidosis (pH <7.1) and hypercapnia (paCO2 > 7) were the only two intermittent items to reach significance at a 1% level.

Multivariate logistic regression analyses were performed on the 14 risk factors for PVH and the ten for PVL. The GLIM equation for PVH can be described as:

$$\log P/1\text{-}P = 12.27 - 0.414a - 1.845b + 1.935c + 2.770d$$

and for any degree of PVL as:

$$\log P/1\text{-}P = -3.50 - 1.860b + 1.556e + 0.013f + 3.649d + 1.305g$$

where the numbers represent statistically derived constant values and a = gestational age in weeks; b = 1, if Hb <10 gm/dl at any time, otherwise 0; c = 1, if any clotting disorder, otherwise 0; d = proportion of time paCO2 >7; e = 1, if pneumothorax, otherwise 0; f = maximum bilirubin level; and g = 1, if any surgical procedure, otherwise 0. The surgical procedures performed are listed in Table 19. P represents the probability of an event (haemorrhage or PVL) and when log P/1-P is zero (i.e. the log of 1) then there is a 50% chance of occurrence. If the log value becomes positive then the likelihood of an event becomes less and vice versa.

This means that the risk of developing PVH was negatively correlated with advancing gestational age and anaemia (haemoglobin <10 gm/dl). PVL was also negatively correlated with anaemia. Table 20 summarises these independent variables for both PVH and PVL together with the chi square value for removal from the model.

These models were derived from the 171 infants with complete blood gas data. When the model for PVH was applied to the 113 infants with systolic blood pressure data, it did not significantly improve the fit of the model. Further analyses were performed to distinguish whether there were different risk factors for cystic and precystic PVL compared with prolonged flare alone. Three factors best predicted both these conditions. These were anaemia (negative correlation), pneumothorax and maximum bilirubin level.

Thirty two of the babies in the study were from multiple pregnancies. In addition there were five twins and one triplet whose partners were excluded on birthweight criteria. Of these infants 15 had normal scans, 8 developed PVL and 9 had isolated PVH of which one was a parenchymal extension.

Discussion.

Risk Factors for Haemorrhage.

The first report of clinical factors related to periventricular haemorrhage diagnosed by ultrasound was that of Cooke (1981). From a study of 39 consecutive infants of birthweight less than 1500 grams he concluded that respiratory distress and the need for respiratory support, hypercapnia and metabolic acidosis were the important clinical factors. He found no association with gestation nor birthweight and Cooke suggested that this was because he only studied infants of below 1500 grams. It is also likely to reflect the comparitively small number of babies enrolled. Another drawback of this study is that no attempt was made to time the clinical events in relation to the haemorrhage. All haemorrhages had occurred by one week of age and the clinical events were recorded over this entire period. So, as the title of his paper implies, these were associations rather than true risk factors.

A year later both Levene and Thorburn confirmed the importance of respiratory distress and mechanical ventilation (Levene et al. 1982; Thorburn et al. 1982b). In addition they both made the observation that prematurity was important. Levene and colleagues studied 146 infants of 34 weeks gestation or less and were careful to discriminate the clinical events present before the onset of haemorrhage and which might therefore be considered as possible predisposing factors. They also identified infection and hypothermia as risk factors and interestingly noted a lower incidence of haemorrhage in babies born after in utero transfer. They suggested that this reflected the closer monitoring offered to this high risk group. Using multiple regression analysis respiratory distress syndrome (RDS) and severe acidosis emerged as the strongest predictors of IVH followed by mechanical ventilation and gestation and finally by hypercapnia and infusion of base.

Thorburn and coworkers studied 95 infants of 33 weeks gestation and looked for the antecedents of haemorrhage, i.e. events present before

the bleed was first noted. In addition to the respiratory distress, hypercapnia, mechanical ventilation, acidosis and prematurity mentioned above they too found hypothermia to be significant. They also found pneumothorax, clotting disorder and hypotension to be important. There was a significantly increased incidence of haemorrhage in outborn infants compared to those born within University College Hospital and in those born by vaginal breech delivery. When the risk factors were subjected to multiple regression analysis pneumothorax emerged as the most important independent predictor followed by decreasing gestation and abnormal coagulation. Both Levene and Thorburn noted alkali administration as a significant antecedent and the latter also added tolazoline infusion. Both agree that this probably reflects the extent of acidosis and sickness of the infants rather than a direct effect of these agents. However, as Thorburn comments, tolazoline might have a direct effect on the cerebral vasculature as well as inducing potentially harmful hypotension.

Horbar and colleagues (1983) confined themselves to the study of obstetric risk factors in 77 babies of birthweight 1200 grams or less. On univariate analysis gestation, labour lasting more than six hours and vaginal delivery were significant risk factors. On multivariate analysis no single factor showed statistical significance and Horbar proposed that it is a combination of adverse risk factors that is important.

Szymonowicz et al. (1984b) studied fifty infants of 1250 grams or less at birth in an attempt to discriminate the risk factors preceding haemorrhage. Again prematurity, respiratory distress and hypercapnia were significant and they confirmed Thorburn's observation that both pneumothorax and hypotension were important. They found bruising at birth to be a significant factor and took this to imply a difficult and traumatic delivery rather than a clotting disturbance. Indeed, coagulopathy was not significant in this study. In this context it is also interesting to note that the UCH workers had observed a relatively lower incidence of haemorrhage in their infants born by Caesarean section (Thorburn et al. 1982b). These babies, however, were significantly more mature and this makes it impossible to draw definite conclusions that a less traumatic birth was a factor. Szymonowicz also found a low pH on admission (which the group interpreted as representing perinatal asphyxia) to predispose to haemorrhage. On the other hand, neither subsequent metabolic acidosis nor sodium bicarbonate administration were significant risk factors. Finally tubocurare administration was important, possibly reflecting the sickest

infants with air leaks but as the authors pointed out there might be a more direct effect such as secondary hypercapnia or a primary action on cerebral vasculature. On multivariate analysis hyaline membrane disease was the most important preceding factor followed by hypercapnia and short gestation. They attempted to use the multivariate analysis to discriminate factors predisposing to GLH/IVH (22 infants) from those with parenchymal extension (8 babies). They found hypothermia on admission, low PaO2 : FiO2 ratio and severe bruising at birth to favour a larger bleed. These results must be interpreted with some caution as the numbers are small.

McDonald and colleagues (1984a) examined the antecedents to haemorrhage in fifty infants of 33 weeks gestation or less. Vaginal delivery (vertex or breech), prolonged labour and perinatal asphyxia (Apgar score of less than 5 at five minutes) were significant risk factors. The administration of colloid to treat hypotension was important but hypotension was not a significant risk factor in its own right. This is the only study to report antepartum haemorrhage as a significant factor in causing periventricular haemorrhage. Although 49 of the fifty babies showed respiratory distress and were ventilator dependent this did not reach statistical significance as an antecedent to haemorrhage and nor did hypercapnia, acidosis or pneumothorax. In a separate report based on the same infants they identified coagulation disturbance of various types as important (McDonald et al. 1984b). By demonstrating similar derangement of clotting in those with IVH on the initial scan and those without but who later suffered a bleed McDonald concluded that the haemorrhage was a sequel to the clotting problem and not vice-versa. McDonald's work is open to several criticisms. It is based on a small number of relatively mature babies - only twenty infants suffered haemorrhage during the first 72 hours which was the period they were studying. The number was further reduced by excluding the five with grade 1 haemorrhage from the statistical analysis. No multivariate analysis was done to identify independent risk factors. Finally, the samples for coagulation studies were take via indwelling catheters and this must offer a small risk of contamination with heparin to give erroneous results.

Through the conglomeration of risk factors for PVH the backbone of prematurity and respiratory complications is consistently recognised. Many risk factors which I found on multivariate analysis to predispose to PVH were similar to those previously reported by others. There was an

extremely strong association between prematurity and PVH; indeed this is not unexpected as the germinal matrix tends to involute with increasing gestation. The basic cause of PVH is rupture of the capillaries within the germinal matrix probably in response to acute fluctuations in cerebral blood flow. Mechanical ventilation, hypercapnia, acidosis and fluctuating blood pressure may predispose to these changes in cerebral blood flow. Minor bleeding in the presence of a clotting disorder may cause more extensive haemorrhage into the lateral ventricle. The suggestion that intrauterine growth retardation protects against haemorrhage probably reflects my policy of using birthweight as the criterion for entry. This would lead to inclusion of some small infants who would be "protected" from haemorrhage by their more advanced gestation.

Risk Factors for PVL.

There is considerably less data available concerning the risk factors predicting the onset of PVL based on ultrasound diagnosis. Prior to commencing my study no such reports had been published and subsequently there have only been three series reported (Sinha et al. 1985; Weindling et al. 1985a; Calvert et al. 1987).

Weindling and colleagues (1985a) examined the antecedents to haemorrhage and PVL in 86 preterm infants (1500 grams or below or less than 34 weeks gestation). Thirty four babies suffered PVH and the predisposing factors were hypoxia (both perinatal and subsequently), acidosis and hypercapnia. For PVL two variables reached statistical significance which were antepartum haemorrhage and hypoxia at birth. It is of note that all the infants with PVL required mechanical ventilation. The major drawback of this study is the small numbers for there were only 7 babies with PVL.

In the same year Sinha and coworkers (1985) reported on 219 infants of 32 weeks gestation or less. Haemorrhage occurred in 106 babies and echodense ischaemic lesions in 39; 27 babies had evidence of both lesions. Associated with haemorrhage were antepartum haemorrhage, perinatal asphyxia, hyaline membrane disease, mechanical ventilation, pneumothorax, recurrent apnoea, patent ductus arteriosus, septicaemia and seizures. The associations with ischaemia were identical except that hyaline membrane disease was not statistically significant. Some factors were significant only at the 5% level, notably antepartum haemorrhage and pneumothorax in relation to ischaemia. Another problem in interpretation

of the results is the failure to give definitions for some of the clinical factors studied. Although the authors propose hypotension as the final common pathway they do not include blood pressure measurements in their analysis. Sinha does not state whether the clinical events were studied only up to the time of scan abnormality but this seems unlikely as he comments that the group were not looking for a chronological relationship between clinical events and ischaemic damage. As with the early haemorrhage papers this makes interpretation more difficult and these can not be considered as predisposing factors to the lesions but merely associations.

Calvert et al. (1987) compared 15 infants with cystic PVL with 15 matched controls. Antepartum haemorrhage again reached statistical significance and so did hypocapnia (PaCO2 <3.3 kPa) and this will be further discussed in a later section. The duration of mechanical ventilation was significantly higher in the control infants. Seven of the infants with PVL were described as "poorly perfused" at birth (compared to none of the controls) but there was no documentation of blood pressure measurements.

The Role of Cerebral Perfusion.

Hypotension has been strongly implicated as a cause of periventricular leucomalacia with a failure of autoregulation resulting in cerebral ischaemia. Although it was not significant in my study, antepartum haemorrhage had proved important in all three of the earlier reports (Weindling et al. 1985a; Sinha et al. 1985; Calvert et al. 1987). Both Weindling and Calvert propose that APH results in decreased perfusion of the foetal brain and subsequent infarction. Presumably, therefore, similar mechanisms might operate postnatally. In newborn dogs severe hypotension induced either by exsanguination or administration of E. coli endotoxin was shown to produce a significant fall in the perfusion of the periventricular and occipital white matter (Young et al. 1982). Perfusion of the grey matter remained well preserved and Young proposed this as an explanation of the pathogenesis of periventricular leucomalacia. Although I regularly measured blood pressure in sick infants I was surprised to find, as Weindling et al. (1985a) had previously reported that there was no correlation between hypotension and PVL. It is of interest, however, that infants who developed haemorrhage showed a significantly shorter proportion of their time with systolic blood pressure less than 55 mmHg than infants without haemorrhage. Before dismissing blood

pressure as unimportant in the development of PVL, a study using direct and continuous blood pressure recordings would be valuable.

In a series of experiments on neonatal beagles Ment and colleagues showed that hypotension induced by blood-letting was associated with a fall in blood flow to the temporal and parietal white matter (Ment et al. 1985). In contrast the perfusion of the grey matter was comparitively well preserved. What is more they found that the same insult increased the local glucose utilisation of the white matter but not other areas. They propose that this uncoupling of cerebral blood flow and the metabolic requirement of the periventricular white matter may be an important factor in the aetiology of PVL. Anecdotally we have observed severe cystic PVL in one preterm infant (not included in this study) who suffered marked neonatal hypoglycaemia but no other apparent insult. Also we have seen extensive PVL develop in infants with a good central blood pressure at all times and Ment's attractive theory requires further evaluation.

The Role of Infection and Shock.

Faix and Donn (1985) reported 12 infants who suffered group B streptococcal septicaemia within 24 hours of birth. Seven infants were shocked and the four survivors subsequently developed PVL whereas all five who were not shocked escaped this complication. Only one of the babies had meningitis. They identified four other cases of PVL during the study period of whom three had suffered non-septic shock. It is interesting that four babies survived gram negative septicaemia and shock and did not develop PVL. Also there were 24 other survivors of non-septic shock who did not develop PVL. On this evidence shock would appear to be an important aetiological factor in PVL and if induced by group B streptococcal septicaemia the risk is particularly high.

Gram negative infection has been implicated in the aetiology of perinatal telencephalic leukoencephalopathy (PTL) which closely resembles early PVL. This condition was first described by Gilles and Murphy (1969) in a series of brains of infants of between 6 months of gestation and 4 months postnatal age. Indeed, this group claimed not to see it below 28 weeks of gestation and prematurity (gestation < 36 weeks) did not predispose to the condition (Leviton and Gilles 1973). Although macroscopic lesions might be seen in the form of opaque white spots in the white matter, the key to the diagnosis was microscopy showing a characteristic appearance of hypertrophic astrocytes and amphophilic

globules. They noted that the changes were often bilateral and areas undergoing myelination seemed the most vulnerable. Initially they felt that central cyanosis and lack of nutrition were important in the aetiology (Gilles and Murphy 1969) but subsequent work showed that post-mortem bacteraemia was the most significant factor. Twenty of the 41 babies with PTL had bacteraemia and in 85% the organism was gram negative (Leviton and Gilles 1973). The group pursued this finding by injecting E. Coli endotoxin into the peritoneal cavity of kittens and producing dose-related changes in the white matter consisting of astrogliosis and in some cases cystic lesions (Gilles et al. 1976). They could not produce these effects in adult cats. They subsequently produced similar changes in monkeys (Gilles et al. 1977). They noted that the distribution of the lesions resembled those described by Banker and Larroche (1962). Indeed, in a letter in 1981 this group used the term periventricular leukomalacia (Leviton and Gilles 1981). In a review article in 1984 they indicated that the necrotic foci of perinatal leukoencephalopathy usually represent PVL and it was in this group that prematurity was an important factor (Leviton and Gilles 1984). In the animals which they studied the circulation appeared to have been well maintained. Gilles and colleagues proposed that the endotoxin might have induced local areas of thrombosis and endothelial damage or that it might act at a cellular level to block oxidative phosphorylation. In my study infection did not appear as a significant risk factor. Twenty four babies developed septicaemia of whom six were in the prolonged flare group, three had cystic or precystic PVL and fifteen had no PVL.

Is Congenital Heart Disease Important?

Another factor implicated by the earlier autopsy studies was congenital heart disease. Banker and Larroche reported it in 13 of their 51 cases and they suggested it as one of the factors leading to the anoxia which was the basis of PVL (Banker and Larroche 1962). Three of de Reuck's 13 babies had congenital heart lesions (de Reuck et al. 1972) as did five of the 28 reported by Armstrong and Norman (1974). Interestingly four of the five had varying degrees of hypoplastic left heart which one might speculate as a cause of a poorly perfused brain. In my series five babies had congenital heart disease but none of these developed PVL or a prolonged flare.

The Role of the pCO2.

In my analysis hypercapnia (pCO2 > 7.0kPa) was a significant risk factor for PVL. This is contrary to Calvert's observation which is alluded to in an earlier section (Calvert et al. 1987). She found that a pCO2 < 3.3 kPa predisposed to PVL. This is an interesting finding in the light of studies relating pCO2 to cerebral blood flow. Hauge and colleagues studied six healthy young adults (Hauge et al. 1980). Using a pulsed ultrasound Doppler system they measured the blood flow velocity in the carotid and vertebral arteries whilst varying the alveolar pCO2 either by hyperventilating or by increasing the FiCO2 up to values of 8%. The blood flow velocity showed an almost linear relationship to pCO2 and was consistent in all individuals. At an alveolar pCO2 of 3 kPa it fell to about 45% of the resting value whilst a pCO2 of 7.5 kPa induced a level of around 160% of the resting value. Leahy et al. (1980) studied 12 infants of gestation below 34 weeks who were given 2-3% CO2 to breathe. Using venous occlusion plethysmography he observed a rise in the mean cerebral blood flow and estimated that the response was approximately twice that seen in the adult. The mean postnatal age was 8 days (oldest 24 days) and the most immature was 32 weeks gestation and this begs the question of an even greater effect in infants of extreme prematurity soon after birth. Using duplex Doppler ultrasound Levene and colleagues have recently studied nineteen ventilated infants of gestation 33 weeks or less (Levene et al. 1988). In a series of 45 studies they showed a highly significant relationship between a small rise in arterial pCO2 and increasing cerebral blood flow velocity. In the 21 infants assessed within 24 hours of birth the cerebral blood flow velocity rose by 44% for a 1 kPa rise in pCO2 and in the 20 infants examined after 24 hours the equivalent figure was 53%. In three studies there was no change in cerebral blood flow velocity with a rise in pCO2 and on seven occasions it actually fell.

In a clinical context Lou and coworkers reported 63 infants of <1350 grams birthweight all of whom were electively intubated and ventilated at birth (Lou et al. 1982). They found that the seven babies with IVH had significantly higher pCO2 values than the matched controls. Indeed, the latter group were relatively hypocapnic with pCO2 values often <25 mmHg. They proposed that hyperventilation at birth might prevent IVH, but added the rider that the safety of the technique needed to be established before such a policy could be widely adopted. Four years later this issue was again brought into question by Lou and his colleagues in

Copenhagen (Greisen et al. 1986). They compared eight infants with severe hypocapnia (at least one pCO2 value of less than 2.0 kPa) with eight matched controls whose pCO2 was consistently >3.3 kPa. In the former group there was only one IVH compared to six in the latter group. However, when seven infants from each group were assessed at age 18 months three of the severe hypocapnia group showed neurological abnormality - two with spastic diplegia and one dystonic. This compared to no handicap in the control group. Greisen advocates that hypocapnia may induce ischaemic damage (although the group make no comment on ultrasound evidence of PVL).

Why should I find hypercapnia to be important in causing PVL in contrast to Calvert and indeed also to what one might logically expect? I feel that two points should be made. As I have mentioned in a previous Chapter my definition of PVL includes some infants with venous infarction related to ipsilateral IVH. This association is, therefore, likely to influence the factors predisposing to PVL. As hypercapnia is a very important precursor to haemorrhage it is likely that it will also be related to PVL albeit to a lesser degree. Secondly, I cannot exclude hypocapnia as a precursor to PVL on the basis of this study as the infants were rendered normocapnic. This contrasts with the Copenhagen workers who aimed for moderate hypocapnia (pCO2 3.0 - 4.5 kPa) in the first 24 - 48 hours.

On the basis of current evidence, both from my study and the available literature it would seem pragmatic to maintain the pCO2 within the accepted range of normal. Both hyper- and hypocapnia appear to carry a risk of significant cerebral injury.

The Role of Hyperbilirubinaemia.

The significance of hyperbilirubinaemia is of interest. Unconjugated bilirubin may cross the blood-brain barrier, bind itself to membrane phospholipids and then enter the cells (Volpe 1981). Normally intracellular bilirubin is rendered non-toxic by a cytoplasmic binding protein called ligandin. Cerebral tissue is lacking in ligandin and this may predispose the brain to bilirubin induced damage. At a macroscopic level bilrubin staining is most often seen in the basal ganglia and the hippocampus. As Volpe points out and as Armstrong and Norman witnessed (Armstrong and Norman 1974) the periventricular white matter may show bilirubin staining. On electron microscopy of the brain of the Gunn rat (which shows a particular predilection to neonatal jaundice) Jew and Sandquist

showed microstructural changes such as vacuolation and myelin figures (Jew and Sandquist 1979). Although these changes were best seen in the cochlear nuclei and hippocampus they were also seen in some areas of the cortex. It is proposed that the disruption of mitochondrial function might induce certain biochemical sequelae. Oxidative phosphorylation and the citric acid cycle, both important in energy metabolism, might suffer and the effects could be devastating. Kernicterus may occur at much lower bilirubin levels in the preterm infant and especially those who are unwell for factors such as asphyxia and acidosis will facilitate the entry of bilirubin into the brain. Indeed, Keenan describes four sick preterm babies who showed kernicterus at post-mortem (Keenan et al. 1972). In two of them the peak recorded bilirubin level had been no more than 10.6 and 10.5 mg.% respectively. Hansen and Bratlid (1986) also identify the uncoupling of oxidative phosphorylation as an important mechanism of the neuronal damage as a sequel to hyperbilirubinaemia (although they do not recognise PVL within the spectrum of injuries). They agree that insults may be synergistic e.g. acidosis will decrease binding to albumin with a consequent rise in free (neurotoxic) bilirubin and hypercapnia and asphyxia will increase permeability of the blood-brain barrier and thus facilitate bilirubin entry. Hansen and Bratlid also make the point that duration of hyperbilirubinaemia may be important as well as the peak level. One might propose that the neurotoxic effects of bilirubin may be additive to those of other insults and that the periventricular area may be a vulnerable site in the preterm infant. The identification of hyperbilirubinaemia as a risk factor for PVL would support this. This observation has recently been confirmed by a Finnish study of 58 infants of birthweight less than 2000 grams or gestation below 34 weeks (Ikonen et al. 1988). They identified cystic PVL in five infants and the perinatal and neonatal events were compared with 12 control infants of matched gestation. The infants with PVL had a significantly higher level of mean serum total bilirubin in the early days of life. Only two other factors reached statistical significance and these were vaginal delivery and a higher mean pH in the first 72 hours in the PVL group. Exchange transfusion was performed in two of the five with PVL and three of the twelve controls. They propose that the unconjugated bilirubin crosses the blood-brain barrier, lodges in the periventricular area (amongst its other sites) and delayed clearance due to hypoperfusion allows it to perform its nefarious deeds. A final shred of evidence to support the theory of bilirubin toxicity is the follow up study of

Boggs et al. (1967). Assessing 23,000 children at age 8 months they found a positive relationship between the maximum bilirubin level in the neonatal period and subsequent mental and motor handicap, although they failed to expand on the pattern of motor deficit. They noted that low birthweight and low Apgar scores exacerbated the effects of the raised bilirubin level.

Other Points from This Study.

My study differed from the others by enrolling a larger number of very low birthweight infants, the prospective nature of the data collection and the multivariate regression analysis performed on the risk factors. Unlike the other studies I found ventilatory complications (pneumothorax and hypercapnia) to be independently associated with the diagnosis of PVL. Of the infants who underwent surgery and also developed PVL an abdominal operation for necrotising enterocolitis (NEC) was the commonest underlying reason. Necrotising enterocolitis has been associated with the late onset of PVL in some infants (de Vries et al. 1986) but in my study, NEC in its own right did not reach statistical significance as a risk factor. It is likely that the infants undergoing surgery were amongst the sickest babies and the most likely to develop cerebral insults.

There was an inverse relationship between anaemia and the development of both PVH and PVL. The reason for this is probably related to our policy of transfusing the sickest infants more frequently than less ill babies thereby preventing this high risk group from becoming anaemic. Those infants who were less ill were, therefore, allowed a lower concentration of haemoglobin and this is the group least likely to develop intracranial complications.

Comparing and Contrasting Haemorrhage and PVL.

In Chapter 5 I discussed how PVH and PVL commonly occur in the same infant and statistical analysis showed that they shared eight risk factors reaching significance on univariate analysis. It would appear that these lesions are most likely to occur in the sickest infants but it is of interest that although immaturity was very closely related to the frequency of haemorrhage, it was not associated with the onset of PVL. Although the risk of PVH reduces with increasing gestational age the infant's brain may remain susceptible to PVL for a longer period of time.

Recently de Vries et al. (1988) have compared the risk factors for large haemorrhage (grade 2b and 3) with those for cystic PVL. They found

that leucomalacia was significantly more common in the outborn babies and those delivered by emergency caeasarean section. The neonatal risk factors reaching statistical sigificance were similar in the two groups i.e. birth asphyxia, positive pressure ventilation, pneumothorax, NEC, hypotension, need for dopamine therapy, recurrent apnoea and patent ductus arteriosus. On logistic regression the independent risk factors for leucomalacia were emergency section, outborn and prolonged ventilation. De Vries proposed that the cause of both lesions was similar and that the sequel might reflect level of maturity for the mean gestation of the infants with haemorrhage was 28.2 weeks and of those with PVL was 30.1 weeks. This conclusion closely matches my findings.

Final Points.

A degree of caution should be exercised in regard to the interpretation of studies such as mine which look at predisposing risk factors to PVH and PVL. Firstly, because of the limitation of multiple significance testing which may produce spurious results and secondly it is possible that PVL is the result of a variety of quite disparate factors. Lumping them all together may well obscure some of the occasional but nevertheless important causal factors. There are babies in this study who sustained a dramatic event such as cardiac arrhythmia with hypotension and who developed PVL shortly afterwards (Shortland et al. 1987). It is possible also that imprecise methods for detecting some conditions such as foetal distress may produce a false negative result for this variable. Because these associations were rarely seen they may not have reached statistical significance in our cohort.

Finally our analysis shows that the risk factors for prolonged flare are similar to those for cystic and precystic PVL. This adds further weight to the hypothesis that prolonged flare is not an artefactual appearance but represents the milder end of the PVL spectrum.

Chapter 8

Concluding Comments

Periventricular leucomalacia is the major ischaemic lesion of the preterm brain for in the immature infant the cerebral circulation leaves vulnerable watershed areas in the periventricular white matter if the cerebral blood flow should be jeopardised in any way. Although recognised by the pathologists over a hundred years ago it is only in the last five years or so that we have been consistently able to study the lesion during life by the use of real-time ultrasound scanning. Following preliminary reports of a high incidence of handicap in the survivors of this lesion we decided to perform a prospective study which commenced in January 1984.

Using carefully defined definitions this prospective study has defined the incidence of cystic PVL (9.5%), precystic PVL (4%) and prolonged flare (12.5%) in a large cohort of consecutive infants of birthweight 1500 grams or less. The prolonged flare is likely to represent the milder end of the PVL spectrum. The range of ultrasound appearances of PVL was, therefore, seen in 52 babies representing an incidence of 26%. This is considerably higher than any previous report. We found parenchymal haemorrhage to be comparatively rare, occurring in only 8 of the 200 babies examined.

Our definitions were borne out by the pathological correlation in thirty of the babies who died with an accuracy for both haemorrhage and periventricular leucomalacia of 88%. Real-time ultrasound scanning appears an excellent method of identifying the entire spectrum of PVL lesions. It is of particular interest that apparently normal macroscopic brain appearances are echodense in the presence of microscopic calcification and gliosis. Both the specificity and sensitivity of ultrasound is high for the

diagnosis and exclusion of these lesions. The ultrasound discrimination between the various patterns of parenchymal lesion is a realistic proposition.

I attempted to identify the risk factors which might predispose to periventricular leucomalacia and these were pneumothorax, maximum bilirubin level, surgery and hypercapnia. Perhaps rather surprisingly in view of the likely ischaemic nature of the condition I could not demonstrate a link between hypotension and PVL.

Finally, we have reported the outcome in the babies from my study (Graham et al. 1987). Of the 158 survivors, one died at 14 months of age; 156 were assessed at 18 months corrected age with both neurological and Griffiths assessments. Severe handicap was classified as cerebral palsy, corrected DQ <71, hearing aids or visual impairment. Thirteen (8.3%) had severe handicap of whom twelve had cerebral palsy. Seventy seven (49.4%) had haemorrhage (3 parenchymal), 24 (15.4%) had prolonged flare and 13 (8.3%) had cystic PVL (11 associated with haemorrhage). Five with post-haemorrhagic ventricular dilatation needed shunts (3 associated with PVL). In 64 (41%) there was no ultrasound abnormality and cerebral palsy developed in two. No child with haemorrhage confined to the ventricles and without parenchymal flare or cysts developed severe handicap (all three with parenchymal haemorrhage had contralateral flare or cysts). Not surprisingly the four infants with spastic quadriplegia had the lowest median DQ which was 33 and the corresponding figures for spastic hemiplegia (4 infants) and spastic diplegia (4 infants) were 92.5 and 98.5 respectively. For comparison the figures for prolonged flare, any degree of haemorrhage and a normal scan were 109, 107 and 108 respectively. Of the thirteen with severe handicap five had a corrected DQ <70 (4 quadriplegics and 1 diplegic), one was cortically blind, six others had visual problems (mainly squints) and two were deaf. Of the 13 with cystic PVL eight developed cerebral palsy and five were entirely normal. Of the 24 with prolonged flare two developed cerebral palsy (one associated with a contralateral parenchymal haemorrhage). A consistently normal scan was associated with a normal outcome in 97% of cases. If cysts are present there is a 62% chance of cerebral palsy and in their absence 97% will be spared cerebral palsy at 18 months of age. For prolonged flare and haemorrhage the respective figures are 9% and 11% positive prediction and 92% and 95% negative prediction. A single cavity irrespective of size is not associated with severe cerebral palsy in any

infant, although one has mild cerebral palsy but was walking by the age of 18 months. Only one of the eight with more than one cyst was normal at follow up and occipital cysts carry a worse prognosis.

Several unanswered questions remain. What is the underlying aetiology and pathology of these parenchymal lesions? Is parenchymal haemorrhage an extension of bleeding from within the ventricle into the cerebral parenchyma or, as Rushton suggests, are all parenchymal haemorrhages primarily ischaemic i.e. a re-bleeding phenomenon (Rushton et al. 1985)? Although I have concentrated the earlier comments around the infants with PVL I do not wish to give the impression that this is a totally distinct lesion from PVH - indeed 25 of the babies with PVL and 11 of those with flares had associated haemorrhage. Almost certainly a second pattern of parenchymal lesion and resulting in PVL is that of venous infarction secondary to distension of a ventricle with blood and leading to obstruction of the terminal vein. Finally, the remaining babies with PVL suffer hypoxic-ischaemic insult as a sequel to arterial insufficiency and this may or may not be associated with haemorrhage; it accounts for cases of both cystic PVL and the lesser pattern of prolonged flare which our histological evidence (albeit limited) suggests to be due to microscopic calcification and gliosis. Hopefully studies using Doppler techniques may further clarify the role and importance of ischaemia in the various patterns of cerebral insult.

We need to explore ways of preventing the condition. With a larger cohort of infants it may be possible to identify other risk factors. However, our data clearly shows the association between respiratory conditions and PVL. The prevention of neither prematurity nor hyaline membrane disease appears imminent and so it behoves us to refine our respiratory management as best we can with a view to preventing hypercapnia and pneumothorax.

Finally, we need to pursue our follow-up studies at a later age. Obviously the more severe is the degree of handicap then the earlier it will declare itself. Cystic PVL is a good marker of severe handicap in 2/3 of the cases and this has shown itself by 18 months. It will be interesting to review the children with prolonged flare, for although only 2 of the 24 developed cerebral palsy, perhaps this may be a marker for more subtle neurodevelopmental problems - studies at about 5 years of age are needed to see if there is any correlation.

Appendix 1

The Categorical Data Recorded

Maternal.

Age

Cigarette smoking

Multiple pregnancy

Pre-eclampsia

Antepartum haemorrhage

Drugs in pregnancy

- antihypertensive agents
- others

Drugs in labour

- dexamethasone
- ritodrine
- opiate
- epidural
- general anaesthetic
- others

Plasma oestriol

High vaginal swab (HVS) culture

Prolonged rupture of membranes

> 24 hours

Foetal distress

abnormal cardiotocograph

meconium staining of the liquor

abnormal scalp blood pH

Placental condition

Mode of delivery

spontaneous vertex vaginal

vertex presentation, forceps

vertex presentation, ventouse

breech presentation

elective Caesarean section

emergency caesarean section

Place of birth

inborn

in utero transfer

postnatal transfer

Neonatal.

Sex

Race

caucasian

Indian subcontinent

other

Low Apgar score

< or = 5 at five minutes

Resuscitation at birth

endotracheal intubation

alkali administration

Intrauterine growth

birthweight

weight centile

Hypothermia

< or = 35 °C

Recurent apnoea and/or bradycardia

Respiratory support

head box oxygen

continuous positive airway pressure (CPAP)

mechanical ventilation

Respiratory variables

- maximum pressure
- maximum rate
- maximum inspired oxygen concentration
- duration of ventilation

Pneumothorax

Drugs

- sodium bicarbonate or THAM
- caffeine or aminophylline
- antibiotics
- indomethacin
- tolazoline
- dopamine
- anticonvulsants

Duration of TPN

Hypoglycaemia

- < 1 mMol/L.

Persistent ductus arteriosus

Arrythmia

tachycardia >/= 200/minute for three minutes or more

bradycardia </= 80/minute for three minutes or more

other ECG evidence of conduction disorder but normal rate

Congenital heart disease

Positive blood culture

Pneumonia

Necrotising enterocolitis

Surgery

ventriculo-peritoneal shunt

abdominal

PDA ligation

other

more than one operative procedure

Maximum bilirubin level

Exchange transfusion

Coagulation disorder

platelet count < 20000

clotting times 3x control values

Anaemia

haemoglobin < or = 10gm/L.

Transfusion with blood products

blood

plasma

Hypernatraemia

> 150 mMol/L.

Hyponatraemia

< 125 mMol/L.

Hyperkalaemia

> 8 mMol/L.

Hypocalcaemia

< 1.4 mMol/L.

Raised plasma creatinine

> 120 mMol/L.

Convulsion

Outcome

Appendix 2

Definitions of Statistical Terms

Accuracy : the proportion of hemispheres in which the correct positive or negative diagnosis was made by ultrasound.

$$\frac{\text{True positive} + \text{True negative}}{\text{Total number}}$$

Sensitivity : the proportion of hemispheres with a lesion at autopsy which was correctly identified on ultrasound.

$$\frac{\text{True positive}}{\text{True positive} + \text{false negative}}$$

Specificity : the proportion of hemispheres without a lesion which were correctly identified.

$$\frac{\text{True negative}}{\text{True negative} + \text{false positive}}$$

Each result is expressed as a per centage.

PATIENT

DATA

1.M 27 880 (40) Alive	SVD Inborn 8,8,8	8 days 14cm 80%	APH Hypothermia HMD Pneumonia Hypoglycaemia Transfusion x3 SBR 100 umol/L	Na bicarbonate Vitamin E Aminophylline
2.M 35 1060 (<3) Alive	LSCS Inborn 7,8,8	- - Air	Foetal distress (CTG) Hypothermia Hypoglycaemia SBR 231 umol/L	Nil
3.F 29 1300 (50) Alive	SVD Outborn 2,4,5	66 days 40cm 100%	Ruptured membranes for 7 weeks Hypothermia HMD Staphylococcal pneumonia Lung abscess Staph. aureus septicaemia Thrombocytopaenia Renal failure Arrythmias (SVT & bradycardia) Hypoglycaemia Hypernatraemia Hyponatraemia Hyperkalaemia Hypokalaemia Hypocalcaemia Transfusion x18 SBR 175 umol/L	Na bicarbonate THAM Morphine Pancuronium Frusemide Tolazoline Dopamine Calcium resonium Insulin Ca gluconate Caffeine
4.F 33 1410 (5) Alive	LSCS Inborn 4,8,8	- - 30%	PET SBR 170 umol/L	Nil
5.F 29 1410 (60) Alive	LSCS Inborn 6,7,8	6 days 20cm 80%	PET Foetal distress (CTG) HMD PDA Hypernatraemia Hyponatraemia Transfusion x1 SBR 103 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E Caffeine
6.F 26 870 (60) Alive	Vag. breech Inborn 5,8,8	3 days 14cm 25%	Recurrent apnoea PDA Hypoglycaemia Hyponatraemia Transfusion x2 SBR 150 umol/L	Na bicarbonate Indomethacin Vitamin E Aminophylline

7.28	9.35	5.42	-7	ND	**Normal**
7.15-7.52	*2.7-15.9*	*2.0-8.8*	*-14/+8*		
(53)	(53)	(53)	(53)		
ND	ND	ND	ND	ND	**Normal**
Pre-Haemorrhage					
7.15	5.59	9.17	-6	43	**IVH (3)**
6.84-7.36	*2.3-11.3*	*6.6-19.2*	*-21/+5*	*24-70*	**Lt cystic PVL (5)**
(26)	(26)	(26)	(26)	(23)	**Lt subdural haem (6)**
					Prog vent dil
Pre-PVL					
7.23	7.79	7.88	-4	66	
6.84-7.44	*2.3-17.0*	*4.1-19.2*	*-21/+7*	*24-74*	
(45)	(45)	(45)	(45)	(37)	
7.34	10.35	5.70	-5	54	**Normal**
7.28-7.39	*10.2-10.5*	*4.4-7.0*	--	*30-70*	
(2)	(2)	(2)	(1)	(11)	
7.27	8.51	5.57	-8	51	**Normal**
7.15-7.46	*2.4-17.6*	*2.8-8.9*	*-12/-2*	*50-52*	
(39)	(39)	(39)	(39)	(3)	
7.28	8.34	4.81	-9	ND	**Small haem (16)**
7.17-7.42	*5.7-12.1*	*3.2-6.5*	*-14/-1*		
(23)	(17)	(24)	(22)		

7.F 29 970 (20) Alive	LSCS Inborn (IUT) 8,8,8	42 days 16cm 80%	Hypertensive throughout pregnancy Hypothermia HMD Lt pneumothorax (3) Left PIE Multiple left pleurotomies Pneumonia Staph. epiderimidis septicaemia Hyponatraemia Transfusion x5 SBR 150 umol/L	Na bicarbonate Frusemide Vitamin E Atrovent Aminophylline
8.F 27 830 (50) Alive	SVD Outborn 2,8,6	18 days 18cm 60%	HMD PDA Hypocalcaemia Transfusion x4 SBR 127 umol/L	Na bicarbonate Indomethacin Vitamin E Aminophylline
9.F 27 980 (55) Died	SVD Outborn 8,8,8	8 days 40cm 100%	APH Foetal distress (CTG) Hypothermia HMD Lt pneumothorax (2) Rt pneumothorax (2) Arrythmia (variable bradycardia and tachycardia) Staph. epidermidis septicaemia Strep. faecalis septicaemia Hyponatraemia Hyperkalaemia Hypocalcaemia Persistent metabolic acidosis Transfusion x2 SBR 175 umol/L	Na bicarbonate THAM Pancuronium Frusemide Tolazoline Dopamine Insulin Ca gluconate
10.F 27 950 (50) Alive	Vag. breech Inborn 7,8,8	50 day 25cm 100%	HMD Lt pneumothorax (2) Pneumonia Arrythmia (broad complex bradycardia & VT) PDA Hyponatraemia Hyperkalaemia Hypocalcaemia NEC Ileostomy Transfusion x9 SBR 98 umol/L	Na bicarbonate Morphine Frusemide Indomethacin Tolazoline Dopamine Vitamin E Atrovent Loperamide Ca gluconate Aminophylline

7.26	7.94	6.34	-6	67	**Bilat prolonged flare (31)**
6.97-7.65	*4.3-17.3*	*2.4-14.2*	*-17/+8*	*41-86*	
(122)	(108)	(120)	(120)	(29)	

7.36	6.75	4.93	-4	ND	**IVH (1)**
7.27-7.43	*5.2-9.2*	*3.6-5.9*	*-7/-2*		**Non-prog vent dil**
(4)	(4)	(4)	(4)		

Pre-Haemorrhage					
7.25	7.66	6.24	-6	43	**IVH (4)**
7.06-7.36	*1.8-22.1*	*4.3-9.6*	*-17/-1*	*30-56*	**Lt echodense PVL (5)**
(48)	(48)	(48)	(48)	(31)	
Pre-PVL					
7.26	7.95	6.13	-6	44	
7.06-7.38	*1.8-22.1*	*4.3-9.6*	*-17/0*	*30-56*	
(53)	(53)	(53)	(53)	(36)	

Pre-Haemorrhage					
7.17	7.25	7.49	-10	56	**IVH (2)**
6.93-7.32	*5.0-10.8*	*4.7-13.9*	*-13/-4*	*26-86*	**Bilat prolonged flare (7)**
(15)	(15)	(15)	(14)	(31)	
Pre-PVL					
7.28	8.87	5.44	-8	58	
6.93-7.50	*4.9-19.7*	*2.4-13.9*	*-19/+5*	*26-99*	
(44)	(44)	(44)	(43)	(112)	

11.F 31 1470 (30) Alive	Vag. breech Inborn 5,8,8	- - Air	SBR 145 umol/L	Nil
12.M 36 1500 (<3) Alive	LSCS Inborn (IUT) 8,8,8	- - Air	PET Foetal distress (CTG) Hypoglycaemia Convulsion Polycythaemia SBR 223 umol/L	Nil
13.M 27 1100 (85) Died	SVD Inborn 2,7,8	15 hours 30cm 95%	H influenzae septicaemia Pneumonia Hyponatraemia	THAM Pancuronium Tolazoline Dopamine Ca gluconate
14.M 30 880 (8) Alive	LSCS Outborn 3,1,8	6 days 20cm 60%	Eclamptic convulsion Hypothermia HMD PDA Recurrent apnoea Transfusion x4 SBR 121 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E Cimetidine Aminophylline
15.F 32 1500 (15) Alive	LSCS Inborn (IUT) 8,8,8	- - Air	Triplet 2 SBR 131 umol/L	Nil
16.F 30 1400 (50) Alive	SVD Inborn 1,8,8	- - 55%	Hypoglycaemia SBR 220 umol/L	Nil
17.F 27 980 (50) Died	LSCS Inborn (IUT) 3,2,8	9 days 18cm 50%	APH Hypothermia HMD PDA Persistent metabolic acidosis E Coli septicaemia NEC Seizures Hyponatraemia Hyperkalaemia Transfusion x3 SBR 116 umol/L	Na bicarbonate Morphine Frusemide Indomethacin Dopamine Phenobarbitone Aminophylline

ND	ND	ND	ND	ND	**Normal**
ND	ND	ND	ND	ND	**Normal**
7.26 *7.11-7.36* (8)	5.03 *1.7-8.7* (8)	5.08 *4.0-6.7* (8)	-9 *-13/-6* (8)	44 *28-60* (7)	**IVH (1)**
7.29 *7.14-7.57* (54)	7.74 *4.1-16.0* (47)	5.72 *1.8-11.0* (53)	-5 *-18/+10* (53)	ND	**Normal**
ND	ND	ND	ND	ND	**Normal**
7.36 *7.29-7.46* (5)	8.12 *5.6-13.2* (5)	4.06 *3.1-5.1* (5)	-8 *-10/-1* (5)	55 *48-60* (6)	**IVH (4)**
7.26 *6.87-7.40* (20)	8.87 *4.4-11.3* (20)	4.44 *2.7-10.3* (20)	-12 *-21/-5* (20)	63 *37-82* (25)	**Rt parench haem (5)** **Prog vent dil**

18.M 27 900 (40) Alive	SVD Inborn 8,8,8	24 days 24cm 85%	APH Hypothermia HMD Recurrent apnoea PDA Staph. epidermidis septicaemia Thrombocytopaenia Arrythmia (SVT & bradycardia) Hypernatraemia Hyponatraemia Hyperkalaemia Transfusion x8 SBR 170 umol/L	Na bicarbonate Frusemide Indomethacin Caffeine
19.F 29 1380 (55) Alive	LSCS Inborn (IUT) 6,8,8	- - 40%	Twin 1 Polycythaemia Partial plasma exchange SBR 180 umol/L	Caffeine
20.F 29 900 (10) Died	LSCS Inborn (IUT) 2,7,8	1 day 22cm 50%	Twin 2 Foetal distress (CTG) Hypothermia Group B Strep. septicaemia Hypoglycaemia Transfusion x2	Na bicarbonate THAM Frusemide
21.M 26 890 (70) Died	Vag. breech Outborn 1,3,5	2 days 20cm 100%	Gestational diabetes Hypothermia HMD Lt pneumothorax (1) Rt pneumothorax (1) Hypernatraemia Hyperkalaemia Convulsions Transfusion x1 SBR 92 umol/L	Na bicarbonate Tolazoline Dopamine Phenobarbitone
22.M 34 1400 (<3) Alive	LSCS Inborn 8,8,8	- - Air	Gestational diabetes Hypoglycaemia	Nil
23.M 28 950 (30) Alive	Vag. breech Outborn 3,7,8	5 days 18cm 100%	Twin 2 (twin 1 stillborn) HMD Pneumonia Hyponatraemia Transfusion x2 SBR 151 umol/L	Na bicarbonate Vitamin E Aminophylline
24.M 27 1480 (>97) Alive	SVD Inborn (IUT) 4,8,8	3 hours 16cm 35%	APH SBR 99 umol/L	Vitamin E Aminophylline

7.28 *7.12-7.45* (103)	6.84 *2.3-24.0* (103)	7.16 *3.0-12.8* (103)	-2 *-10/+7* (101)	62 *30-82* (67)	**Small haem (56)**
7.37 *7.27-7.45* (7)	13.79 *4.1-31.3* (7)	5.09 *3.8-6.5* (7)	-3 *-6/0* (7)	76 *52-90* (11)	**Normal**
7.32 *7.20-7.53* (6)	11.78 *3.8-20.4* (6)	4.92 *3.1-7.9* (6)	-7 *-12/-1* (6)	46 *35-60* (8)	**IVH (2)**
7.16 *7.03-7.24* (7)	5.88 *4.4-10.5* (6)	5.17 *4.2-6.0* (7)	-14 *-22/-9* (7)	44 *29-64* (32)	**IVH (2)**
7.35 ---- (1)	12.00 ----- (1)	4.70 ---- (1)	-4 -- (1)	ND	**Normal**
7.31 *7.17-7.46* (38)	9.99 *3.7-16.5* (39)	4.69 *2.7-8.2* (39)	-8 *-16/+3* (39)	ND	**Normal**
7.36 *7.30-7.40* (10)	8.81 *6.9-11.3* (10)	4.19 *2.5-5.7* (10)	-6 *-13/+2* (10)	ND	**Normal**

25.M 30 1420 (45) Alive	SVD Inborn (IUT) 7,8,8	- - 40%	Foetal distress (CTG) SBR 170 umol/L	Caffeine
26.F 35 1400 (<3) Alive	SVD Outborn 8,8,8	- - Air	Polycythaemia Partial plasma exchange	Nil
27.M 28 705 (<3) Died	LSCS Outborn 1,4,8	10 days 20cm 65%	PET APH Wilson-Mikity PDA Pneumonia Milk aspiration Klebsiella septicaemia Hypoglycaemia Hyponatraemia Hyperkalaemia Hypocalcaemia Renal failure Liver failure Clotting disorder Exchange transfusion Transfusion x6 SBR 256 umol/L	Na bicarbonate Frusemide Spironolactone Vitamin E Aminophylline
28.M 26 920 (75) Alive	SVD Outborn 6,8,8	28 days 16cm 45%	Foetal distress (meconium) HMD Recurrent apnoea PDA Arrythmia (ventricular ectopics) E coli septicaemia Hyponatraemia Transfusion x4 SBR 150 umol/L	Na bicarbonate Indomethacin Vitamin E Aminophylline
29.F 26 660 (10) Alive	SVD Inborn Not done	- - 40%	Hypothermia Recurrent apnoea Transfusion x4 SBR 128 umol/L	Na bicarbonate Frusemide Vitamin E Aminophylline
30.M 29 1260 (50) Died	Vag. breech Outborn 3,6,8	15 days 34cm 100%	APH Hypothermia HMD Lt pneumothorax (2) Rt pneumothorax (2) PDA Arrythmia (profound bradycardia) Renal failure Hypoglycaemia Transfusion x4 SBR 210 umol/L	Na bicarbonate THAM Morphine Pancuronium Frusemide Indomethacin Dopamine Ca gluconate

7.34 *7.32-7.37* (3)	6.27 *4.4-8.9* (3)	5.27 *5.0-5.7* (3)	-4 *-5/-3* (3)	54 *46-62* (2)	**Small haem (2)**
ND	ND	ND	ND	ND	**Normal**
7.35 *7.12-7.48* (10)	8.19 *5.0-16.1* (8)	4.33 *2.9-5.6* (10)	-7 *-17/+1* (10)	ND	**Small haem (6)**
7.32 *7.06-7.50* (70)	6.47 *3.1-14.7* (65)	6.41 *3.0-9.1* (69)	-1 *-18/+17* (70)	ND	**Normal**
7.35 *7.31-7.38* (2)	4.70 --- (1)	6.10 *5.8-6.4* (2)	-1 *-2/+1* (2)	ND	**Small haem (2)**
Pre-Haemorrhage = Pre-PVL					
7.20 *6.89-7.36* (26)	6.16 *2.0-15.9* (25)	7.17 *5.2-11.6* (25)	-7 *-16/+3* (25)	44 *36-50* (8)	**IVH (2)** **Bilat cystic PVL (2)** **Prog vent dil**

31.M 36 1440 (<30) Alive	LSCS Inborn 6,8,8	- - Air	PET Foetal distress (CTG) Hypoglycaemia	Nil
32.M 30 1500 (50) Died	LSCS Inborn 4,8,8	4 days 40cm 100%	PET HMD PDA E coli septicaemia Pneumonia Hypoglycaemia Transfusion x1 SBR 124 umol/L	Na bicarbonate Surfactant Pancuronium Frusemide Tolazoline Dopamine
33.F 29 1350 (60) Alive	Forceps vertex Outborn 5,6,8	- - Air	Twin 1 Recurrent apnoea PDA SBR 158 umol/L	Vitamin E Aminophylline
34.M 32 650 (<3) Died	LSCS Inborn 7,8,8	2 days 16cm 65%	Oligohydramnios Foetal distress (CTG) Hypothermia Poor respiratory drive Fallot's tetralogy Hypoglycaemia SBR 103 umol/L	Na bicarbonate
35.M 26 960 (85) Died	Vag. breech Inborn 7,8,8	11 hours 26cm 90%	Hypothermia HMD Lt pneumothorax (1) Rt pneumothorax (1) Transfusion x1	Nil
36.F 25 740 (65) Died	Vag. breech Born at home ND,ND,ND	2 days 26cm 100%	Hypothermia HMD Rt pneumothorax (2) Hypoglycaemia Hyperkalaemia Transfusion x1 SBR 155 umol/L	THAM Morphine Frusemide Tolazoline Ca gluconate
37.F 28 980 (40) Alive	LSCS Inborn 2,8,8	1 day 16cm 35%	APH Foetal distress (CTG) HMD Recurrent apnoea Staph. epidermidis septicaemia Benign neonatal myoclonus Hypoglycaemia Transfusion x1 SBR 175 umol/L	Frusemide Caffeine

ND	ND	ND	ND	ND	Normal
Pre-Haemorrhage					
7.16	8.44	6.99	-9	56	IVH (3)
6.86-7.31	*3.0-14.5*	*4.5-12.0*	*-25/0*	*46-78*	Bilat cystic PVL
(19)	(18)	(19)	(18)	(18)	(scan/PM; died D6)
Pre-PVL					
7.17	7.98	6.31	-11	46	
6.86-7.39	*3.0-14.5*	*3.4-12.0*	*-26/0*	*25-78*	
(35)	(33)	(35)	(34)	(58)	
ND	ND	ND	ND	ND	Small haem (4)
7.15	6.03	5.54	-14	63	No haem or PVL
6.87-7.33	*3.2-8.4*	*3.4-8.3*	*-23/-10*	*54-73*	Agenesis corp call
(15)	(15)	(14)	(15)	(3)	Intravent adhesions
ND	ND	ND	ND	42	Normal
				40-44	
				(4)	
Pre-Haemorrhage					
7.26	7.39	5.13	-9	40	IVH (1)
7.01-7.54	*3.6-14.5*	*3.2-10.4*	*-16/-2*	*30-62*	Lt echodense PVL (2)
(14)	(14)	(14)	(14)	(18)	
Pre-PVL					
7.26	7.14	5.06	-9	39	
7.01-7.54	*3.6-14.5*	*3.2-10.4*	*-16/-2*	*24-62*	
(16)	(16)	(16)	(16)	(20)	
7.35	9.37	4.91	-5	51	Small haem (1)
7.28-7.40	*5.2-13.3*	*3.9-6.2*	*-7/-2*	*46-56*	
(7)	(7)	(7)	(7)	(6)	

38.F 29 1380 (55) Died	Vag. breech Inborn 4,8,8	1 hour ND 30%	Cebocephaly Poor respiratory effort Lt pneumothorax (1)	Nil
39.M 30 1360 (40) Alive	SVD Inborn 8,8,8	- - 30%	APH 14 days ruptured membranes SBR 180 umol/L	Nil
40.F 31 1240 (10) Alive	LSCS Inborn 3,7,8	- - 80%	Foetal distress (meconium) Twin 1 Hypoglycaemia SBR 205 umol/L	Nil
41.F 31 1400 (30) Alive	LSCS Inborn 2,2,5	6 days 38cm 100%	Twin 2 HMD Cardiac failure (cause uncertain) Hypoglycaemia Hypocalcaemia SBR 195 umol/L	Na bicarbonate Pancuronium Frusemide Caffeine
42.F 26 860 (60) Alive	SVD Outborn 8,8,8	7 days 16cm 50%	Twin 1 Hypothermia PDA Intestinal obstruction (?cause) Ileostomy Thrombocytopaenia Hyponatraemia Hyperkalaemia Transfusion x3 SBR 108 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E
43.M 26 1000 (95) Died	Vag. breech Outborn 2,6,8	20 days 36cm 100%	Twin 2 Hypothermia HMD Rt pneumothorax (4) PDA Ileal perforation Ileostomy Convulsions Clotting disorder Hypoglycaemia Hyponatraemia Hypocalcaemia Transfusion x5 SBR 238 umol/L	Na bicarbonate Morphine Tolazoline Dopamine Phenobarbitone Vitamin E Atrovent Isosorbide
44.M 33 1250 (3) Alive	LSCS Inborn 8,8,8	- - 35%	Twin 2 Foetal distress (CTG) Transient tachypnoea SBR 182 umol/L	Vitamin E

ND	ND	ND	ND	ND	**Holoprosencephaly**
7.32	13.80	5.20	-5	80	**IVH (1)**
----	-----	----	--	*60-99*	
(1)	(1)	(1)	(1)	(2)	
7.28	14.10	5.80	-1	50	**Normal**
----	-----	----	--	*40-66*	
(1)	(1)	(1)	(1)	(4)	
7.34	8.82	6.08	-1	65	**Normal**
7.24-7.57	*2.1-15.7*	*3.1-7.6*	*-7/+18*	*52-80*	
(63)	(63)	(63)	(63)	(35)	
Pre-Haemorrhage					
7.35	8.90	4.57	-6	ND	**IVH (3)**
7.27-7.40	*6.2-12.5*	*3.6-5.6*	*-8/-5*		**Bilat cystic PVL (6)**
(3)	(3)	(3)	(3)		
Pre-PVL					
7.29	9.99	4.15	-11	ND	
6.77-7.42	*6.0-14.0*	*2.8-5.9*	*-30/-5*		
(11)	(10)	(11)	(11)		
Pre-Haemorrhage					
7.17	7.71	6.65	-10	63	**Bilat parench haem (3)**
6.99-7.26	*4.5-13.6*	*4.8-9.1*	*-20/-1*	*37-96*	**Rt cystic PVL (13)**
(15)	(15)	(15)	(15)	(27)	**Prog vent dil**
Pre-PVL					
7.26	8.26	5.79	-7	78	
6.90-7.50	*4.4-21.0*	*2.3-12.3*	*-20/+3*	*37-99*	
(60)	(60)	(60)	(60)	(181)	
7.41	8.08	4.26	-3	ND	**Normal**
7.30-7.50	*5.9-13.6*	*3.1-5.6*	*-9/0*		
(5)	(5)	(5)	(5)		

45.M 24 780 (95) Died	SVD Inborn 3,7,8	1 day 20cm 95%	Hypothermia HMD Hyponatraemia Transfusion x1	Na bicarbonate Dopamine
46.M 29 1480 (70) Died	SVD Inborn 4,8,8	9 days 20cm 60%	Foetal distress (CTG) HMD Pneumonia PDA E coli septicaemia Meningitis Convulsions Thrombocytopaenia Hypoglycaemia Hypernatraemia Hyponatraemia Transfusion x2 SBR 188 umol/L	THAM Frusemide Dopamine Isoprenaline Phenobarbitone Caffeine
47.M 30 1450 (50) Alive	SVD Inborn 8,8,8	- - Air	SBR 196 umol/L	Vitamin E
48.M 30 1200 (25) Alive	Forceps vertex Inborn 8,8,8	- - Air	E coli urinary infection Glucose-6-Phosphate Dehydrogenase deficiency SBR 191 umol/L	Vitamin E
49.F 27 1080 (80) Alive	SVD Born at home 7,8,8	12 days 20cm 32%	Hypothermia Recurrent apnoea PDA Hyponatraemia Transfusion x5 SBR 170 umol/L	Frusemide Indomethacin Doxapram Caffeine
50.M 32 1200 (5) Alive	LSCS Outborn 8,8,8	2 days 24cm 60%	Polyhydramnios PET HMD SBR 156 umol/L	Vitamin E
51.M 29 1240 (45) Alive	SVD Inborn 1,8,8	24 days 32cm 85%	PET Twin 1 HMD Lt pneumothorax (2) Rt pneumothorax (2) Pneumonia PDA Transfusion x7 SBR 220 umol/L	Morphine Frusemide Caffeine

7.35 *7.18-7.43* (10)	12.1 *3.9-26.6* (10)	4.63 *3.6-5.8* (10)	-6 *-12/-1* (10)	43 *30-70* (9)	Normal
ND	ND	ND	ND	58 *44-70* (7)	IVH (2)
ND	ND	ND	ND	ND	Normal
7.39 ---- (1)	11.80 ---- (1)	4.70 --- (1)	00 -- (1)	ND	No haem or PVL Intravent adhesions
7.35 *7.18-7.53* (71)	6.89 *3.4-18.9* (69)	6.40 *2.9-11.3* (71)	00 *-9/+4* (71)	72 *43-92* (59)	Normal
7.32 *7.18-7.47* (15)	7.87 *2.8-17.7* (15)	5.96 *2.7-8.8* (15)	-3 *-13/+4* (15)	ND	Normal
Pre-Haemorrhage 7.24 *7.19-7.35* (17)	8.86 *4.5-12.9* (17)	6.52 *4.5-7.9* (17)	-6 *-9/-3* (17)	58 *32-72* (11)	IVH (2) Bilat prolonged flare (15)
Pre-PVL 7.27 *7.10-7.40* (87)	9.11 *4.2-23.4* (87)	6.02 *3.7-8.5* (87)	-6 *-10/-1* (87)	70 *32-99* (52)	

52.M 29 1050 (30) Alive	SVD Inborn 7,8,8	15 days 26cm 80%	PET Twin 2 HMD Lt pneumothorax (2) Rt pneumothorax (2) Pneumonia Hyponatraemia Transfusion x7 SBR 170 umol/L	Na bicarbonate THAM Morphine Frusemide Caffeine
53.M 28 1390 (80) Alive	SVD Outborn 6,8,8	7 days 26cm 100%	Hypothermia HMD PDA Recurrent apnoea Strep. faecalis septicaemia Hypernatraemia Transfusion x5 SBR 210 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E Aminophylline
54.F 32 1340 (10) Alive	Vag. breech Inborn 5,8,8	- - 40%	Hyperkalaemia SBR 190 umol/L	Caffeine
55.F 35 1300 (<3) Alive	Vag. breech Inborn 6,8,8	- - Air	PET Twin 2	Nil
56.F 28 1280 (70) Alive	SVD Inborn 4,8,8	3 days 16cm 35%	APH Poor respiratory drive Transfusion x1 SBR 195 umol/L	Vitamin E Aminophylline
57.F 28 1150 (60) Alive	SVD Inborn 4,ND,ND	6 hours 14cm 75%	Exchange transfusion SBR 200 umol/L	Vitamin E
58.F 29 1320 (55) Died	SVD Born in ambulance 3,6,8	6 days 26cm 75%	Hypothermia HMD Abnormal clotting profile Convulsions Persisting metabolic acidosis Transfusion x1 SBR 235 umol/L	Na bicarbonate THAM Morphine Pancuronium Frusemide Dopamine Phenobarbitone
59.M 32 1440 (10) Alive	SVD Inborn 8,8,8	- - 30%	Hypoglycaemia Hyperkalaemia SBR 185 umol/L	Caffeine

Pre-Haemorrhage					
7.24	9.45	6.47	-6	62	**IVH (3)**
7.16-7.30	*4.5-21.4*	*4.7-8.8*	*-9/-2*	*46-74*	**Bilat prolonged**
(22)	(22)	(22)	(22)	(15)	**flare (11)**
Pre-PVL					
7.28	10.74	5.56	-7	70	
7.16-7.48	*4.5-26.2*	*3.0-8.8*	*-12/-2*	*46-92*	
(58)	(58)	(58)	(58)	(36)	
7.32	8.84	5.73	-4	ND	**IVH (5)**
6.81-7.58	*3.4-14.9*	*3.0-11.5*	*-24/+6*		
(25)	(25)	(24)	(25)		
7.42	10.90	4.30	-3	60	**Normal**
----	-----	----	--	*50-72*	
(1)	(1)	(1)	(1)	(6)	
ND	ND	ND	ND	ND	**Normal**
7.36	10.53	4.99	-1	ND	**Bilat prolonged**
7.27-7.50	*7.1-15.0*	*3.9-6.1*	*-4/+6*		**flare (3)**
(10)	(10)	(10)	(10)		
7.31	8.42	4.27	-9	ND	**Small haem (2)**
7.11-7.42	*6.0-12.8*	*2.9-6.9*	*-15/+2*		
(9)	(9)	(9)	(9)		
Pre-Haemorrhage					
7.29	10.51	5.91	-7	52	**IVH (2)**
7.00-7.50	*4.5-24.0*	*2.9-14.1*	*-12/-4*	*44-59*	**Bilat echodense**
(18)	(18)	(18)	(17)	(11)	**PVL (6)**
Pre-PVL					
7.26	11.40	5.50	-8	53	
7.00-7.50	*4.1-24.0*	*2.9-14.1*	*-18/+2*	*30-94*	
(43)	(43)	(43)	(42)	(35)	
ND	ND	ND	ND	ND	**Bilat cystic PVL (3)**

60.F 26 910 (70) Alive	Vag. breech Inborn 5,8,8	10 days 16cm 55%	APH Hypothermia HMD PDA Recurrent apnoea DIC Arrythmia (bradycardia & VT) Hyperkalaemia Ventriculo-peritoneal shunt Transfusion x5 SBR 152 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E Calcium resonium Isosorbide Aminophylline
61.F 31 1020 (5) Alive	LSCS Inborn 8,8,8	6 days 22cm 60%	HMD Recurrent apnoea Staph. aureus septicaemia Hypoglycaemia SBR 195 umol/L	Morphine Caffeine
62.M 26 1020 (95) Alive	SVD Inborn (IUT) 6,8,8	14 days 18cm 70%	Hypothermia HMD Recurrent apnoea Staph. epidermidis septicaemia Hypoglycaemia Hypokalaemia Transfusion x4 SBR 177 umol/L	Frusemide Vitamin E Atrovent Naloxone Aminophylline
63.F 29 1220 (50) Alive	LSCS Outborn 7,8,8	6 days 22cm 90%	PET Foetal distress (CTG) HMD Lt pneumothorax (3) Convulsion Transfusion x2 SBR 95 umol/L	Morphine Frusemide Phenobarbitone Vitamin E
64.M 32 1260 (8) Alive	LSCS Inborn 2,7,8	4 days 22cm 80%	PET APH Foetal distress (CTG) Hypothermia HMD Recurrent apnoea Staph. epidermidis septicaemia E coli UTI E coli septicaemia Transfusion x3 SBR 193 umol/L	Frusemide Vitamin E Aminophylline
65.M 31 1330 (20) Alive	LSCS Inborn 8,8,8	- - Air	PET APH SBR 143 umol/L	Nil

7.25 *6.91-7.44* (20)	9.01 *4.5-14.4* (21)	4.89 *3.3-8.2* (21)	-7 *-19/+5* (20)	59 *31-96* (38)	**IVH (3)** **Prog vent dil**
7.32 *7.24-7.45* (35)	7.40 *2.6-20.4* (35)	6.01 *3.7-7.8* (35)	-3 *-8/+4* (35)	67 *56-80* (24)	**Bilat prolonged flare (2)**
7.43 *7.34-7.58* (9)	9.88 *5.0-17.6* (9)	4.33 *3.1-5.9* (9)	-3 *-6/+1* (9)	ND	**Small haem (2)**
7.32 *7.20-7.50* (27)	7.71 *4.6-12.1* (27)	5.51 *3.2-7.7* (27)	-5 *-10/0* (26)	ND	**Small haem (8)**
7.33 *7.20-7.45* (31)	9.52 *3.7-17.7* (31)	5.15 *3.0-6.9* (31)	-5 *-12/+7* (31)	ND	**Normal**
ND	ND	ND	ND	ND	**Normal**

66.M 27 1170 (97) Died	Vag. breech Outborn 5,5,4	47 days 27cm 100%	APH Foetal distress (CTG) Hypothermia HMD Rt pneumothorax (2) Pneumomediastinum PDA NEC Ileostomy Convulsions Hypocalcaemia Hypokalaemia Exchange transfusion Transfusion x9 SBR 234 umol/L	Na bicarbonate Morphine Frusemide Indomethacin Tolazoline Dopamine Vitamin E Narcan
67.F 26 740 (30) Died	Vag. breech Inborn (IUT) 1,5,8	14 days 32cm 100%	APH Hypothermia HMD PIE PDA Hypernatraemia Hyperkalaemia Transfusion x4 SBR 111 umol/L	Na bicarbonate Diamorphine Frusemide Indomethacin Tolazoline Vitamin E
68.M 31 1330 (20) Alive	SVD Outborn 7,8,8	3 days 20cm 50%	HMD PDA Hypocalcaemia SBR 185 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E
69.M 33 1350 (5) Alive	LSCS Inborn 7,8,8	- - Air	PET Foetal distress (CTG) SBR 274 umol/L	Nil
70.M 27 800 (20) Died	LSCS Inborn (IUT) 8,8,8	3 days 26cm 100%	PET Foetal distress (CTG) HMD Hypoglycaemia Transfusion x1 SBR 117 umol/L	Na bicarbonate Frusemide Tolazoline Dopamine Vitamin E
71.F 30 1320 (35) Alive	SVD Inborn (IUT) 8,8,8	- - 25%	Clotting disorder (?cause) Gut haemorrhage Transfusion x1 SBR 193 umol/L	Cimetidine Aminophylline

Pre-Haemorrhage					
7.29	8.05	5.42	-6	56	**IVH (3)**
7.03-7.41	*2.3-18.2*	*3.3-7.6*	*-13/+1*	*46-69*	**Bilat cystic PVL (7)**
(20)	(20)	(20)	(20)	(47)	**Non-prog vent dil**
Pre-PVL					
7.33	9.11	5.20	-5	54	
7.03-7.60	*2.3-18.2*	*2.9-9.5*	*-14/+5*	*40-86*	
(41)	(41)	(41)	(41)	(141)	
7.28	7.15	5.75	-6	53	**Normal**
7.01-7.71	*2.6-14.3*	*2.2-11.5*	*-20/+10*	*35-81*	
(65)	(65)	(64)	(63)	(37)	
7.35	8.54	5.10	-5	ND	**Small haem (6)**
7.00-7.50	*4.3-16.0*	*3.2-9.2*	*-21/+1*		
(22)	(22)	(21)	(21)		
7.44	13.60	4.40	00	ND	**Small haem (3)**
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(1)	(1)	(1)	(1)		
Pre-Haemorrhage = Pre-PVL					
7.22	7.19	5.47	-11	62	**IVH (5)**
7.02-7.40	*4.1-15.4*	*3.5-8.6*	*-24/+1*	*39-77*	**Rt echodense PVL (5)**
(20)	(20)	(20)	(20)	(28)	
7.54	14.10	3.00	-2	ND	**IVH (4)**
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(1)	(1)	(1)	(1)		

72.M 29 1370 (60) Alive	SVD Outborn 5,6,8	7 days 34cm 100%	APH Hypothermia HMD Lt pneumothorax (3) VSD Ventriculo- peritoneal shunt Transfusion x1 SBR 200 umol/L	Morphine Pancuronium Caffeine
73.M 35 1400 (<3) Alive	LSCS Inborn 8,8,8	- - Air	Oligohydramnios Foetal distress (CTG) SBR 200 umol/L	Nil
74.M 30 1260 (30) Died	LSCS Outborn 4,5,ND	47 days 20cm 90%	Eclamptic fits HMD Pneumonia Tracheo-oesophageal fistula Tracheostomy Gastrostomy Serratia septicaemia DIC Convulsions Hypoglycaemia Hyponatraemia Hypocalcaemia Transfusion x14 SBR 215 umol/L	Na bicarbonate Morphine Pancuronium Frusemide Dopamine Phenobarbitone Diazepam Caffeine
75.F 30 1120 (15) Alive	SVD Inborn 8,8,8	2 days 16cm 30%	Recurrent apnoea PDA Hyponatraemia Hyperkalaemia Transfusion x2 SBR 162 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E Aminophylline
76.M 32 1460 (10) Alive	LSCS Inborn 4,8,8	- CPAP 4cm 80%	PET Twin 1 HMD PIE Hypoglycaemia SBR 165 umol/L	Nil
77.F 29 1100 (35) Alive	Vag. breech Outborn 8,8,8	- - 40%	APH TTN Hypoglycaemia Exchange transfusion SBR 223 umol/L	Vitamin E
78.F 31 1430 (30) Alive	Vag. breech Outborn 8,8,8	- - 45%	Twin 2 Hypoglycaemia Hypernatraemia SBR 200 umol/L	Nil

7.34 *7.21-7.43* (16)	10.91 *5.7-18.8* (16)	5.19 *4.0-6.7* (16)	-5 *-11/-1* (16)	56 *50-64* (13)	**IVH (1)** **Prog vent dil**
ND	ND	ND	ND	ND	**Small haem (7)**
7.39 *7.32-7.48* (12)	13.16 *5.6-35.5* (12)	4.44 *2.2-5.6* (12)	-4 *-8/0* (9)	54 *44-64* (5)	**Bilat prolonged flare (1)**
ND	ND	ND	ND	ND	**IVH (3)**
7.37 *7.25-7.51* (23)	8.08 *4.2-13.9* (23)	5.51 *2.4-8.5* (23)	-1 *-7/+6* (23)	ND	**Normal**
7.29 *7.15-7.37* (13)	10.06 *4.9-16.0* (13)	5.13 *4.4-6.9* (13)	-7 *-16/-4* (13)	ND	**Small haem (16)**
7.32 *7.26-7.37* (6)	11.92 *6.4-18.2* (6)	6.22 *4.7-8.0* (6)	-2 *-5/-1* (6)	55 *46-62* (7)	**Bilat prolonged flare (1)**

79.F 29 1100 (35) Alive	Forceps vertex Outborn 3,6,7	1 day 18cm 70%	Recurrent apnoea NEC Hypocalcaemia Exchange transfusion SBR 205 umol/L	Vitamin E Aminophylline
80.M 29 910 (15) Alive	LSCS Inborn (IUT) 8,8,8	29 days 32cm 100%	PET Foetal distress (CTG) HMD Pneumonia PDA Renal failure Hypoglycaemia Transfusion x9 SBR 280 umol/L	Na bicarbonate THAM Morphine Frusemide Indomethacin
81.F 30 1380 (45) Alive	Forceps vertex Outborn 8,8,8	13 days 28cm 80%	HMD Rt pneumothorax (2) PDA E coli septicaemia Thrombocytopaenia Hyoglycaemia Hyponatraemia Hypocalcaemia Transfusion x7 SBR 185 umol/L	Na bicarbonate Pancuronium Frusemide Indomethacin Atrovent Ca gluconate Caffeine
82.M 34 1330 (<3) Alive	LSCS Inborn 2,8,8	1 day 18cm 80%	Foetal distress (CTG) Foeto-maternal bleed Hb 6.2gm% at birth Poor respiratory drive PDA Transfusion x1 SBR 257 umol/L	Frusemide Tolazoline Dopamine
83.F 28 1200 (70) Alive	Vag. breech Outborn 3,6,8	4 days 24cm 100%	Liquor leakage from 18 weeks gestation Hypothermia HMD Pneumonia PDA Hypocalcaemia Transfusion x2 SBR 174 umol/L	Na bicarbonate Frusemide Indomethacin Tolazoline Dopamine Vitamin E Ca gluconate
84.M 32 1240 (5) Alive	SVD Inborn 6,8,8	- - Air	PET APH SBR 168 umol/L	Nil

7.41 *7.36-7.49* (10)	7.38 *4.8-10.5* (9)	4.15 *2.8-5.4* (10)	-3 *-8/0* (10)	ND	IVH (3) Non-prog vent dil
7.37 *7.37-7.38* (4)	9.20 *7.8-11.0* (4)	4.45 *4.2-4.8* (4)	-5 *-7/-4* (4)	60 -- (1)	Bilat prolonged flare (1)
Pre-Haemorrhage 7.27 *6.94-7.60* (19)	9.38 *3.3-17.5* (19)	4.65 *3.9-5.9* (19)	-10 *-21/+17* (18)	59 *50-70* (8)	Rt parench haem (2) Lt cystic PVL (7)
Pre-PVL 7.31 *6.94-7.60* (50)	11.02 *3.3-18.6* (50)	5.19 *3.3-12.4* (50)	-6 *-21/+17* (49)	54 *40-70* (27)	
7.30 *7.18-7.44* (11)	6.51 *4.5-9.5* (11)	5.14 *3.4-6.4* (11)	-7 *-10/-2* (11)	52 *43-60* (21)	Normal
7.28 *7.00-7.45* (59)	8.17 *3.5-16.0* (59)	5.71 *2.9-9.8* (59)	-6 *-16/+4* (58)	55 *38-76* (44)	Small haem (17)
ND	ND	ND	ND	ND	Small haem (6) External hydrocephalus

85.F 27 760 (15) Died	LSCS Inborn (IUT) 6,8,8	9 days 26cm 100%	APH PET Poor respiratory drive E coli septicaemia Arrythmia (profound bradycardia,SVT,VT) NEC Thrombocytopaenia Hypoglycaemia Hyponatraemia Hypocalcaemia Transfusion x3 SBR 172 umol/L	Na bicarbonate THAM Frusemide Dopamine Ca gluconate Caffeine
86.F 30 1320 (40) Alive	LSCS Inborn (IUT) 7,8,8	9 days 28cm 100%	PET HMD Lt pneumothorax (2) Rt pneumothorax (2) PDA Transfusion x1 SBR 240 umol/L	Morphine Pancuronium Frusemide Caffeine
87.F 25 770 (70) Alive	SVD Inborn 8,8,8	17 days 20cm 40%	PET APH Hypothermia Pneumonia Recurrent apnoea PDA E coli septicaemia NEC Hyponatraemia Hypocalcaemia Transfusion x7 SBR 90 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E Ca gluconate Aminophylline
88.M 27 1120 (90) Alive	Vag. breech Inborn 1,8,8	13 days 20cm 60%	HMD Recurrent apnoea Staph. epidermidis septicaemia Transfusion x5 SBR 230 umol/L	Frusemide Caffeine Doxapram
89.F 30 1000 (10) Alive	LSCS Inborn 8,8,8	2 days 24cm 80%	PET Hypothermia HMD SBR 180 umol/L	Na bicarbonate

7.41	15.18	4.46	-3	51	**IVH (3)**
7.33-7.58	*8.5-29.9*	*2.6-5.4*	*-6/-1*	*42-56*	
(16)	(16)	(16)	(16)	(12)	

7.30	7.66	5.81	-6	50	**Small haem (2)**
7.01-7.53	*4.3-10.0*	*2.3-10.6*	*-11/-1*	*40-58*	
(16)	(16)	(16)	(16)	(11)	

Pre-Haemorrhage					
7.32	7.23	5.23	-5	ND	**Small haem (70)**
7.05-7.53	*3.6-15.0*	*2.8-13.1*	*-18/+8*		**Bilat prolonged**
(64)	(64)	(64)	(62)		**flare (14)**
Pre-PVL					
7.29	8.02	4.85	-7	ND	
7.05-7.51	*3.6-15.0*	*3.2-7.8*	*-18/+8*		
(33)	(33)	(33)	(33)		

7.31	10.15	5.47	-5	56	**IVH (3)**
7.13-7.49	*6.4-21.4*	*3.6-9.2*	*-8/0*	*38-70*	
(23)	(23)	(23)	(23)	(13)	

Pre-Haemorrhage					
7.31	10.85	5.52	-5	52	**Small haem (19)**
7.19-7.46	*6.2-33.4*	*3.3-7.8*	*-12/-2*	*47-60*	**Bilat prolonged**
(31)	(31)	(31)	(31)	(16)	**flare (3)**
Pre-PVL					
7.30	11.10	5.71	-5	54	
7.19-7.46	*6.2-33.4*	*3.3-7.8*	*-12/-2*	*47-62*	
(22)	(22)	(22)	(22)	(10)	

90.F 34 1370 (<3) Alive	LSCS Inborn 2,8,8	2 days 24cm 40%	Oligohydramnios PET Foetal distress (CTG and meconium) HMD Thrombocytopaenia Hypoglycaemia SBR 200 umol/L	Nil
91.M 33 1420 (5) Alive	LSCS Inborn 2,7,8	- - Air	PET Hypoglycaemia SBR 117 umol/L	Nil
92.F 26 740 (30) Died	SVD Born in GP surgery ND ("poor condition")	13 days 32cm 97%	No antenatal care Young mother aged 15 Hypothermia HMD Lt pneumothorax (2) Pneumonia PDA Staph. epidermidis septicaemia Arrythmia (nodal rhythm with broad complexes) Renal failure Hypoglycaemia Hyperkalaemia Persistent metabolic acidosis Transfusion x3 SBR 160 umol/L	Na bicarbonate THAM Pancuronium Frusemide Indomethacin Dopamine Calcium resonium Insulin Ca gluconate Caffeine
93.M 35 1170 (<3) Died	LSCS Inborn 1,2,8	3 days 22cm 60%	Foetal distress (CTG) Hypothermia Trisomy 18 Truncus arteriosus Hypernatraemia SBR 238 umol/L	Nil
94.M 33 970 (<3) Died	LSCS Outborn 5,7,8	1 day 20cm 50%	Empty twin sac on scan at 13 weeks PET Foetal distress (CTG) NEC Ileostomy Hypoglycaemia Hyponatraemia Transfusion x1 SBR 135 umol/L	Na bicarbonate Dopamine Vitamin E Insulin
95.F 30 1460 (50) Alive	LSCS Inborn 8,8,8	- - 25%	Twin 1 SBR 132 umol/L	Nil

Pre-Haemorrhage					
7.36	11.04	5.37	-3	62	IVH (3)
7.20-7.45	*4.5-23.1*	*3.3-9.5*	*-8/-1*	*50-70*	Rt cystic PVL (1)
(13)	(13)	(13)	(13)	(7)	Non-prog vent dil
Pre-PVL					
7.22	6.40	8.70	-2	ND	
7.20-7.23	*6.3-6.5*	*7.9-9.5*	*-3/-1*		
(2)	(2)	(2)	(2)		
ND	ND	ND	ND	ND	Normal
Pre-Haemorrhage					
7.24	9.88	5.76	-8	41	Lt parench haem (3)
7.04-7.41	*3.3-20.0*	*3.8-8.4*	*-17/-5*	*30-54*	Rt echodense PVL (5)
(26)	(26)	(26)	(26)	(19)	
Pre-PVL					
7.24	10.10	5.79	-8	41	
7.04-7.41	*3.3-20.0*	*3.8-8.4*	*-17/-3*	*30-54*	
(35)	(35)	(35)	(35)	(28)	
7.33	7.42	6.91	+1	73	Normal
7.17-7.43	*3.0-10.8*	*5.1-8.9*	*-4/+5*	*62-86*	
(19)	(19)	(19)	(19)	(16)	
7.26	11.30	4.37	-12	ND	Lt occipital infarct
7.18-7.33	*8.6-14.9*	*3.4-5.4*	*-14/-10*		(neonatal stroke)
(3)	(3)	(3)	(3)		Agenesis corp call
ND	ND	ND	ND	ND	Normal

96.F 31 1480 (35) Alive	SVD Inborn 8,8,8	- - Air	APH Foetal distress (CTG & meconium) SBR 195 umol/L	Nil
97.F 29 1200 (50) Alive	LSCS Inborn 6,8,8	- - Air	APH Haemolytic anaemia (?cause) UTI Hyponatraemia Transfusion x2 SBR 200 umol/L	Frusemide Vitamin E Aminophylline
98.M 28 960 (35) Died	LSCS Inborn 2,7,8	13 days 26cm 100%	Hypothermia HMD Lt pneumothorax (6) Rt pneumothorax (2) Pneumomediastinum Pneumonia PDA Hypoglycaemia Hypernatraemia Hypocalcaemia Transfusion x4 SBR 149 umol/L	Na bicarbonate Frusemide Indomethacin Tolazoline
99.F 33 1450 (5) Alive	SVD Inborn 8,8,8	- - 30%	TTN SBR 222 umol/L	Aminophylline
100.F 28 1380 (>97) Alive	SVD Outborn 7,6,8	- - 40%	Twin 1 Recurrent apnoea NEC Hypoglycaemia Transfusion x4 SBR 117 umol/L	Frusemide Ca gluconate Theophylline
101.M 28 1300 (95) Died	SVD Outborn 7,8,8	1 day 28cm 100%	Twin 2 HMD Lt pneumothorax (2) Rt pneumothorax (2) Hyponatraemia Transfusion x1 SBR 50 umol/L	Na bicarbonate Tolazoline
102.M 30 1120 (20) Died	LSCS Inborn 8,8,8	3 days 24cm 90%	PET HMD Lt pneumothorax (3) Pneumonia Pseudomonas septicaemia Hypernatraemia SBR 80 umol/L	Na bicarbonate Dopamine

7.35	5.60	5.90	-1	ND	**Normal**
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(1)	(1)	(1)	(1)		
ND	ND	ND	ND	ND	**Normal**

Pre-Haemorrhage = Pre-PVL

7.26	7.20	6.13	-7	48	**IVH (4)**
6.80-7.55	*2.9-12.3*	*2.9-15.2*	*-18/+13*	*39-56*	**Rt echodense PVL (4)**
(27)	(27)	(27)	(27)	(43)	**Non-prog vent dil**

Pre-Haemorrhage = Pre-PVL

7.26	9.95	5.55	-9	ND	**IVH (31)**
7.24-7.27	*6.8-13.1*	*5.3-5.8*	*-9/-8*		**Lt cystic PVL (13)**
(2)	(2)	(2)	(2)		
7.37	10.87	4.53	-5	ND	**Normal**
7.26-7.47	*5.6-17.3*	*2.7-6.0*	*-6/-4*		
(3)	(3)	(3)	(2)		
7.10	6.45	6.80	-14	ND	**Small haem (2)**
6.76-7.35	*4.5-9.8*	*3.7-10.6*	*-27/-9*		
(6)	(6)	(6)	(4)		
7.30	7.50	5.52	-5	33	**Normal**
7.10-7.65	*3.8-16.0*	*2.0-8.5*	*-14/-1*	--	
(23)	(23)	(23)	(23)	(1)	

103.M 28 1280 (90) Alive	LSCS Inborn 5,8,8	27 days 26cm 90%	HMD Lt pneumothorax (3) Rt pneumothorax (3) PDA Streptococcal (Group B and viridans) septicaemia NEC Ileostomy & colectomy Hyponatraemia Transfusion x6 SBR 160 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E
104.M 30 1410 (40) Alive	Forceps vertex Inborn 8,8,8	- - Air	APH SBR 120 umol/L	Aminophylline
105.M 30 1390 (40) Alive	SVD Outborn 7,8,8	1 day 20cm 60%	APH HMD Pneumonia Recurrent apnoea PDA Hyperkalaemia Hyponatraemia Transfusion x2 SBR 209 umol/L	Frusemide Vitamin E Aminophylline
106.F 37 1280 (<3) Died	LSCS Inborn 1,7,8	- - 40%	Foetal distress (CTG) Trisomy 18 Tracheo-oesophageal fistula Convulsions	Nil
107.F 28 950 (30) Alive	SVD Outborn 3,8,8	11 days 20cm 40%	HMD Pneumonia Recurrent apnoea Hypoglycaemia Hypocalcaemia Transfusion x8 SBR 170 umol/L	Na bicarbonate THAM Frusemide Caffeine Doxapram
108.F 32 1410 (10) Alive	LSCS Inborn 8,8,8	- - Air	Raised serum AFP PET Polycythaemia SBR 176 umol/L	Nil
109.M 29 1200 (40) Alive	LSCS Inborn 6,8,8	2 days 20cm 70%	APH HMD Chronic pulmonary insufficiency of prematurity Recurrent apnoea Hypocalcaemia Transfusion x1 SBR 190 umol/L	Frusemide Caffeine

Pre-Haemorrhage					
7.29	7.04	6.81	-4	69	**Small haem (35)**
7.07-7.58	*2.6-19.0*	*2.4-12.1*	*-12/+5*	*51-98*	**Bilat prolonged**
(93)	(93)	(93)	(89)	(17)	**flare (7)**
Pre-PVL					
7.31	6.98	5.81	-3	69	
7.07-7.52	*2.6-15.0*	*2.4-12.1*	*-10/+4*	*51-98*	
(27)	(27)	(27)	(27)	(17)	
ND	ND	ND	ND	ND	**Normal**
7.31	8.65	5.65	-6	ND	**IVH (4)**
7.18-7.53	*3.5-16.7*	*3.2-7.8*	*-10/0*		
(20)	(20)	(20)	(18)		
7.21	6.76	8.00	-4	66	**Normal**
7.15-7.33	*4.5-10.5*	*6.7-9.5*	*-9/+1*	*60-72*	
(5)	(5)	(5)	(5)	(7)	
7.30	8.18	5.30	-6	64	**Normal**
7.14-7.58	*4.4-18.5*	*2.7-8.3*	*-11/0*	*44-82*	
(82)	(82)	(82)	(82)	(74)	
ND	ND	ND	ND	ND	**Normal**
7.38	8.11	5.52	-1	60	**Bilat prolonged**
7.21-7.52	*2.8-21.6*	*2.7-9.2*	*-5/+6*	*30-80*	**flare (5)**
(39)	(39)	(39)	(39)	(21)	

110.M 31 1400 (30) Alive	LSCS Inborn (IUT) 8,8,8	- - Air	PET Salmonella enteritis Bilateral inguinal herniae SBR 190 umol/L	Caffeine
111.M 30 1170 (15) Alive	SVD Inborn (IUT) 8,8,8	1 day 16cm 30%	Recurrent apnoea Staph. epidermidis septicaemia Hyponatraemia SBR 170 umol/L	Na bicarbonate Aminophylline
112.M 29 1200 (40) Alive	SVD Inborn 5,8,8	- - Air	PDA Transfusion x1 SBR 197 umol/L	Frusemide Vitamin E Aminophylline
113.M 26 990 (90) Died	SVD Outborn 8,8,8	15 days 18cm 30%	Twin 1 HMD Recurrent apnoea PDA NEC DIC Hypoglycaemia Hyponatraemia Hypokalaemia Transfusion x13 SBR 332 umol/L	Na bicarbonate Frusemide Indomethacin Phenobarbitone Vitamin E Aminophylline
114.M 26 970 (90) Alive	SVD Outborn 0,0,8	41 days 16cm 65%	Twin 2 HMD Pneumonia Recurrent apnoea PDA NEC Klebsiella septicaemia Hypoglycaemia Hyperglycaemia Hyponatraemia Hypernatraemia Hypokalaemia Transfusion x12 SBR 273 umol/L	Na bicarbonate Frusemide Indomethacin Phenobarbitone Vitamin E Cimetidine Atrovent Insulin Ca gluconate Aminophylline

7.33	5.80	5.00	-5	58	**Normal**
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(1)	(1)	(1)	(1)	(6)	
7.33	6.64	4.97	-5	ND	**Normal**
7.17-7.43	*3.6-11.9*	*3.4-6.6*	*-10/-1*		
(11)	(11)	(11)	(11)		
ND	ND	ND	ND	ND	**Normal**
Pre-Haemorrhage = Pre-PVL					
7.33	9.81	5.24	-5	ND	**IVH (4)**
7.09-7.51	*2.5-17.7*	*2.5-8.9*	*-16/-1*		**Rt cystic PVL (4)**
(25)	(25)	(25)	(25)		**Non-prog vent dil**
7.28	7.93	5.82	-5	ND	**No haem or PVL**
6.89-7.56	*1.8-14.4*	*3.6-11.5*	*-20/+6*		**Atrophy**
(135)	(135)	(135)	(135)		

115.M 26 780 (35) Alive	SVD Inborn 8,8,8	68 days 30cm 100%	Clomiphene pregnancy Amnionitis Twin 1 Recurrent apnoea Pneumonia PDA Staph. epidermidis septicaemia E coli septicaemia Thrombocytopaenia Gastric bleeding Persistent hyperglycaemia Hyponatraemia Hyperkalaemia Hypokalaemia Transfusion x15 SBR 276 umol/L	Frusemide Indomethacin Tolazoline Vitamin E Cimetidine Atrovent Insulin Ca gluconate Aminophylline
116.F 26 780 (35) Alive	Vag. breech Inborn 3,6,8	52 days 20cm 100%	Clomiphene pregnancy Amnionitis Twin 2 HMD Lt pneumothorax (1) Pneumonia PDA Renal failure Thrombocytopaenia Persistent hyperglycaemia Hypernatraemia Hyperkalaemia Hypokalaemia Hypocalcaemia Transfusion x12 SBR 114umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E Atrovent Insulin Gaviscon Aminophylline
117.M 25 870 (90) Died	SVD Inborn 8,8,8	1 day 40cm 95%	HMD Lt pneumothorax (1) Rt pneumothorax (1)	THAM Pancuronium Tolazoline Dopamine
118.F 29 1100 (30) Alive	LSCS Inborn 7,8,8	- - Air	APH Foetal distress (CTG) SBR 151 umol/L	Vitamin E
119.M 29 1340 (50) Died	LSCS Inborn 2,3,6	1 day 44cm 100%	APH Hypothermia HMD PDA Arrythmia (SVT, VT and VF) Hyponatraemia SBR 50 umol/L	THAM Pancuronium Indomethacin Tolazoline Dopamine Insulin Ca gluconate

7.40 *7.35-7.50* (4)	6.38 *4.1-8.5* (4)	4.88 *3.4-6.0* (4)	-1 *-3/0* (3)	ND	**IVH (1)** **Non-prog vent dil**
7.30 *6.91-7.58* (137)	7.47 *2.5-21.1* (137)	5.27 *1.9-11.3* (137)	-6 *-16/+1* (137)	55 *40-70* (20)	**Small haem (58)**
7.21 *7.09-7.35* (7)	6.73 *3.2-14.5* (7)	6.11 *4.2-8.2* (7)	-9 *-12/-7* (7)	42 *38-48* (4)	**Normal**
ND	ND	ND	ND	ND	**Small haem (26)**
7.22 *7.11-7.34* (13)	4.54 *1.8-9.5* (13)	7.79 *5.7-10.4* (13)	-4 *-12/+1* (13)	44 *20-60* (6)	**IVH (2)**

120.F 26 880 (65) Died	Vag. breech Inborn 3,4,8	1 day 26cm 80%	HMD Lt pneumothorax (2) Rt pneumothorax (2) Arrythmia (SVT) Renal failure Hypoglycaemia Hyponatraemia Hyperkalaemia Hypocalcaemia Transfusion x1 SBR 140 umol/L	Na bicarbonate THAM Pancuronium Frusemide Dopamine Calcium resonium Insulin Ca gluconate
121.F 28 1220 (80) Died	Vag. breech Inborn 2,8,8	8 days 25cm 60%	Maternal hypertension Foetal distress (CTG) Hypothermia HMD PDA Persistent metabolic acidosis Hyperkalaemia Hyponatraemia Transfusion x4 SBR 180 umol/L	Na bicarbonate Pancuronium Frusemide Dopamine Hydrocortisone Calcium resonium Ca gluconate Caffeine
122.M 30 1400 (40) Alive	LSCS Inborn 4,8,8	9 days 25cm 90%	Twin 1 HMD Lt pneumothorax (2) Arrythmia (profound bradycardia) Hypocalcaemia Transfusion x4 SBR 170 umol/L	Na bicarbonate Pancuronium Frusemide Ca gluconate Caffeine
123.M 30 1320 (30) Alive	LSCS Inborn 4,8,8	2 days 22cm 60%	Twin 2 HMD Transfusion x2 SBR 150 umol/L	Pancuronium Frusemide Caffeine
124.M 29 1340 (50) Alive	LSCS Inborn 4,6,8	- - 50%	APH Foetal distress (CTG) HMD Klebsiella septicaemia Hypernatraemia Transfusion x4 SBR 220 umol/L	Frusemide Caffeine
125.M 29 1190 (40) Alive	LSCS Inborn 2,6,8	6 days 23cm 90%	APH Foetal distress (CTG) HMD Lt pneumothorax (2) Pneumonia Hyponatraemia Hypocalcaemia Transfusion x3 SBR 190 umol/L	Pancuronium Frusemide Ca gluconate Caffeine

7.28 *6.87-7.48* (14)	10.44 *5.2-28.7* (14)	5.51 *2.6-7.3* (14)	-7 *-22/+1* (14)	47 *32-58* (8)	**IVH (2)**
7.30 *7.07-7.46* (21)	11.24 *7.4-19.0* (21)	4.73 *2.6-8.2* (21)	-8 *-21/-2* (21)	52 *38-58* (15)	**Rt parench haem (3)** **Non-prog vent dil**
7.25 *6.79-7.40* (24)	9.31 *3.6-17.2* (24)	5.65 *4.4-10.1* (24)	-8 *-26/+2* (24)	61 *42-76* (18)	**IVH (4)** **Prog vent dil**
7.29 *7.16-7.46* (44)	9.71 *4.6-20.7* (44)	6.51 *3.8-8.6* (44)	-3 *-9/+5* (44)	60 *40-80* (38)	**Normal**
7.34 *7.27-7.44* (33)	9.82 *3.9-21.8* (33)	6.01 *2.5-7.9* (33)	-2 *-15/+6* (33)	67 *50-82* (37)	**Normal**
7.30 *7.11-7.45* (46)	9.78 *5.8-17.2* (46)	5.26 *3.2-8.8* (46)	-7 *-14/-3* (46)	64 *54-80* (37)	**Bilat prolonged flare (2)**

126.F 28 1180 (70) Alive	LSCS Outborn 6,8,8	9 days 22cm 100%	Clomiphene pregnancy APH HMD Lt pneumothorax (2) Convulsions Ventriculo- peritoneal shunt Hypocalcaemia Transfusion x5 SBR 128 umol/L	Na bicarbonate Frusemide Tolazoline Phenobarbitone Diazepam Isosorbide Vitamin E Atrovent Ca gluconate Aminophylline
127.F 28 1160 (70) Alive	LSCS Outborn 6,8,8	13 days 28cm 100%	PET HMD Lt pneumothorax (3) PIE PDA Persistent hyperglycaemia Transfusion x3 SBR 144 umol/L	Na bicarbonate Frusemide Vitamin E Insulin Aminophylline
128.M 30 1120 (15) Alive	LSCS Inborn 5,8,8	3 days 18cm 50%	PET HMD Pneumonia PDA Staph. epidermidis septicaemia Transfusion x1 SBR 120 umol/L	Frusemide Vitamin E
129.M 31 1370 (25) Alive	Vag. breech Inborn ND,8,8	- - Air	SBR 169 umol/L	Vitamin E
130.M 26 1020 (95) Alive	SVD Inborn (IUT) 2,3,8	29 days 22cm 100%	APH Hb 10.8gm% at birth HMD Pneumonia Recurrent apnoea PDA Convulsions DIC Hypoglycaemia Hypernatraemia Transfusion x9 SBR 160 umol/L	Na bicarbonate Morphine Frusemide Tolazoline Phenobarbitone Vitamin E Aminophylline
131.F 29 1210 (50) Alive	LSCS Inborn 4,8,8	- - 30%	APH Foetal distress (CTG) NEC Klebsiella aerogenes septicaemia Thrombocytopaenia Microcephaly SBR 130 umol/L	Frusemide Vitamin E Aminophylline

Pre-Haemorrhage = Pre-PVL					
7.25	7.12	5.36	-8	60	Rt parench haem (4)
6.88-7.44	*4.0-10.0*	*3.5-8.2*	*-24/-1*	*44-93*	Lt cystic PVL (4)
(28)	(27)	(28)	(27)	(64)	Prog vent dil
Pre-Haemorrhage = Pre-PVL					
7.19	9.33	7.89	-9	54	IVH (4)
6.80-7.49	*4.6-18.5*	*3.9-19.5*	*-19/+2*	*44-63*	Rt cystic PVL (4)
(29)	(28)	(29)	(26)	(28)	Non-prog vent dil
7.30	7.86	5.37	-6	ND	Small haem (38)
7.20-7.53	*5.2-12.0*	*3.0-6.8*	*-10/0*		
(35)	(35)	(35)	(35)		
ND	ND	ND	ND	ND	Small haem (2) Intravent adhesions
Pre-Haemorrhage					
7.35	7.21	5.74	-1	66	Lt parench haem (3)
7.01-7.45	*1.3-12.0*	*3.8-8.4*	*-15/+7*	*30-99*	Rt prolonged
(27)	(27)	(27)	(27)	(70)	flare (14)
Pre-PVL					
7.35	7.83	5.23	-4	58	
7.01-7.46	*1.3-12.0*	*3.2-18.4*	*-15/+7*	*29-99*	
(79)	(79)	(79)	(79)	(146)	
ND	ND	ND	ND	ND	IVH (17) Bilat prolonged flare (3)

132.M 30 1440 (50) Alive	SVD Outborn 4,3,6	7 days 27cm 70%	Maternal bowel resection @ 20 weeks gestation APH HMD Lt pneumothorax (2) Rt pneumothorax (3) PDA Ventriculo-peritoneal shunt DIC Hyponatraemia Hypokalaemia Hypocalcaema Transfusion x7 SBR 180 umol/L	Na bicarbonate THAM Pancuronium Frusemide Calcium resonium Ca gluconate
133.F 28 1020 (40) Alive	LSCS Inborn (IUT) 8,8,8	3 days 26cm 70%	PET Hypothermia HMD Recurrent apnoea Transfusion x2 SBR 168 umol/L	Na bicarbonate Pancuronium Caffeine
134.M 30 1240 (30) Alive	LSCS Inborn 8,8,8	- - Air	Clomiphene pregnancy PET SBR 145 umol/L	Vitamin E
135.F 32 1360 (10) Alive	LSCS Inborn 8,8,8	- - Air	PET PDA SBR 113 umol/L	Vitamin E
136.M 28 1380 (>97) Alive	SVD Inborn 8,8,8	1 day 20cm 35%	Bleed (10 mls) from umbilical artery Transfusion x3 SBR 160 umol/L	Frusemide Caffeine
137.M 32 1360 (10) Alive	SVD Outborn ND,ND,ND	3 days 18cm 50%	Twin 1 Born at home Hypothermia HMD Recurrent apnoea SBR 218 umol/L	Vitamin E Aminophylline
138.F 32 1480 (15) Alive	SVD Outborn ND,ND,ND	6 days 18cm 70%	Twin 2 Born at home Hypothermia HMD SBR 178 umol/L	Na bicarbonate Vitamin E Aminophylline

Pre-Haemorrhage = Pre-PVL					
7.23	10.57	6.49	-7	65	**IVH (2)**
7.02-7.34	*4.7-26.3*	*5.0-12.0*	*-18/-2*	*40-98*	**Bilat cystic PVL (2)**
(10)	(10)	(10)	(9)	(19)	**Prog vent dil**
7.29	8.97	5.77	-5	71	**Small haem (15)**
7.12-7.41	*3.9-16.5*	*3.3-10.3*	*-13/-2*	*48-92*	
(31)	(31)	(31)	(31)	(28)	
ND	ND	ND	ND	ND	**Small haem (5)**
ND	ND	ND	ND	ND	**Normal**
7.34	9.35	5.14	-4	59	**Normal**
7.17-7.45	*4.9-22.0*	*3.5-8.3*	*-8/-2*	*40-76*	
(19)	(19)	(19)	(19)	(14)	
7.31	7.62	5.17	-6	ND	**Normal**
7.20-7.40	*4.2-17.1*	*2.6-6.8*	*-11/-3*		
(25)	(25)	(25)	(24)		
7.30	7.34	4.70	-8	ND	**Normal**
7.19-7.43	*3.8-13.5*	*2.6-6.9*	*-13/-4*		
(38)	(38)	(38)	(37)		

139.F 28 1160 (70) Alive	SVD Inborn (IUT) 3,7,8	6 days 18cm 40%	HMD PDA Convulsions Hypoglycaemia Hypocalcaemia Transfusion x2 SBR 167 umol/L	Na bicarbonate Frusemide Indomethacin Phenobarbitone Vitamin E Ca gluconate Aminophylline
140.F 29 1350 (55) Alive	SVD Inborn 8,8,8	- - Air	Hyperkalaemia SBR 206 umol/L	Vitamin E
141.M 29 700 (<3) Died	LSCS Inborn (IUT) 6,8,8	13 days 24cm 100%	PET Oligohydramnios Hypothermia Poor respiratory drive Lt pneumothorax (4) Pneumonia Staph. aureus septicaemia Thrombocytopaenia Hypoglycaemia Hypocalcaemia Transfusion x2 SBR 120 umol/L	Na bicarbonate THAM Pancuronium Frusemide Dopamine Phenobarbitone Ca gluconate Caffeine
142.M 27 1120 (90) Alive	Vag. breech Inborn 2,8,8	31 days 22cm 60%	HMD Pneumonia E coli and Strep. faecalis septicaemia UTI NEC Jejunostomy DIC Hyperglycaemia Hyponatraemia Hypokalaemia Hypocalcaemia Transfusion x15 SBR 166 umol/L	Na bicarbonate Frusemide Tolazoline Vitamin E Atrovent Cimetidine Insulin Aminophylline
143.M 29 1020 (30) Alive	LSCS Inborn 2,6,8	7 days 26cm 70%	PET HMD Pneumonia Staph. epidermidis septicaemia Hyperkalaemia Transfusion x4 SBR 120 umol/L	Pancuronium Frusemide Caffeine

Pre-Haemorrhage = Pre-PVL					
7.30	11.50	4.15	-9	ND	**IVH (4)**
7.16-7.47	*6.8-35.1*	*2.9-6.2*	*-12/-5*		**Bilat prolonged**
(22)	(22)	(22)	(20)		**flare (4)**
ND	ND	ND	ND	ND	**IVH (4)**
					Rt prolonged
					flare (4)
Pre-Haemorrhage					
7.33	6.77	5.58	-5	52	**IVH (5)**
7.08-7.52	*3.6-11.9*	*2.6-9.6*	*-9/0*	*40-64*	**Lt echodense PVL (2)**
(28)	(28)	(28)	(28)	(27)	
Pre-PVL					
7.35	7.52	5.65	-3	50	
7.16-7.52	*4.8-11.9*	*2.7-8.7*	*-8/0*	*40-60*	
(14)	(14)	(14)	(14)	(12)	
7.30	5.64	5.79	-4	67	**Small haem (43)**
7.00-7.54	*3.0-9.3*	*2.1-10.3*	*-13/+5*	*47-91*	
(82)	(82)	(82)	(81)	(93)	
7.28	7.82	6.67	-3	66	**Small haem (11)**
7.00-7.40	*4.4-21.1*	*3.8-12.0*	*-7/+9*	*46-85*	
(55)	(55)	(55)	(55)	(38)	

144.M 27 940 (50) Alive	LSCS Inborn 5,8,8	1 day 16cm 45%	APH Foetal distress (CTG) Recurrent apnoea Chronic pulmonary insufficiency of prematurity PDA Staph. aureus septicaemia Neutropaenia Transfusion x4 SBR 150 umol/L	Caffeine
145.M 33 1120 (<3) Alive	Forceps vertex Inborn 8,8,8	- - Air	PET Foetal distress (CTG) Ring Y chromosome Hypoglycaemia SBR 195 umol/L	Nil
146.M 26 960 (85) Alive	Vag. breech Inborn 3,8,8	33 days 16cm 40%	Hypothermia Poor respiratory drive Pneumonia Staph. aureus septicaemia Hypoglycaemia Hypernatraemia Hyponatraemia Transfusion x7 SBR 120 umol/L	Na bicarbonate Frusemide Vitamin E Atrovent Metoclopramide Aminophylline
147.M 28 1170 (70) Alive	SVD Inborn (IUT) 5,8,8	1 day 16cm 40%	Overdose at 8 weeks (Benylin,Ponstan and alcohol) Poor respiratory drive Recurrent apnoea PDA NEC Hypocalcaemia Transfusion x2 SBR 121 umol/L	Frusemide Indomethacin Vitamin E Ca gluconate Aminophylline
148.F 27 1130 (90) Alive	SVD Inborn (IUT) 5,8,8	- - 30%	HMD Recurrent apnoea Klebsiella septicaemia SBR 101 umol/L	Vitamin E Aminophylline
149.F 32 1280 (10) Alive	LSCS Outborn 8,8,8	5 days 24cm 70%	PET HMD PDA Hyponatraemia Transfusion x1 SBR 140 umol/L	Pancuronium Frusemide Caffeine

7.38 *7.21-7.50* (19)	6.25 *2.3-24.5* (19)	4.93 *3.0-8.7* (19)	-3 *-8/+2* (19)	63 *42-84* (35)	**Normal**
7.35 *7.34-7.36* (4)	10.70 *7.7-14.3* (4)	3.93 *3.7-4.2* (4)	-8 *-9/-8* (4)	72 -- (1)	**Bilat prolonged flare (3)**
7.28 *7.07-7.51* (45)	6.63 *3.2-18.6* (45)	5.38 *3.0-7.8* (45)	-7 *-15/+5* (45)	ND	**IVH (10)**
7.41 *7.32-7.53* (11)	10.30 *5.7-20.5* (11)	4.05 *2.8-5.0* (11)	-4 *-6/-2* (11)	ND	**Bilat prolonged flare (8)**
7.36 *7.31-7.40* (7)	7.23 *4.9-8.6* (7)	5.46 *5.0-6.0* (7)	-2 *-4/0* (7)	ND	**Bilat prolonged flare (4)**
7.33 *7.11-7.48* (51)	11.13 *4.9-22.3* (51)	5.81 *3.6-9.5* (51)	-3 *-10/+1* (51)	66 *56-90* (28)	**Normal**

150.F 28 1340 (>97) Alive	LSCS Inborn 5,8,8	- - 40%	Foetal distress (CTG) Hyperkalaemia Hypernatraemia Transfusion x1 SBR 208 umol/L	Frusemide
151.M 27 910 (40) Alive	SVD Inborn (IUT) 3,8,8	- - 40%	Hypothermia Recurrent apnoea PDA Ventriculo-peritoneal shunt Hypernatraemia Exchange transfusion Transfusion x7 SBR 330 umol/L	Frusemide Caffeine
152.M 34 1500 (<3) Alive	SVD Inborn 8,8,8	- - Air	Twin 2 SBR 178 umol/L	Nil
153.F 29 1380 (55) Alive	SVD Inborn 3,8,8	1 day 18cm 40%	HMD Transfusion x1 SBR 229 umol/L	Frusemide Vitamin E Aminophylline
154.F 30 1400 (10) Alive	Vag. breech Inborn 3,6,8	1 day 22cm 65%	HMD SBR 270 umol/L	Nil
155.F 29 1410 (60) Alive	SVD Outborn 5,5,5	6 days 20cm 75%	Born in ambulance HMD Pneumonia PDA SBR 200 umol/L	Na bicarbonate Frusemide Indomethacin Aminophylline
156.F 28 1050 (45) Alive	SVD Inborn 7,7,8	- CPAP 4cm 30%	APH Neutropaenia Thrombocytopaenia Hypernatraemia SBR 189 umol/L	Nil
157.M 29 1450 (70) Alive	LSCS Inborn 1,8,8	8 days 20cm 90%	Foetal distress (CTG) Pneumonia PDA Neutropaenia UTI Hyponatraemia Hypocalcaemia Transfusion x6 SBR 215 umol/L	Pancuronium Frusemide Indomethacin Caffeine

7.35	6.37	6.03	-1	53	IVH (1)
7.22-7.44	*4.0-13.1*	*4.8-7.2*	*-10/+2*	*40-62*	
(6)	(6)	(6)	(6)	(4)	
Pre-Haemorrhage = Pre-PVL					
7.42	15.01	4.54	-1	66	IVH (2)
7.36-7.50	*9.3-23.9*	*3.4-5.3*	*-3/+2*	*40-72*	Rt cystic PVL (2)
(8)	(8)	(8)	(2)	(12)	Prog vent dil
ND	ND	ND	ND	54 -- (1)	Normal
7.37	9.07	4.91	-3	45	Bilat prolonged flare (2)
7.29-7.48	*6.9-11.5*	*3.5-7.1*	*-7/+1*	*33-52*	
(15)	(15)	(15)	(15)	(24)	
7.38	6.48	4.95	-3	78	Rt prolonged flare (2)
7.36-7.41	*5.8-7.8*	*4.0-5.6*	*-5/-1*	*40-99*	
(4)	(4)	(4)	(4)	(13)	
7.30	7.40	5.70	-5	49	IVH (4)
7.06-7.57	*3.3-17.0*	*2.2-11.5*	*-13/0*	*24-96*	
(28)	(28)	(28)	(28)	(62)	
7.40	9.28	4.75	-2	56	IVH (1)
7.37-7.50	*4.7-15.1*	*3.4-5.8*	*-4/-1*	*40-82*	
(4)	(4)	(4)	(4)	(6)	
Pre-Haemorrhage					
7.34	10.21	5.69	-3	58	IVH (2)
7.20-7.54	*3.7-21.2*	*3.1-8.2*	*-6/+1*	*39-74*	Rt cystic PVL (4)
(17)	(17)	(17)	(17)	(8)	Prog vent dil
Pre-PVL					
7.34	9.55	5.36	-4	65	
7.20-7.60	*3.7-21.2*	*2.1-8.2*	*-9/+1*	*39-99*	
(28)	(28)	(28)	(28)	(14)	

158.M 28 1280 (40) Alive	SVD Inborn 8,8,8	18 days 20cm 60%	HMD Recurrent apnoea Pneumonia Group B Strep. septicaemia PDA (ligated) Transfusion x4 SBR 154 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E Atrovent Aminophylline
159.F 29 1020 (30) Died	SVD Inborn 2,8,8	1 day 18cm 60%	Hypothermia HMD SBR 107 umol/L	Pancuronium Caffeine
160.F 28 980 (35) Alive	LSCS Outborn 3,6,8	17 days 30cm 100%	APH Foetal distress (CTG) HMD Pneumonia Recurrent apnoea Staph. epidermidis septicaemia Renal failure Hypoglycaemia Hypernatraemia Hyperkalaemia Hypocalcaemia Transfusion x9 SBR 164 umol/L	Na bicarbonate THAM Pancuronium Frusemide Tolazoline Atrovent Calcium resonium Caffeine
161.M 28 800 (5) Alive	LSCS Inborn (IUT) 3,8,8	5 days 18cm 40%	PET Hypothermia HMD PDA Staph. epidermidis septicaemia Transfusion x5 SBR 113 umol/L	THAM Pancuronium Frusemide Caffeine
162.F 29 1100 (40) Alive	LSCS Inborn 7,8,8	5 days 26cm 50%	PET Hypothermia HMD PDA NEC Hypoglycaemia Transfusion x4 SBR 110 umol/L	Na bicarbonate THAM Frusemide Indomethacin Caffeine
163.F 28 1120 (55) Alive	LSCS Inborn 2,7,8	12 days 20cm 100%	Twin 1 HMD Lt pneumothorax (2) Rt pneumothorax (2) Pneumomediastinum Pneumonia Hypernatraemia Hypocalcaemia Transfusion x5 SBR 125 umol/L	Na bicarbonate Frusemide Vitamin E Atrovent Ca gluconate Aminophylline

7.31 *7.20-7.43* (13)	7.96 *5.2-11.3* (13)	5.69 *3.4-8.0* (13)	-4 *-9/-1* (13)	ND	**IVH (3)** **Bilateral thalamic microcalcification**
7.29 *7.08-7.45* (12)	6.94 *4.3-19.0* (12)	5.78 *3.8-11.7* (12)	-6 *-11/-1* (12)	61 *53-73* (6)	**Normal**
7.37 *7.24-7.59* (43)	7.14 *3.4-21.3* (43)	5.68 *2.7-8.2* (43)	-1 *-9/+5* (43)	67 *40-90* (44)	**Small haem (7)** **Two paraventricular cysts left side**
7.34 *7.22-7.53* (64)	9.63 *4.7-20.8* (64)	4.96 *2.3-7.1* (64)	-6 *-10/-1* (64)	74 *46-98* (53)	**Normal**
7.30 *7.12-7.62* (84)	8.90 *4.5-22.0* (84)	5.38 *2.1-7.8* (84)	-6 *-16/+2* (84)	66 *36-99* (60)	**Normal**
7.29 *7.09-7.65* (116)	6.93 *3.2-20.5* (116)	5.98 *1.6-10.0* (116)	-5 *-18/+10* (116)	70 *50-88* (41)	**No haem or PVL** **Bilateral thalamic microcalcification**

164.F 28 720 (<3) Alive	LSCS Inborn 8,8,8	- - 60%	Twin 2 Late onset (day 9) respiratory distress PDA Transfusion x8 SBR 131 umol/L	Frusemide Vitamin E Aminophylline
165.M 28 1450 (>97) Died	Vag. breech Outborn 3,6,8	3 days 30cm 100%	Twin 1 HMD Lt pneumothorax (3) Rt pneumothorax (3) Convulsions Hyperkalaemia Hyponatraemia Hypocalcaemia Transfusion x1 SBR 110 umol/L	Na bicarbonate Morphine Frusemide Tolazoline Dopamine Phenobarbitone Ca gluconate
166.M 28 1290 (95) Alive	SVD Outborn 4,7,8	9 days 20cm 70%	Twin 2 HMD PDA NEC Ileostomy Thrombocytopaenia Hypoglycaemia Hyperkalaemia Hypokalaemia Hyponatraemia Hypocalcaemia Transfusion x4 SBR 218 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E Hydrocortisone Magnesium sulphate Aminophylline
167.M 26 1100 (>97) Died	SVD Outborn 4,8,8	13 days 20cm 70%	APH Trisomy 21 HMD Pneumonia PDA A-V canal defect Hyperkalaemia Hypernatraemia Hyponatraemia Hypocalcaemia Transfusion x3 SBR 107 umol/L	Na bicarbonate Frusemide Indomethacin Digoxin Calcium resonium Ca gluconate Aminophylline
168.M 30 830 (<3) Alive	LSCS Inborn (IUT) 5,8,8	20 days 20cm 80%	Maternal hypertension Poor respiratory drive Pneumonia PDA Meconium ileus Jejunostomy Thrombocytopaenia Hypoglycaemia Hypokalaemia Hypocalcaemia Transfusion x16 SBR 127 umol/L	Na bicarbonate Morphine Frusemide Indomethacin Vitamin E Atrovent Loperamide Aminophylline

7.26 *7.16-7.41* (58)	5.86 *2.4-11.5* (57)	6.26 *4.3-8.9* (57)	-6 *-11/-1* (56)	ND	**No haem or PVL** **Bilateral thalamic microcalcification**
7.27 *6.83-7.46* (15)	6.19 *2.3-11.1* (15)	5.30 *2.3-12.4* (15)	-9 *-22/0* (15)	49 *38-79* (30)	**Rt parench haem (4)**
Pre-Haemorrhage 7.28 *6.99-7.50* (30)	7.15 *3.9-13.2* (30)	5.45 *1.9-14.6* (30)	-7 *-16/-1* (30)	ND	**IVH (5)** **Bilat prolonged flare (26)**
Pre-PVL 7.32 *6.99-7.56* (71)	8.06 *3.9-24.8* (71)	5.11 *1.9-14.6* (71)	-6 *-16/+2* (70)	48 *35-71* (37)	
7.31 *7.11-7.42* (30)	8.55 *2.8-17.1* (30)	4.53 *2.7-8.2* (30)	-8 *-16/-1* (30)	ND	**IVH (4)**
7.29 *7.07-7.51* (36)	7.83 *4.1-13.8* (36)	5.14 *2.5-8.4* (36)	-7 *-13/+1* (36)	60 *40-99* (54)	**IVH (9)**

169.F 31 1470 (35) Alive	LSCS Inborn 4,8,8	4 days 16cm 75%	HMD PDA Transfusion x2 SBR 118 umol/L	Frusemide Vitamin E Aminophylline
170.M 30 1410 (45) Alive	Forceps vertex Outborn 5,7,8	8 days 20cm 70%	APH HMD Pneumonia PDA Hyponatraemia Transfusion x3 SBR 202 umol/L	Frusemide Indomethacin Vitamin E Atrovent Aminophylline
171.M 32 1140 (5) Alive	LSCS Inborn (IUT) 8,8,8	- - Air	PET Hypoglycaemia Hypernatraemia SBR 235 umol/L	Nil
172.F 31 710 (<3) Alive	LSCS Inborn (IUT) 5,8,8	12 hours 13cm 30%	Raised serum AFP PET APH Poor respiratory drive Recurrent apnoea NEC Persisting metabolic acidosis Transfusion x2 SBR 114 umol/L	Na bicarbonate Frusemide Vitamin E Aminophylline
173.M 33 1260 (<3) Alive	LSCS Inborn 8,8,8	- - Air	Omphalitis SBR 143 umol/L	Vitamin E
174.F 26 900 (70) Alive	SVD Inborn (IUT) 4,8,8	9 days 14cm 33%	Clomiphene pregnancy Maternal amnionitis Poor respiratory drive Hypoglycaemia Hypernatraemia Hypocalcaemia Transfusion x2 SBR 150 umol/L	Na bicarbonate Frusemide Aminophylline
175.M 26 1140 (>97) Died	LSCS Inborn 6,8,8	2 days 34cm 100%	HMD Clotting disorder Renal failure Hyperkalaemia Transfusion x1	Na bicarbonate THAM Pancuronium Tolazoline Dopamine Ca gluconate

7.30 *7.15-7.59* (64)	6.91 *2.8-14.9* (64)	5.83 *2.5-18.7* (64)	-4 *-11/+1* (64)	78 *56-99* (39)	**Normal**
7.33 *7.12-7.45* (15)	9.21 *5.7-18.0* (15)	5.05 *3.5-10.2* (15)	-5 *-9/-1* (15)	ND	**Small haem (4)**
7.34 *7.30-7.41* (9)	8.38 *6.6-11.3* (9)	5.53 *3.9-6.3* (9)	-3 *-6/-2* (9)	69 *58-82* (13)	**Normal**
7.28 *7.19-7.36* (35)	7.89 *4.4-20.7* (35)	4.68 *3.9-5.6* (35)	-9 *-13/-3* (35)	ND	**Normal**
ND	ND	ND	ND	ND	**Normal**
7.38 *7.16-7.47* (16)	7.38 *3.9-10.6* (16)	4.87 *3.0-9.1* (16)	-3 *-5/-1* (16)	ND	**IVH (2)**
7.13 *6.97-7.30* (19)	6.44 *1.5-11.8* (19)	6.29 *4.1-8.2* (19)	-13 *-22/-5* (19)	49 *38-66* (9)	**IVH (3)**

176.M 30 1340 (35) Alive	Vag. breech Inborn 1,7,8	3 days 24cm 85%	Twin 1 HMD Hypocalcaemia Transfusion x1 SBR 170 umol/L	Nil
177.F 30 1500 (50) Alive	LSCS Inborn 6,8,8	1 day 20cm 50%	Twin 2 HMD Hypernatraemia Hyponatraemia Hypocalcaemia SBR 180 umol/L	Nil
178.M 28 1080 (50) Died	SVD Outborn 5,5,8	9 days 30cm 100%	Born in ambulance Hypothermia HMD Lt pneumothorax (2) Rt pneumothorax (4) Pneumomediastinum Hypernatraemia Transfusion x1 SBR 103 umol/L	Na bicarbonate Morphine
179.M 28 1250 (90) Alive	Vag. breech Inborn 3,6,8	10 days 34cm 95%	APH Foetal distress (CTG) Hypothermia HMD Lt pneumothorax (2) Rt pneumothorax (2) Pneumonia PDA Staph. epidermidis septicaemia Hyponatraemia Hypocalcaemia Transfusion x9 SBR 160 umol/	Na bicarbonate THAM Pancuronium Frusemide Indomethacin Tolazoline Caffeine
180.M 31 1470 (30) Died	Forceps vertex Inborn (IUT) 3,7,8	2 days 28cm 100%	APH HMD Persistent pulmonary hypertension Lt pneumothorax (2) Rt pneumothorax (2) SBR 64 umol/L	Na bicarbonate Tolazoline Dopamine
181.M 28 1210 (75) Alive	SVD Outborn 5,8,8	13 days 20cm 60%	APH HMD Pneumonia NEC Thrombocytopaenia Convulsions Hyponatraemia Hypocalcaemia Transfusion x6 SBR 177 umol/L	Frusemide Phenobarbitone Paraldehyde Vitamin E Ca gluconate Aminophylline

7.31	9.17	5.80	-5	67	**Small haem (22)**
7.21-7.47	*4.2-26.2*	*3.6-7.9*	*-9/+4*	*50-78*	
(55)	(55)	(55)	(55)	(25)	
7.40	10.66	4.39	-4	60	**Bilat cystic PVL (1)**
7.31-7.53	*5.8-21.0*	*2.8-6.2*	*-10/-1*	*38-72*	
(20)	(20)	(20)	(20)	(14)	
Pre-Haemorrhage = Pre-PVL					
7.21	8.08	7.19	-6	48	**IVH (4)**
6.96-7.40	*3.9-15.9*	*4.7-15.5*	*-15/+1*	*37-64*	**Rt echodense PVL (4)**
(40)	(40)	(40)	(40)	(54)	
7.33	10.19	5.68	-3	68	**Small haem (3)**
7.19-7.46	*3.5-39.2*	*3.6-8.5*	*-6/0*	*48-92*	
(34)	(34)	(34)	(34)	(13)	
7.25	4.96	5.32	-9	46	**Normal**
7.18-7.43	*3.5-6.4*	*3.7-6.4*	*-12/-4*	*40-52*	
(9)	(9)	(9)	(9)	(13)	
7.29	6.72	5.25	-7	ND	**Normal**
7.18-7.42	*3.8-12.8*	*3.2-8.9*	*-13/-1*		
(70)	(70)	(70)	(70)		

182.F 25 760 (70) Alive	Vag. breech Outborn 5,8,8	35 days 20cm 60%	APH Hypothermia HMD Pneumonia Recurrent apnoea Arrythmia (complete heart block and VT) Renal failure Hypoglycaemia Hypernatraemia Hyperkalaemia Hypocalcaemia Transfusion x10 SBR 130 umol/L	Na bicarbonate Frusemide Calcium resonium Insulin Ca gluconate Caffeine
183.M 33 1000 (<3) Alive	LSCS Inborn 8,8,8	- - Air	Raised serum AFP PET Foetal distress (CTG) Transfusion x1 SBR 130 umol/L	Frusemide
184.M 29 1450 (70) Alive	SVD Inborn (IUT) 6,8,8	- - Air	APH Recurrent apnoea Hypernatraemia SBR 192 umol/L	Vitamin E Aminophylline
185.M 26 970 (90) Alive	Vag. breech Inborn 8,8,8	1 day 16cm 45%	Hypothermia Poor respiratory drive PDA Hypernatraemia Hyperkalaemia Transfusion x1 SBR 178 umol/L	Na bicarbonate Frusemide Vitamin E Aminophylline
186.M 27 1100 (85) Alive	Forceps vertex Outborn 8,8,8	- - 28%	Twin 1 HMD SBR 104 umol/L	Na bicarbonate Vitamin E Aminophylline
187.F 27 950 (50) Alive	Vag. breech Outborn 6,7,8	1 day 16cm 40%	Twin 2 HMD Hypoglycaemia Hyperkalaemia Hypocalcaemia Transfusion x1 SBR 100 umol/L	Na bicarbonate Frusemide Vitamin E Ca gluconate Aminophylline
188.M 29 1460 (70) Alive	SVD Outborn ND,ND,ND ("cried at birth")	5 days 16cm 80%	Born at home HMD NEC E coli UTI Hypernatraemia Hyperkalaemia Hypocalcaemia Transfusion x2 SBR 149 umol/L	Na bicarbonate Frusemide Vitamin E Ca gluconate Naloxone Aminophylline

7.30 *7.06-7.51* (108)	11.30 *4.1-21.2* (108)	5.72 *3.1-9.7* (108)	-6 *-11/+5* (108)	60 *42-76* (50)	**Small haem (17)**
7.37 ---- (1)	8.60 ---- (1)	5.70 ---- (1)	-6 -- (1)	78 -- (1)	**Normal**
7.29 *7.22-7.40* (17)	6.54 *4.2-17.5* (17)	5.87 *5.1-7.9* (17)	-4 *-7/0* (17)	ND	**Normal**
7.43 *7.32-7.52* (11)	8.10 *4.5-10.4* (11)	3.57 *2.6-5.4* (11)	-4 *-6/-2* (11)	ND	**IVH (1)**
7.32 *7.31-7.33* (4)	4.38 *3.8-4.9* (4)	5.68 *5.4-5.9* (4)	-4 *-5/-3* (4)	ND	**IVH (3)**
7.31 *7.20-7.45* (35)	7.17 *3.8-14.7* (35)	4.86 *3.0-7.2* (35)	-6 *-13/0* (35)	ND	**Normal**
Pre-Haemorrhage 7.33 *7.20-7.50* (26)	7.49 *3.6-14.3* (26)	4.64 *3.0-8.7* (26)	-7 *-14/-2* (26)	ND	**IVH (6)** **Bilat cystic PVL (2)**
Pre-PVL 7.36 *7.20-7.50* (16)	8.15 *3.6-14.3* (16)	4.89 *3.0-8.7* (16)	-4 *-10/-2* (16)	ND	

189.F 29 1250 (50) Alive	SVD Inborn 8,8,8	- - 30%	Transfusion x1 SBR 205 umol/L	Frusemide
190.F 27 1060 (75) Alive	LSCS Inborn (IUT) 4,8,8	6 days 24cm 80%	Foetal distress (CTG) HMD PDA (ligated) Hyponatraemia Hypocalcaemia Transfusion x2 SBR 160 umol/L	THAM Frusemide Indomethacin Caffeine
191.M 29 1400 (55) Alive	SVD Inborn 8,8,8	- - Air	Transfusion x1 SBR 180 umol/L	Frusemide Caffeine
192.F 30 1460 (50) Alive	Forceps vertex Inborn 3,8,8	3 days 20cm 80%	Foetal distress (CTG) HMD PDA Transfusion x1 SBR 149 umol/L	Na bicarbonate Frusemide Indomethacin Vitamin E Ca gluconate Aminophylline
193.M 31 1470 (35) Alive	LSCS Inborn 5,8,8	7 days 35cm 100%	PET Foetal distress (CTG) Hypothermia HMD PDA Hypoglycaemia Transfusion x4 SBR 150 umol/L	Pethidine Pancuronium Frusemide
194.M 30 1460 (45) Alive	SVD Inborn 5,8,8	1 day 18cm 30%	Foetal distress (meconium) HMD Staph. epidermidis septicaemia SBR 190 umol/L	Caffeine
195.M 29 1500 (75) Alive	SVD Inborn 6,8,8	5 days 30cm 80%	Two months ruptured membranes Oligohydramnios APH ? pulmonary hypoplasia Hypernatraemia Hyperkalaemia Hypocalcaemia Transfusion x1 SBR 182 umol/L	Na bicarbonate Diamorphine Frusemide Tolazoline Vitamin E Ca gluconate Aminophylline

7.36 *7.34-7.38* (4)	10.63 *9.1-12.1* (4)	5.50 *5.1-5.9* (4)	-2 *-5/0* (4)	54 *50-58* (5)	**Small haem (4)**
7.37 *7.21-7.53* (15)	9.52 *3.6-22.1* (15)	4.95 *3.0-7.5* (15)	-4 *-9/-2* (15)	50 *40-56* (10)	**IVH (2)**
ND	ND	ND	ND	ND	**Normal**
7.29 *7.16-7.40* (47)	7.63 *2.7-13.2* (47)	5.15 *2.7-7.8* (47)	-7 *-17/-2* (47)	ND	**Small haem (13)**
7.32 *7.22-7.58* (116)	8.14 *3.3-32.7* (116)	6.61 *2.4-9.4* (116)	00 *-8/+7* (114)	69 *50-94* (52)	**Small haem (51)**
7.39 *7.35-7.50* (11)	10.53 *5.8-16.6* (11)	5.05 *4.1-5.7* (11)	-2 *-5/+1* (11)	58 *48-72* (5)	**IVH (2)** **Lt subdural haem**
Pre-Haemorrhage = Pre-PVL					
7.27 *6.99-7.35* (25)	6.74 *2.2-11.6* (25)	5.84 *2.2-14.6* (25)	-7 *-17/-3* (25)	55 *39-90* (53)	**IVH (3)** **Rt cystic PVL (3)**

196.F 30 940 (8) Alive	LSCS Inborn 8,8,8	- - Air	PET Foetal distress (CTG) Polycythaemia Partial plasma exchange SBR 141 umol/L	Vitamin E
197.M 32 1420 (10) Died	LSCS Outborn 7,8,8	38 days 30cm 100%	PET Foetal distress (CTG) HMD Pneumonia PDA Staph. aureus septicaemia Systemic candidiasis Leucopenia DIC Convulsions Renal failure Hypoglycaemia Hyponatraemia Hyperkalaemia Hypocalcaemia Hypomagnesaemia Transfusion x12 SBR 155 umol/L	Na bicarbonate Frusemide Dopamine Phenobarbitone Clonazepam Ca gluconate Magnesium sulphate Amphotericin 5-Flucytosine
198.F 26 810 (50) Died	SVD Inborn 7,8,8	1 day 38cm 100%	Group B Strep. septicaemia Pneumonia Persistent metabolic acidosis	Na bicarbonate THAM Pancuronium Tolazoline Nitroprusside Dopamine
199.M 29 1500 (75) Alive	LSCS Inborn (IUT) 3,8,8	36 days 30cm 100%	Maternal diabetes HMD Lt pneumothorax (2) Rt pneumothorax (2) Pneumomediastinum Pneumonia Hypoglycaemia Hyponatraemia Hypokalaemia Hypocalcaemia Transfusion x7 SBR 179 umol/L	Na bicarbonate Frusemide Tolazoline Dopamine Vitamin E Atrovent Ca gluconate Aminophylline

7.29 *7.22-7.36* (8)	6.89 *5.6-8.3* (8)	5.93 *5.1-7.1* (8)	-5 *-6/-3* (8)	ND	**Normal**
7.31 *7.08-7.50* (167)	9.55 *3.6-24.5* (167)	5.78 *3.0-10.7* (167)	-4 *-16/+8* (165)	60 *34-99* (150)	**Normal**
7.10 *6.89-7.24* (20)	3.64 *1.4-7.0* (20)	6.21 *3.5-9.6* (20)	-15 *-21/-9* (20)	46 *24-99* (7)	**IVH (1)**
7.26 *6.89-7.50* (64)	6.17 *3.7-11.4* (64)	7.23 *3.8-22.1* (64)	-4 *-22/+3* (64)	59 *28-99* (130)	**Bilat prolonged flare (10)**

200.F	LSCS	23 days	APH	Na bicarbonate
27	Inborn (IUT)	22cm	HMD	Frusemide
970 (55)	8,8,8	100%	Lt pneumothorax (2)	Indomethacin
Alive			Rt pneumothorax (1)	Vitamin E
			Pneumonia	Ca gluconate
			Recurrent apnoea	Aminophylline
			PDA	
			Therapeutic LP (x12)	
			Hypocalcaemia	
			Transfusion x7	
			SBR 137 umol/L	

7.29 *7.06-7.45* (55)	7.33 *4.2-18.4* (55)	5.42 *2.6-10.3* (55)	-7 *-12/-3* (55)	ND	**IVH (9)** **Prog vent dil**

KEY TO PATIENT DATA TABLES.

Left Page

Column 1
Study number. Sex.
Gestation (weeks).
Birthweight (grams). Weight centile.
Final outcome.

Column 2
Mode of delivery.
Inborn (including in utero transfer) or outborn.
Apgar score at 1, 5, 10 minutes (score 8 = 8 or better).

Column 3
Duration of ventilation (IPPV only).
Maximum inspiratory ventilator pressure.
Maximum inspired oxygen concentration.

Column 4
Major clinical events and peak serum bilirubin level.
N.B. Day of pneumothorax given in brackets.
Transfusion refers only to those with blood.

Column 5
Drugs administered excluding antibiotics.

Abbreviations Used.

IUT	in utero transfer
APH	antepartum haemorrhage
PET	pre-eclamptic toxaemia
AFP	alphafetoprotein
CTG	cardiotocograph
SVD	spontaneous vaginal delivery
LSCS	lower segment caesarean section
Vag breech	vaginal breech delivery
HMD	hyaline membrane disease
TTN	transient tachypnoea of the newborn
PIE	pulmonary interstitial emphysema
CPAP	continuous positive airway pressure
PDA	persistent ductus arteriosus
NEC	necrotising enterocolitis
DIC	disseminated intravascular coagulation
UTI	urinary tract infection
LP	lumbar puncture
SBR	serum bilirubin
SVT	supraventricular tachycardia
VT	ventricular tachycardia
VF	ventricular fibrillation
VSD	ventricular septal defect
A-V canal	atrio-ventricular canal
Hb	haemoglobin
Staph	staphylococcus
Strep	streptococcus
H	haemophilus
E	escherichia
Na	sodium
Ca	calcium
THAM	trishydroxymethyl-amino-methane
ND	not done

Right Page

Column 1 pH

Column 2 pO2

Column 3 pCO2

Column 4 Base deficit

Column 5 Systolic blood pressure

For each parameter is given: mean value
range
number of measurements (brackets)

Column 6 Ultrasound scan findings

Figures in brackets signify the day on which the abnormality was initially detected.

Abbreviations Used.

Lt	left
Rt	right
Bilat	bilateral
IVH	intraventricular haemorrhage
Haem	haemorrhage
Parench	parenchymal
PVL	periventricular leucomalacia
Prog vent dil	progressive ventricular dilatation
Non-prog vent dil	non-progressive ventricular dilatation
Corp call	corpus callosum
Intravent	intraventricular
ND	not done

ILLUSTRATIONS

FIGURES AND TABLES

CAPTIONS FOR FIGURES AND TABLES

1. Details summarising the five non-study babies who were included in the section on autopsy correlation.

2. Coding for continuous and intermittent data with stratification bands set for testing blood gas and systolic blood pressure data points.

3. Venn diagram demonstrating the distribution and relationship of haemorrhage and periventricular leucomalacia. (Not drawn to scale).

4. Flow chart showing the distribution of haemorrhage and periventricular leucomalacia. Figures in brackets refer to the numbers of infants with germinal matrix, intraventricular and parenchymal haemorrhage respectively.

* Four babies had extension one side and periventricular leucomalacia the other.

5. The patterns of parenchymal lesions.

6. Histogram to show the time of initial detection of haemorrhage on ultrasound scanning.

7. Histogram to show the time of initial detection of precystic and cystic periventricular leucomalacia on ultrasound scanning.

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9. The sites of cystic periventricular leucomalacia.

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11. Histogram to show the relationship of periventricular leucomalacia and flare to gestation.

12. Histogram to show the relationship of haemorrhage and its severity to birthweight.

13. Histogram to show the relationship of periventricular leucomalacia and flare to birthweight.

14. The correlation between ultrasound and post-mortem diagnoses for the study group of sixty hemispheres. % figures in brackets.

As each hemisphere may have more than one pattern of disease the numbers do not add up to 60.

15. The correlation between post-mortem and ultrasound diagnoses for the study group of sixty hemispheres. % figures in brackets.

16. The risk factors predicting periventricular haemorrhage that reached significance at the 1% level.

17. The risk factors predicting periventricular leucomalacia that reached significance at the 1% level.

18. Analysis of the proportion of time spent with intermittent data point results in each stratification band (Mann - Whitney U test).

19. The surgical procedures performed.

20. Significance for the risk factors associated with periventricular haemorrhage and leucomalacia. The estimate refers to the GLIM equation.

Table 1. The Five Non-study Babies.

Baby	Gestation (Wks.)	B.W. (Gms.)	Problems in Pregnancy	Delivery	Neonatal Problems	Age death	Ultrasound	Pathology
A.C.	30	1640	P.E.T.	S.V.D.	H.M.D. I.P.P.V.	2 days	Normal	Congestion P.V.W.M. bilaterally
J.M.	29	940	Nil	S.V.D.	Birth asphyxia Recurrent apnoea I.P.P.V. Hyperkalaemia Tachyarrhythmia Jaundice	6 mths.	Bilateral cystic P.V.L.	Cerebral atrophy, no cysts
N.H.	34	2040	Epilim Rx	S.V.D.	H.M.D. I.P.P.V. P.D.A. Pseudomonas septicaemia	5 days	Bilateral I.V.H.; Bilateral echodensity P.V.W.M. & cysts	I.V.H.,infarction P.V.W.M., cysts
M.K.	26	1085	A.F.P. upper normal Breech	L.S.C.S.	Birth asphyxia H.M.D. I.P.P.V. P.I.E.	16 hours	Rt. I.V.H. Parenchyma normal	Rt. I.V.H., Parenchyma normal
R.M.	26	900	Placenta praevia A.P.H.	S.V.D.	Birth asphyxia H.M.D. I.P.P.V.	5 hours	Bilateral I.V.H., Echodensity Lt. parenchyma	Bilateral I.V.H., Congestion Lt. P.V.W.M.

Table 2

Coding for Continuous and Intermittent Data with Stratification Bands Set for Testing Blood Gas and Systolic Blood Pressure Data Points

Continuous data

gestational age (weeks)

intrauterine growth (nearest centile)

maximum bilirubin concentration (micromol/L)

Intermittent data

blood gases

pH (proportion of time pH <7, <7.1, <7.2, <7.3)

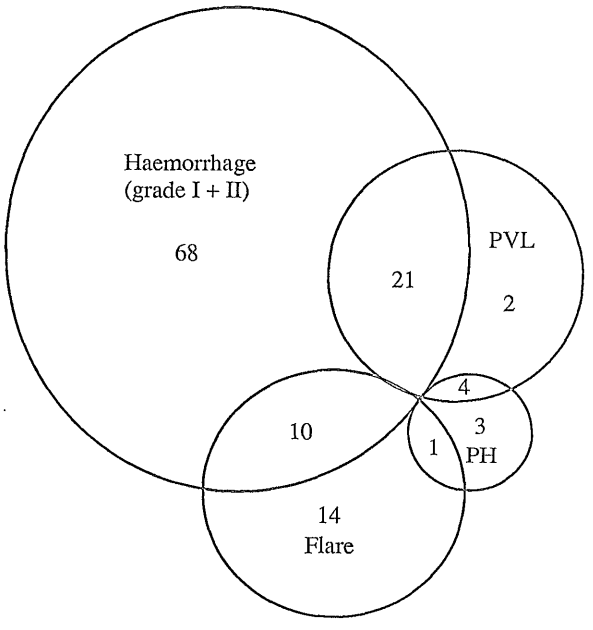
PaO2 (proportion of time <5, <7, <9, <11 kPa)

PaCO2 (proportion of time >/=9, >/=7, >/=5, >/=3 kPa)

base deficit (proportion of time <-12, <-8, <-4 mmol/L)

systolic blood pressure (proportion of time <25, <35, <45, <55 mm Hg).

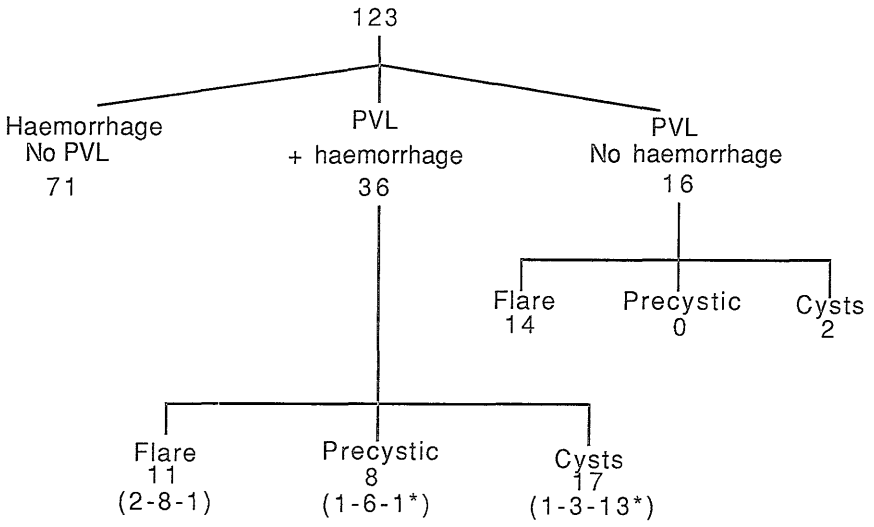
Figure 3. The Distribution of Haemorrhage and Periventricular Leucomalacia.



PH = parenchymal haemorrhage
PVL = periventricular leucomalacia

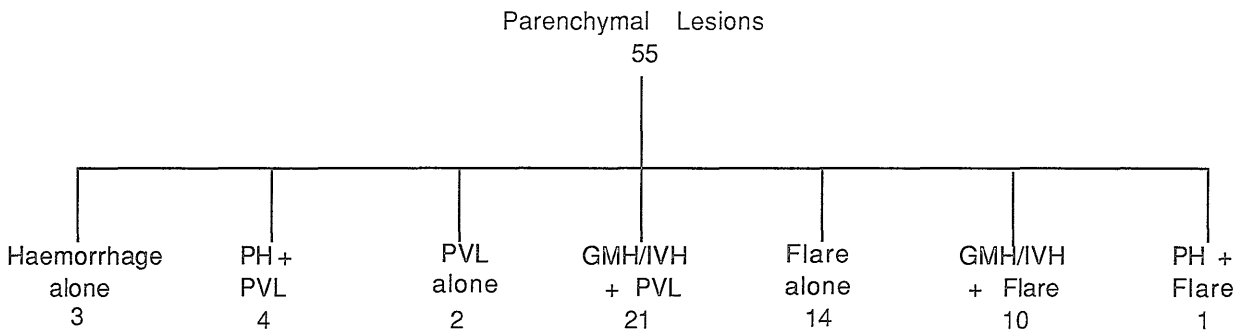
Not totally to scale.

Figure 4. The Distribution of Haemorrhage and Periventricular Leucomalacia.



* Four babies had extension on one side and PVL on the other.

Figure 5. The Pattern of Parenchymal Lesions.



GMH = Germinal Matrix Haemorrhage
IVH = Intraventricular Haemorhage
PH = Parenchymal Haemorrhage
PVL = Periventricular Leucomalacia

Figure 6. Timing of Haemorrhage.

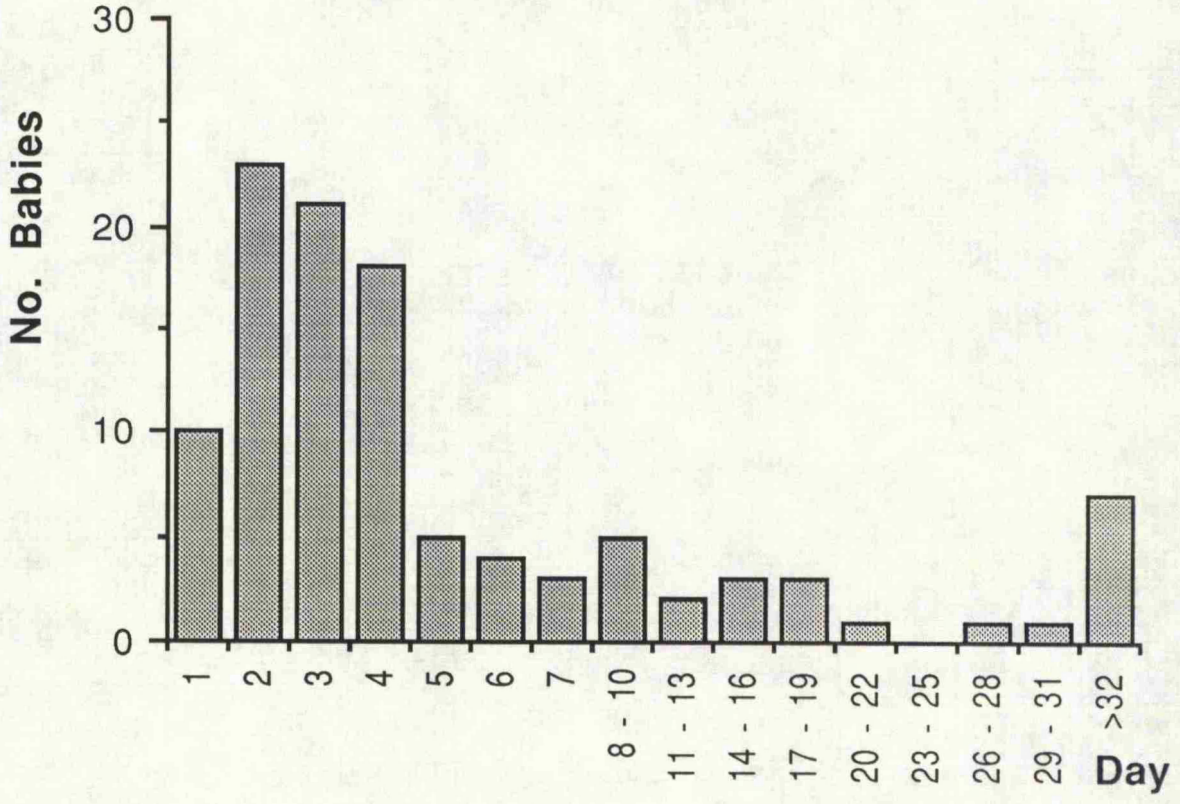


Figure 7. Timing of Precystic and Cystic PVL.

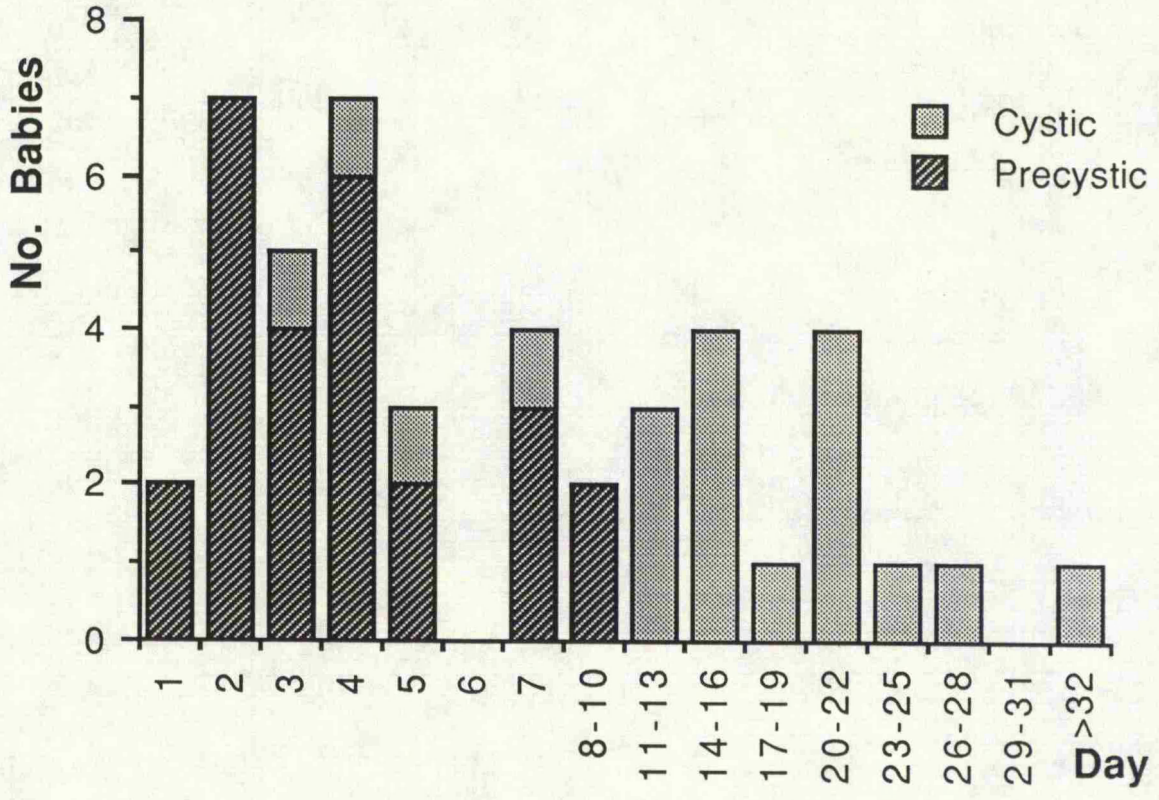


Figure 8. Timing of Prolonged Flare.

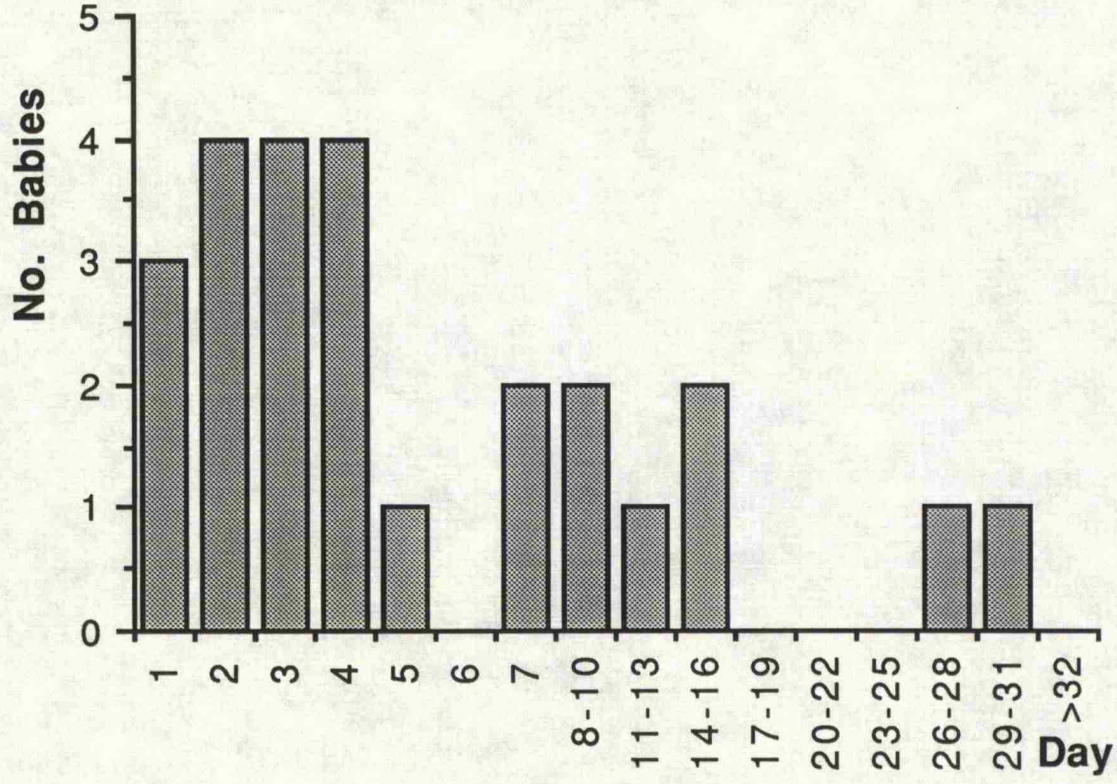


Table 9

The Sites of Cystic Periventricular Leucomalacia.

Bilateral	8
Unilateral	11
Parietal	12
Occipital	9
Frontal	6

In some babies more than one site is affected and hence the total is greater than 19.

Figure 10. Haemorrhage v. Gestation.

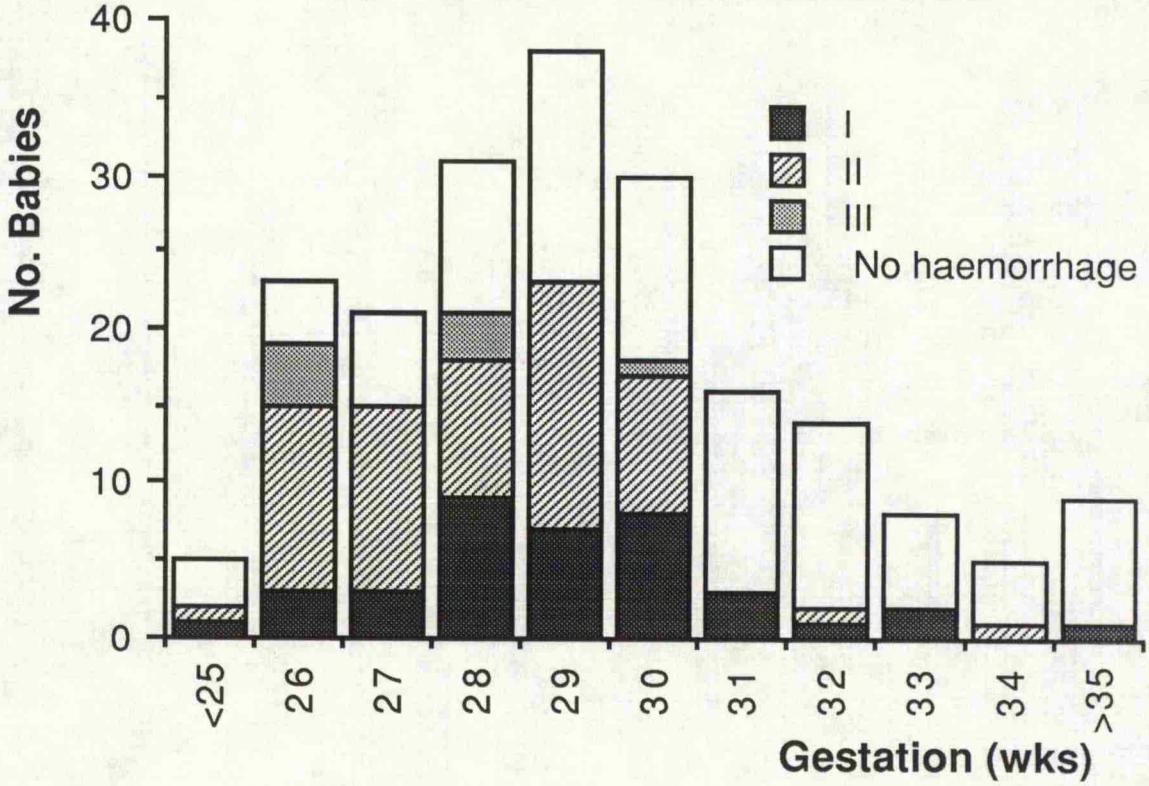


Figure 11. PVL and Flare v. Gestation.

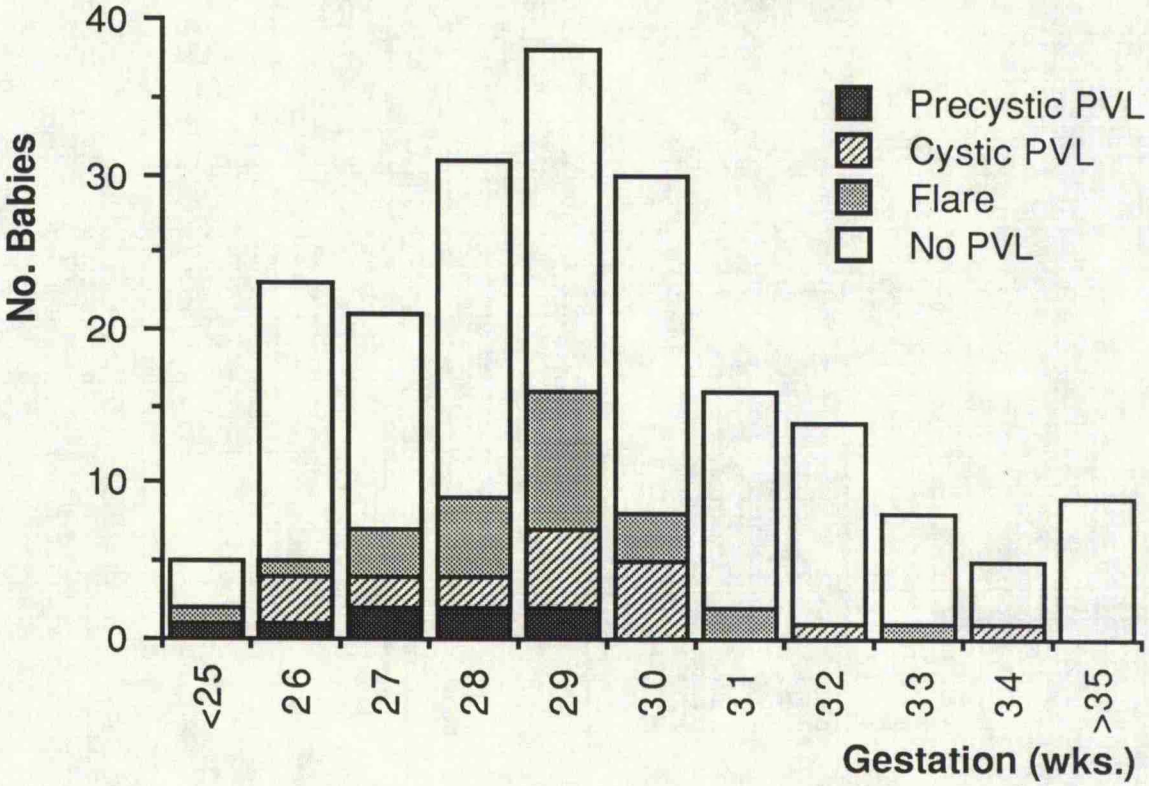


Figure 12. Haemorrhage v. Birthweight.

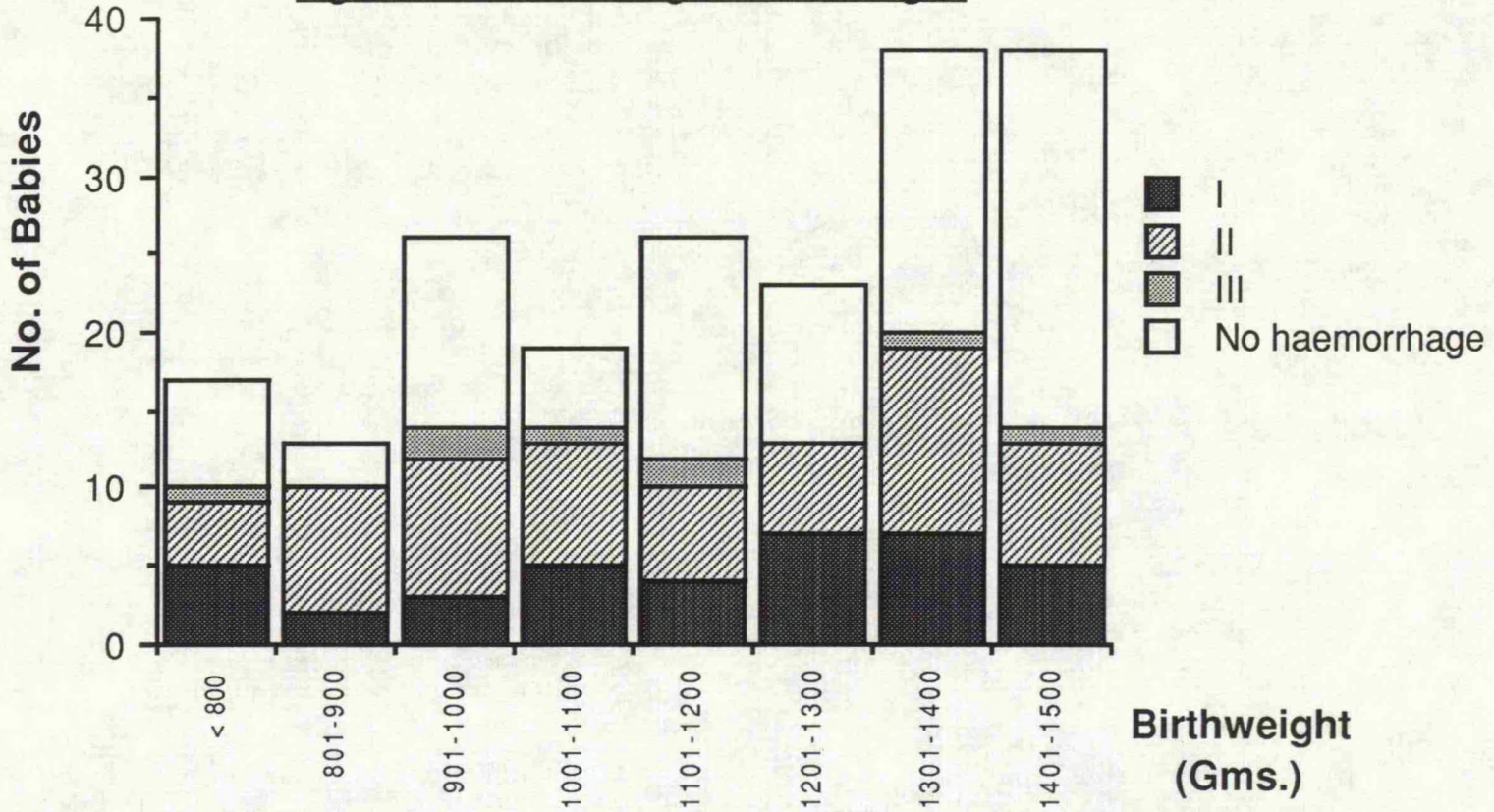


Figure 13. PVL and Flare v. Birthweight.

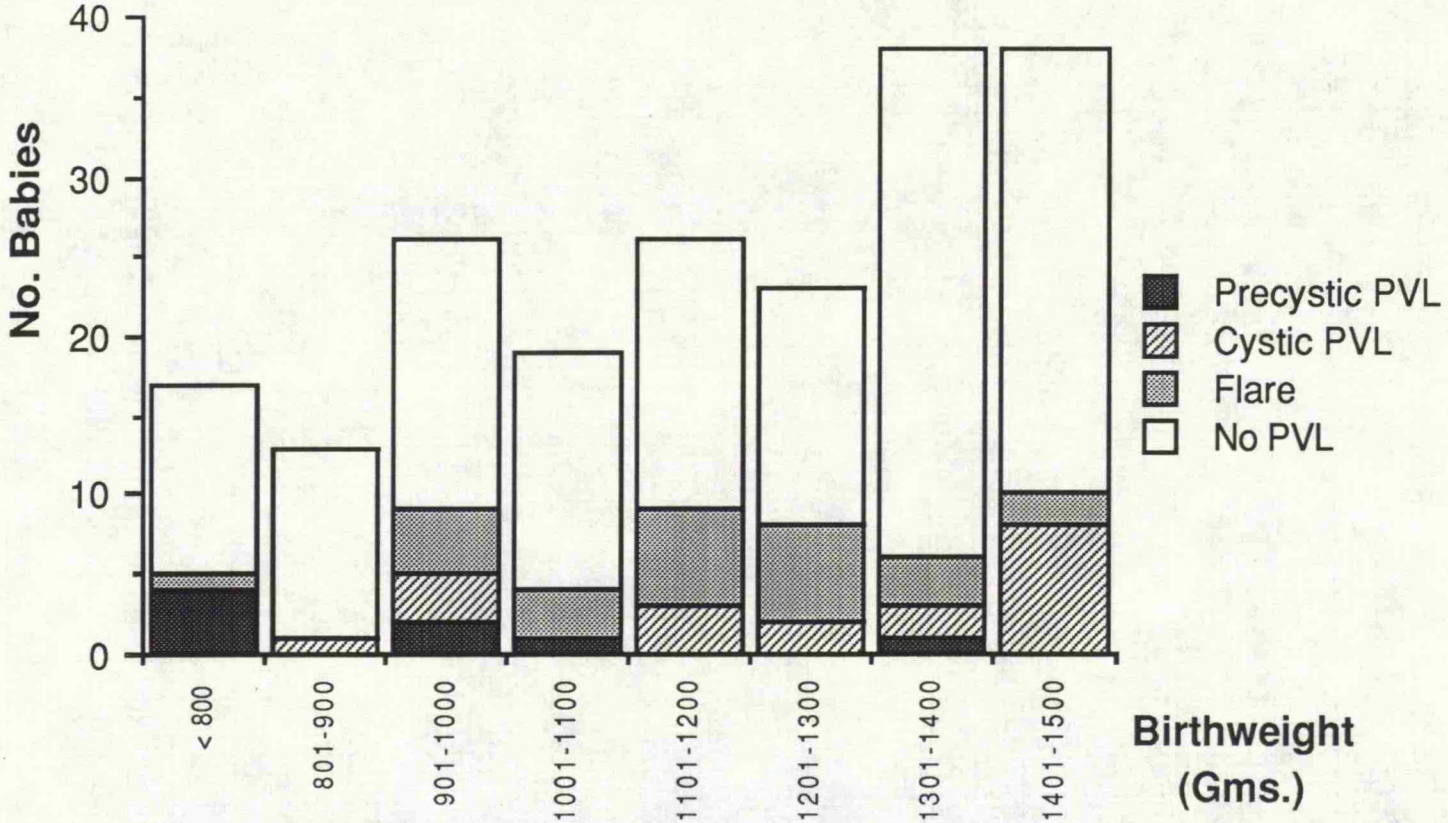


Table 14

Correlation Between Ultrasound and Postmortem Diagnoses for the Study Group of Sixty Hemispheres.

Ultrasound Observation	*Postmortem Observation*		
	Normal	**PVH**	**PVL**
Normal	22 (79)	3 (10.5)	3 (10.5)
PVH	4 (11)	31 (89)	0
PVL	3 (15)	0	17 (85)

Each hemisphere may have more than one pattern of disease and so the numbers do not add up to 60.

The figures in parentheses represent the per centage of each pattern of ultrasound diagnosis compared to the subsequent autopsy finding. For example, 11% of those in whom there was an ultrasound diagnosis of haemorrhage were found to have a normal brain at postmortem.

Table 15

Correlation Between Postmortem and Ultrasound Diagnoses for the Study Group of Sixty Hemispheres.

Postmortem Observation	*Ultrasound Observation*		
	Normal	PVH	PVL
Normal	22 (76)	4 (14)	3 (10)
PVH	3 (9)	31 (91)	0
PVL	3 (15)	0	17 (85)

Each hemisphere may have more than one pattern of disease and so the numbers do not add up to 60.

Figures in parentheses represent the per centage diagnosis on ultrasound for each pattern identified at postmortem. For example, of the hemispheres containing haemorrhage at autopsy 91% had been diagnosed by ultrasound.

Table 16

Risk Factors for Prediction of PVH that Reached Significance at a 1% Level.

Gestational age

Poor intrauterine growth (reduced risk)

Anaemia (reduced risk)

Coagulation disorder

Vaginal delivery v Caesarean section

pH < 7.2

Arrythmia

Need for blood transfusion

Intermittent Positive Pressure Ventilation

Tolazoline infusion

Alkali infusion

PaCO2 > or = 7.0 kPa

Surgery

Systolic blood pressure > 55 mm.Hg

Table 17

Risk Factors for Prediction of Development of PVL that Reached Significance at the 1% Level

Gestational age

Anaemia (reduced risk)

PaCO2 > or = 7.0 kPa

Surgery

pH < 7.1

Maximum bilirubin concentration

Coagulation disorder

Number of blood transfusions

Intermittent positive pressure ventilation

Pneumothorax

Table 18

Analysis of Proportion of Time Spent with Intermittent Data Point Results in Each Stratification Band.

Analysis by Mann-Whitney U Test. NS = not significant.

	Periventricular leucomalacia	*Periventricular haemorrhage*
pH		
< 7.0	p=0.02	p=0.005
< 7.1	p=0.002	p=0.003
< 7.2	NS	p=0.01
< 7.3	NS	NS
PaO2 (kPa)	NS for any strata	NS for any strata
PaCO2 (kPa)		
>/= 9	p=0.009	p=0.002
>/= 7	p=0.004	p=0.01
>/= 5	NS	NS
>/= 3	NS	NS
Base deficit (mmol/L)		
< -12	NS	p=0.03
< -8	NS	p=0.02
< -4	NS	NS
Systolic blood pressure		
> 55 mmHg	NS	p=0.0007
	NS for other strata	NS for other strata

Table 19

The Surgical Procedures Performed.

Procedure	*No of Babies*
Ileostomy	5 (3 for NEC)
Colostomy	2 (1 for NEC)
PDA ligation	2
Jejunostomy	1
Pleurotomy	1

Table 20

Significance for the Risk Factors Associated with Periventricular Haemorrhage and Periventricular Leucomalacia.

The estimate refers to the GLIM equation.

	Estimate	Standard Error of the Estimate	p Value
		Periventricular Haemorrhage	
Gestation	-0.414	0.0937	<0.001
Anaemia	-1.845	0.4374	<0.001
Coagulation disorder	+1.935	0.7047	0.001
Proportion of time PaCO2 >/= 7.0 kPa	+2.770	1.3970	0.038
		Periventricular Leucomalacia	
Anaemia	-1.860	0.4907	<0.001
Maximum bilirubin concentration	+0.013	0.0041	<0.001
Pneumothorax	+1.556	0.5149	0.001
Proportion of time PaCO2 >/= 7.0 kPa	+3.649	1.3270	0.005
Surgery	+1.305	0.5700	0.022

DIAGRAM AND PHOTOGRAPHIC PLATES OF SCANS AND PATHOLOGICAL SPECIMENS

CAPTIONS FOR DIAGRAM AND PHOTOGRAPHIC PLATES

1. Diagram: The different patterns of arterial ending in the periventricular region. (After de Reuck, 1971).

2. Normal midcoronal ultrasound scan of an infant of 28 weeks gestation showing the lateral ventricles (left side marked v) and the cavum septum pellucidum between them.

3. A small right-sided haemorrhage (arrowed) seen in coronal (a) and parasagittal (b) planes.

4. A coronal ultrasound scan showing a left sided parenchymal haemorrhage. The right lateral ventricle is dilated.

5. A post-mortem specimen showing a right sided porencephalic cyst with some residual thrombus. The ependyma of the ventricle is ruptured. This is the appearance of a parenchymal haemorrhage. The left ventricle is dilated.

6. Cystic periventricular leucomalacia seen in posterior coronal (a) and parasagittal (b) planes.

7. Pathological specimens showing cystic periventricular leucomalacia in coronal brain cuts in the right temperoparietal region (a) and bilaterally in the occipital area (b).

8. Coronal ultrasound scans showing large intraventricular haemorrhage with ipsilateral "precystic" PVL seen unilaterally (right side) [a] and bilaterally (b).

9. Posterior coronal section of the brain to show left sided intraventricular haemorrhage with vascular congestion of the ipsilateral periventricular area.

10. Two coronal sections through the same brain showing bilateral intraventricular haemorrhage and infarction of the periventricular region on the right side. The ependyma of the lateral ventricle is intact throughout.

11. Periventricular flare seen bilaterally in the midcoronal scan (a) and in the parasagittal plane lateral to the lateral ventricle (b).

12. Midcoronal ultrasound scans of the same baby showing:

a) day 3 - right sided parenchymal haemorrhage;

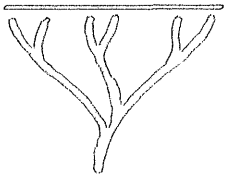
b) day 7 - echodensity in the left periventricular area; the haemorrhage is resolving;

c) day 32 - resolving to a large right sided porencephalic cyst and multiple cysts of PVL on the left. There is a large cavum septum pellucidum (c).

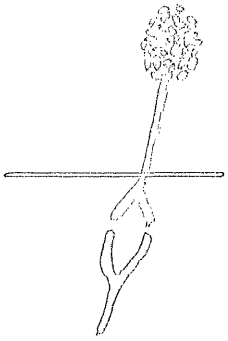
13. Coronal ultrasound scans of the same baby showing a right sided periventricular "flare" on day 3 (a) and a parenchymal haemorrhage in the corresponding site on day 6(b). There is ventricular dilatation in the second scan.

14. Haematoxylin and eosin stain showing generalised spongiosis (vacuolation) of the periventricular white matter (arrows) [a - magnification x400] and microcalcification (arrowhead) [b - magnification x1000].

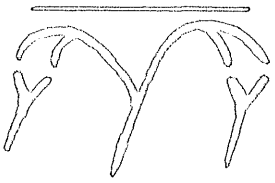
1. Diagram: The Different Patterns of Arterial Ending in the Periventricular Region.



Type I
Ventriculopetal medullary artery ends in the ventricular wall itself.
E.g. in the anterior part of the corpus callosum.



Type II
Ventriculopetal medullary artery meets ventriculofugal branches of a choroidal artery at 3-10mm. from the ventricle wall.
E.g. around posterior horn and posterior part of the inferior horn of the lateral ventricle.



Type III
Between the ventriculopetal and the ventriculofugal branches of the medullary arteries at 3-10mm. from the ventricle wall.
E.g. around the anterior horn, body and anterior part of the inferior horn of the lateral ventricle.

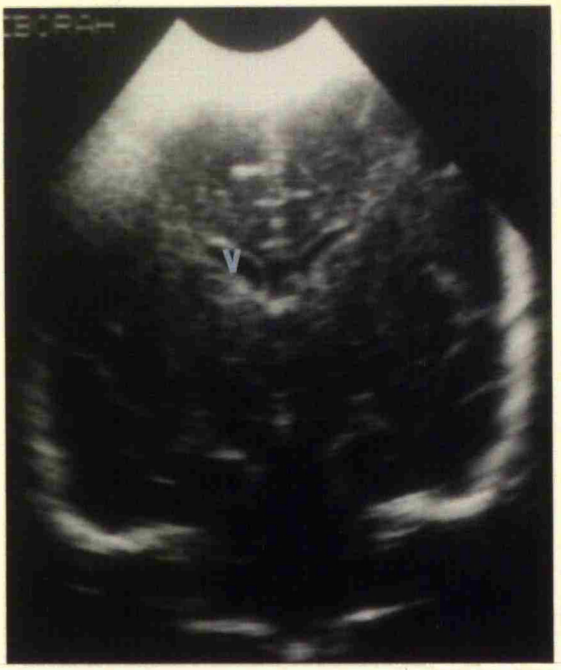
Key:

= ventricle wall

= medullary artery

= choroidal artery

(After de Reuck, 1971)



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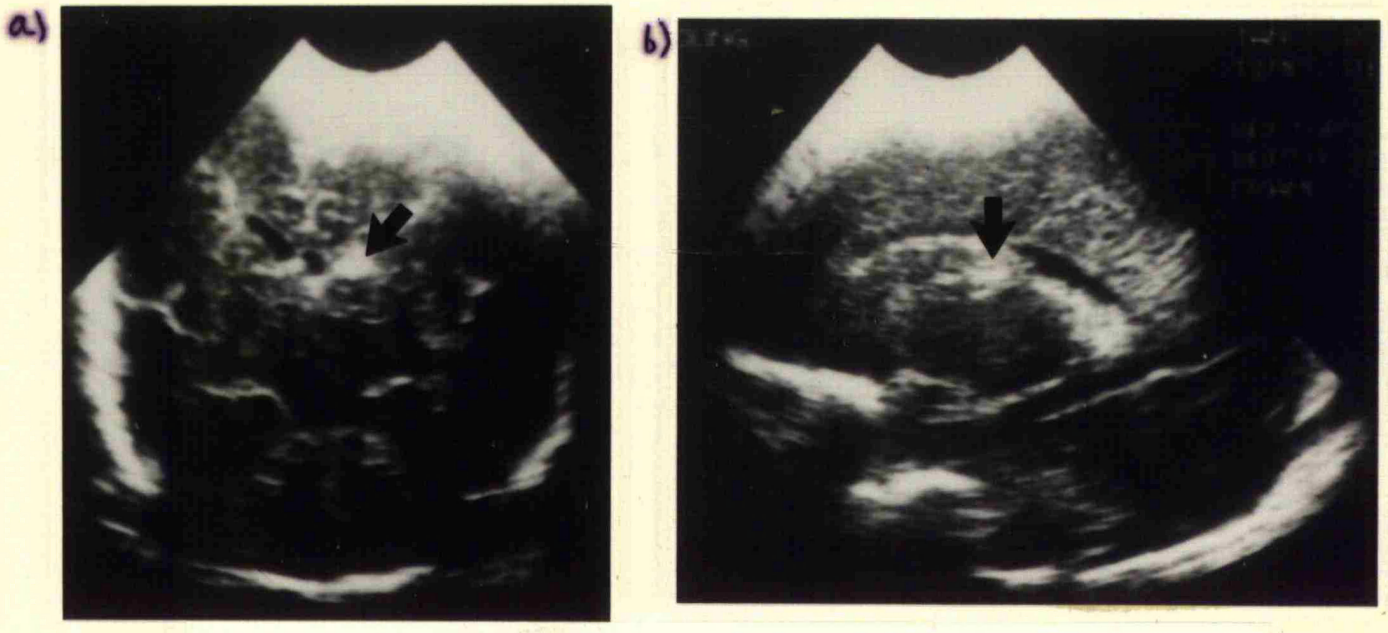

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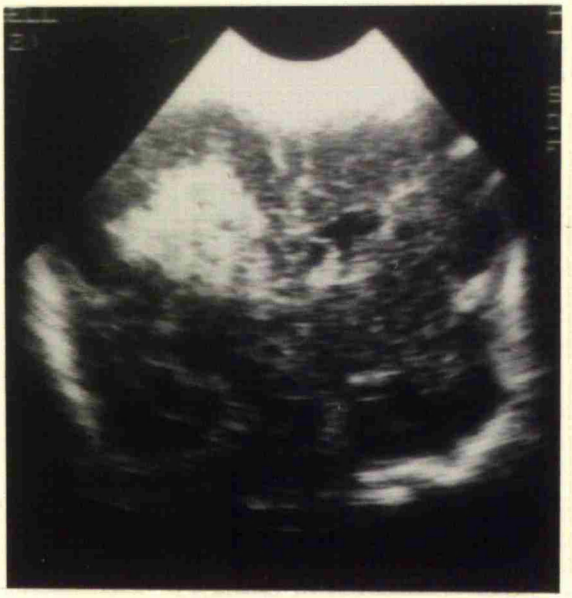
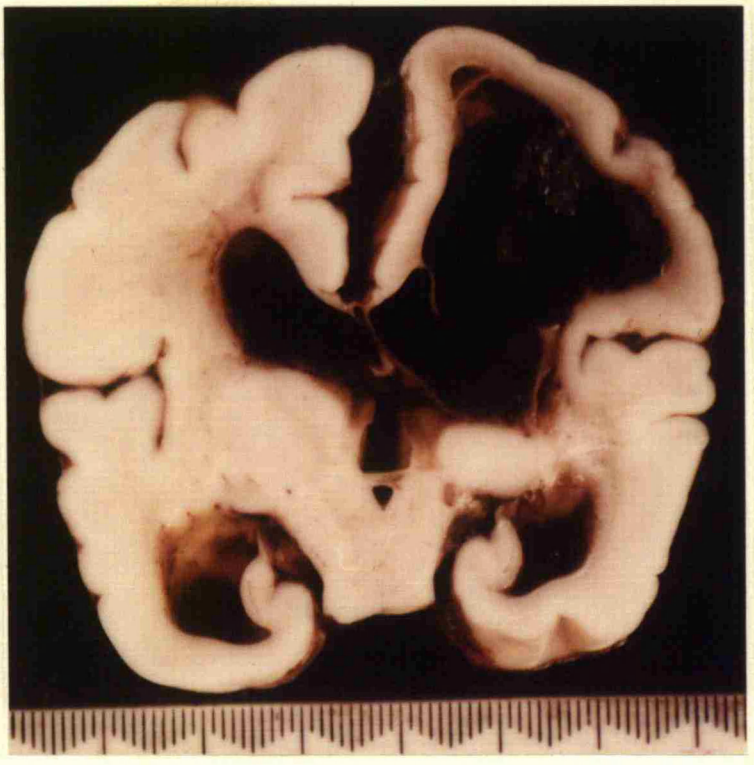


4. A coronal ultrasound scan showing a left sided parenchymal haemorrhage. The right lateral ventricle is dilated.



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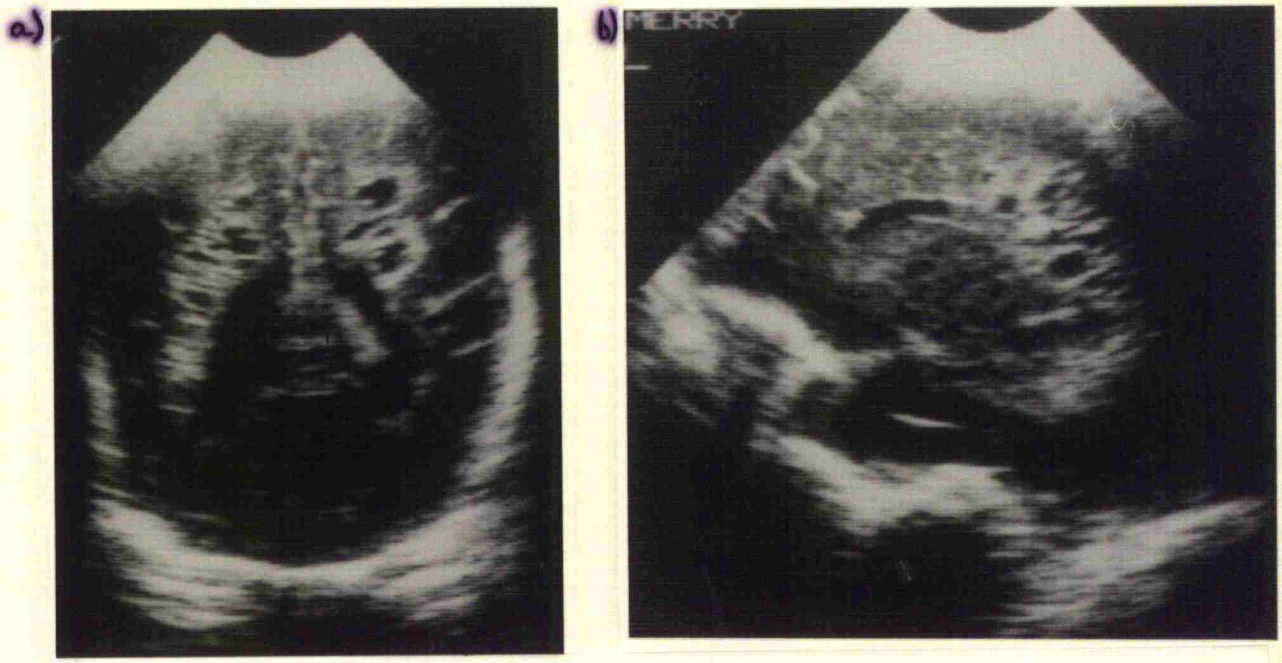
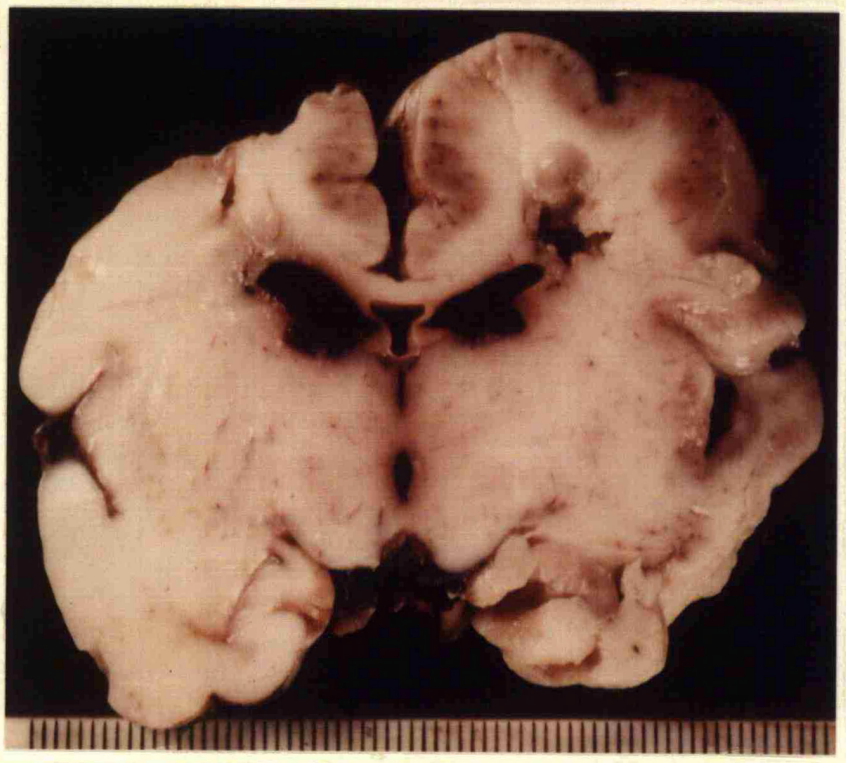
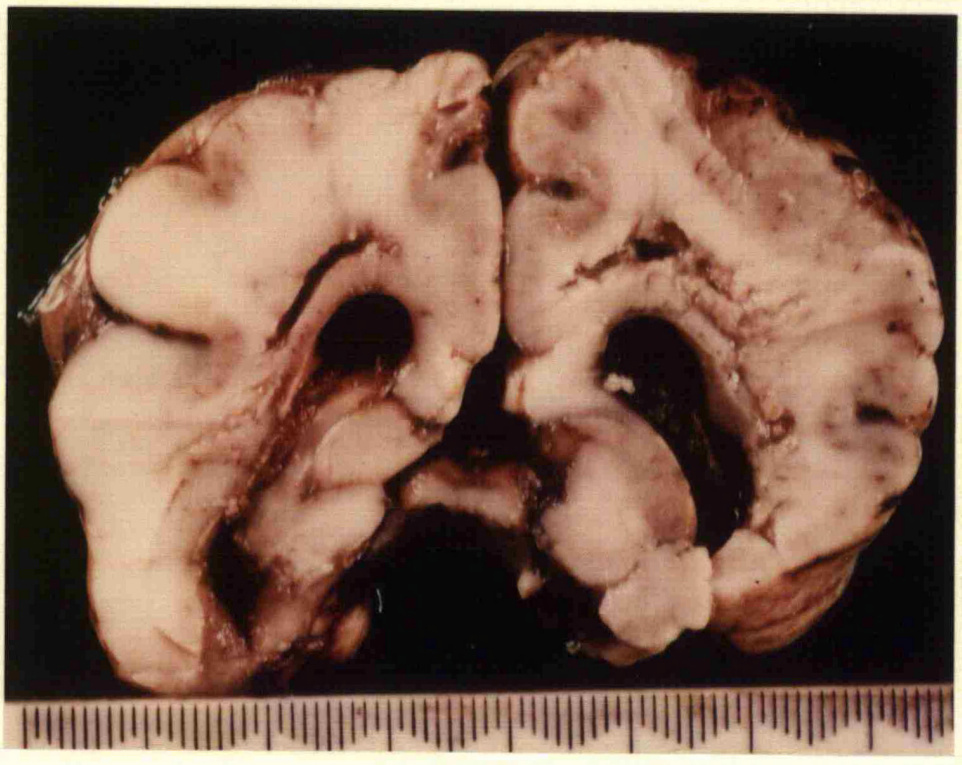


6. Cystic periventricular leucomalacia seen in posterior coronal (a) and parasagittal (b) planes.

a)



b)



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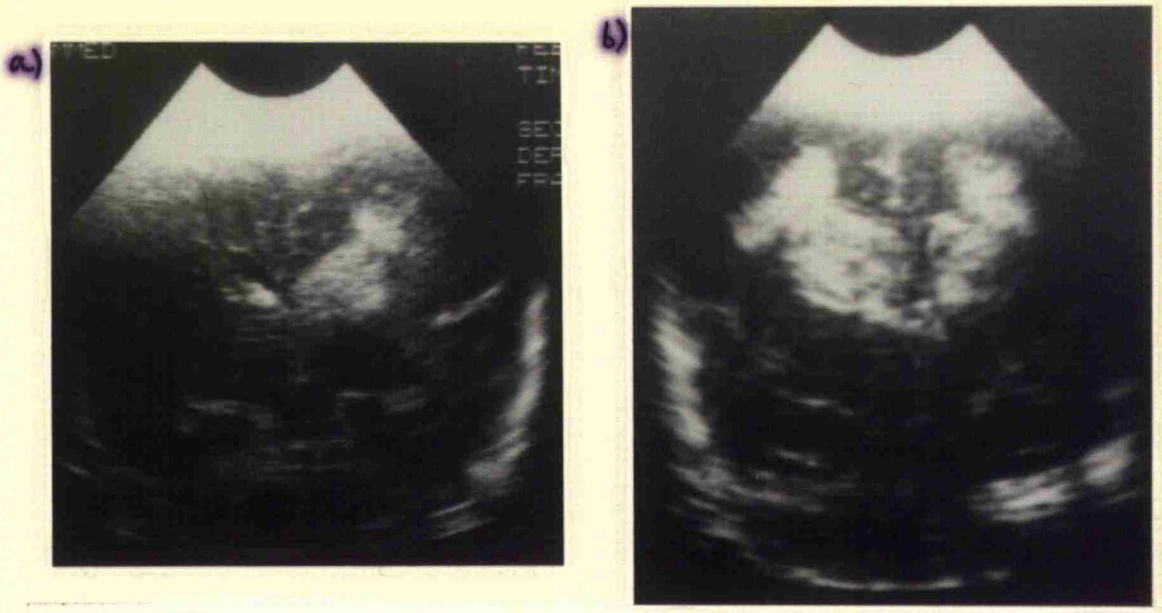

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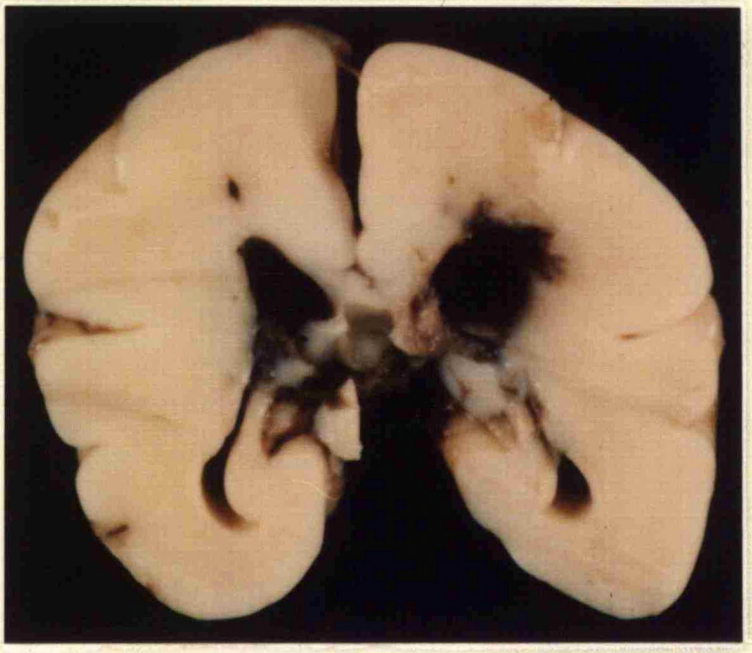

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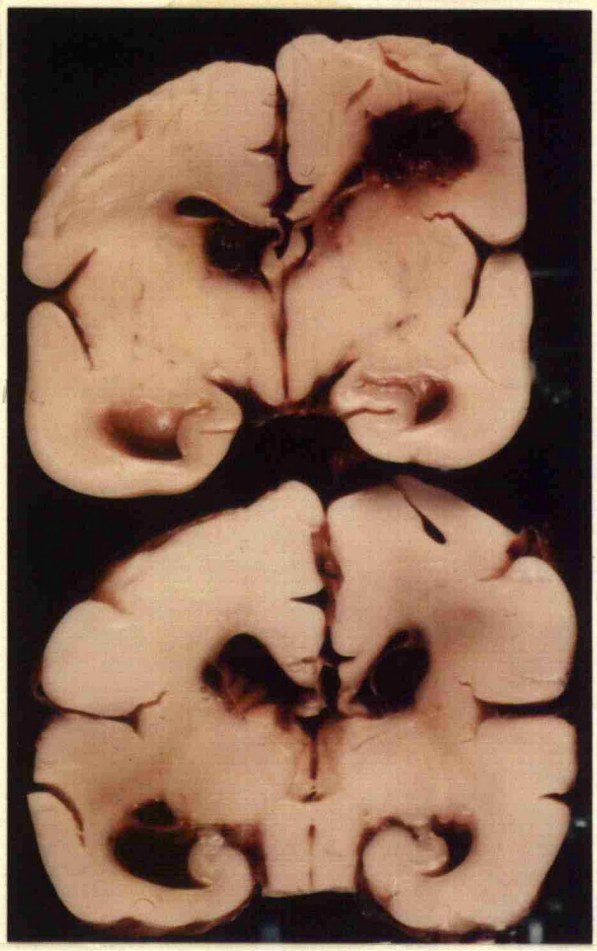

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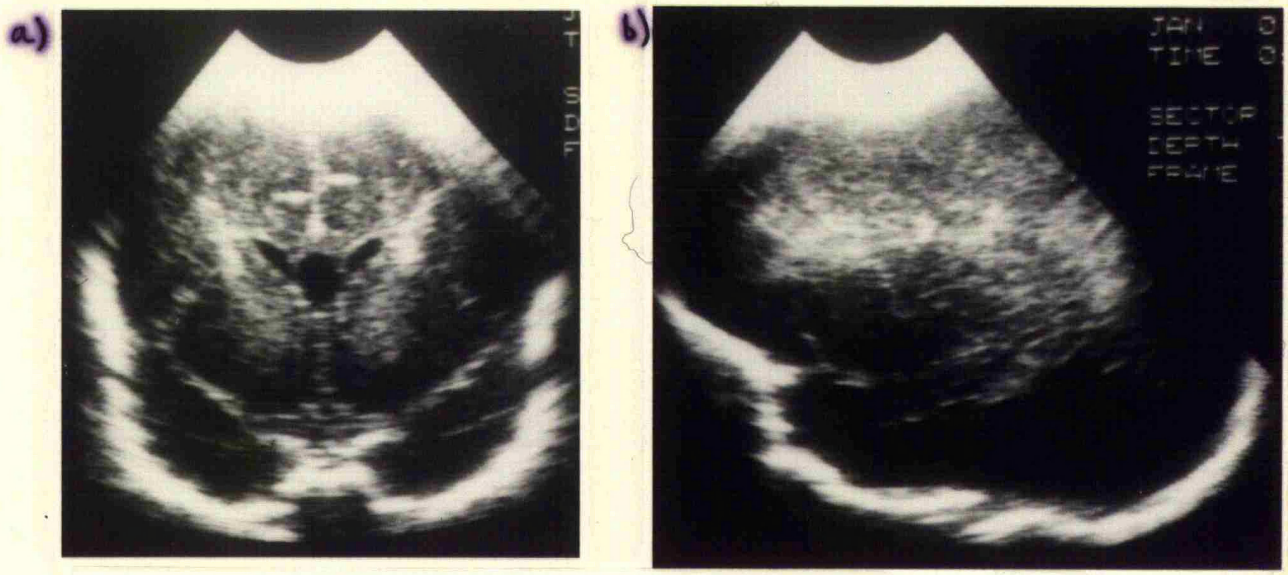

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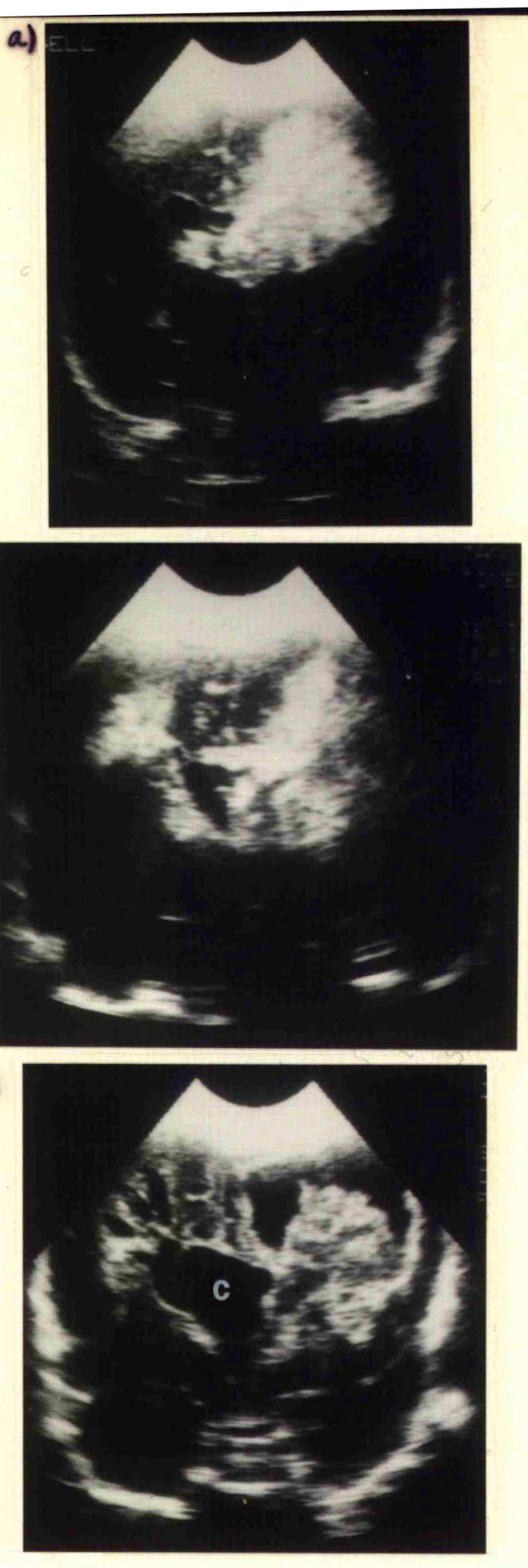

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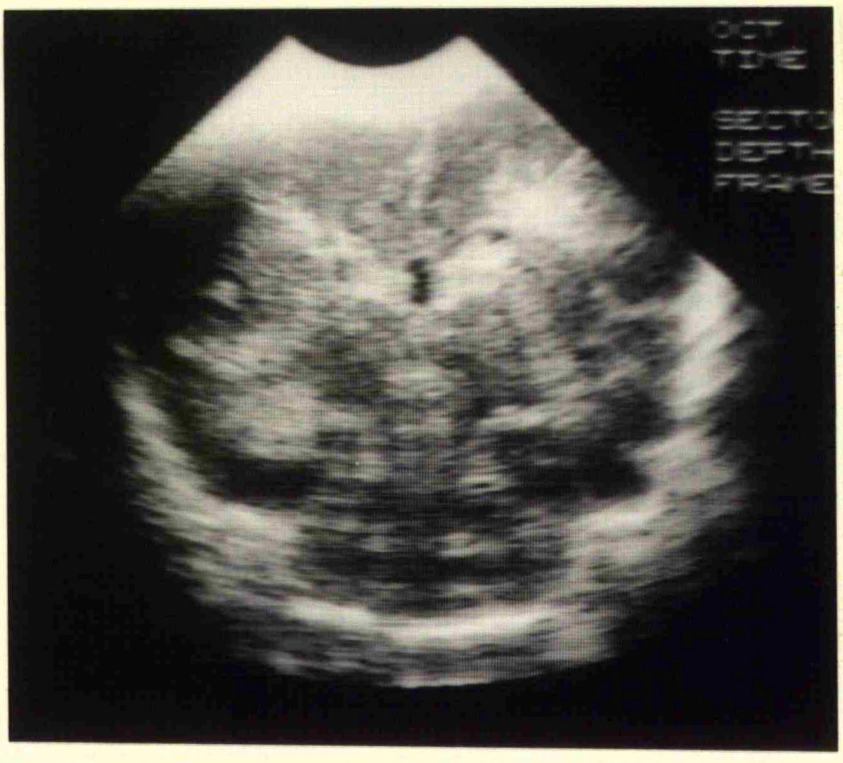
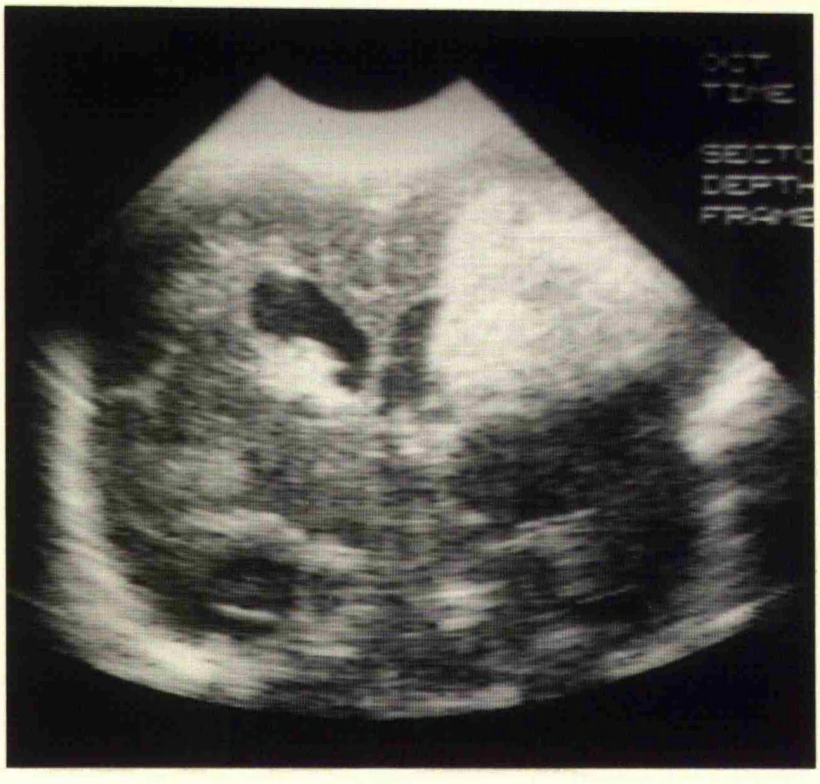
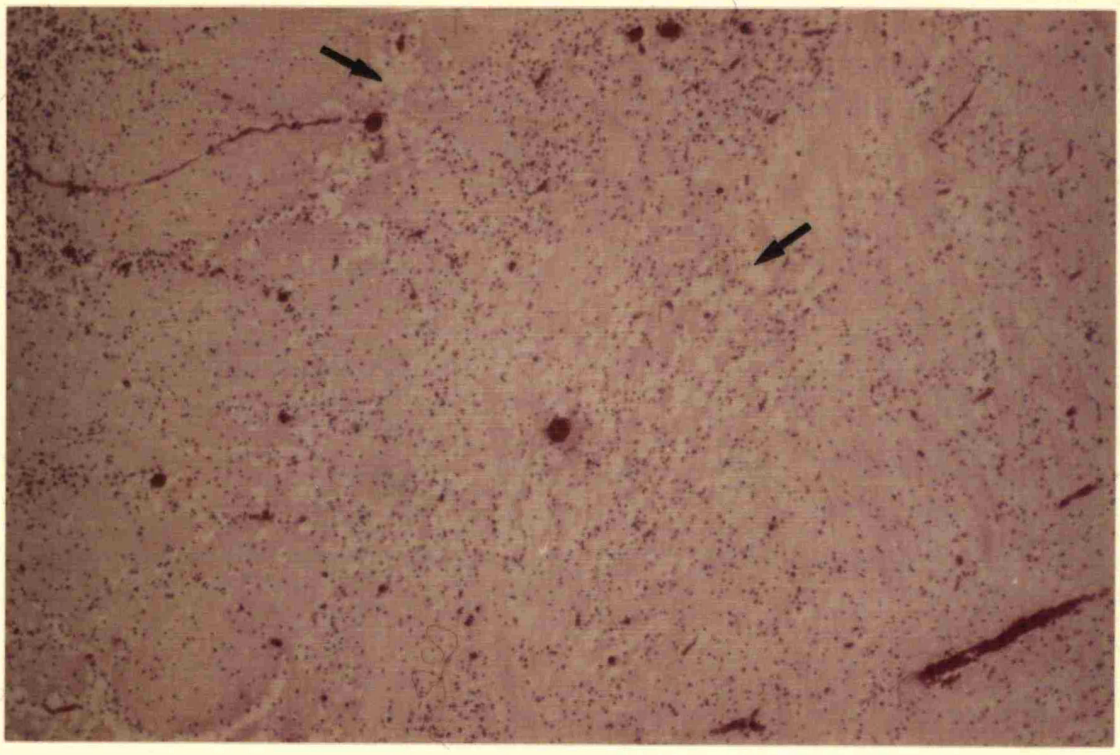


b)

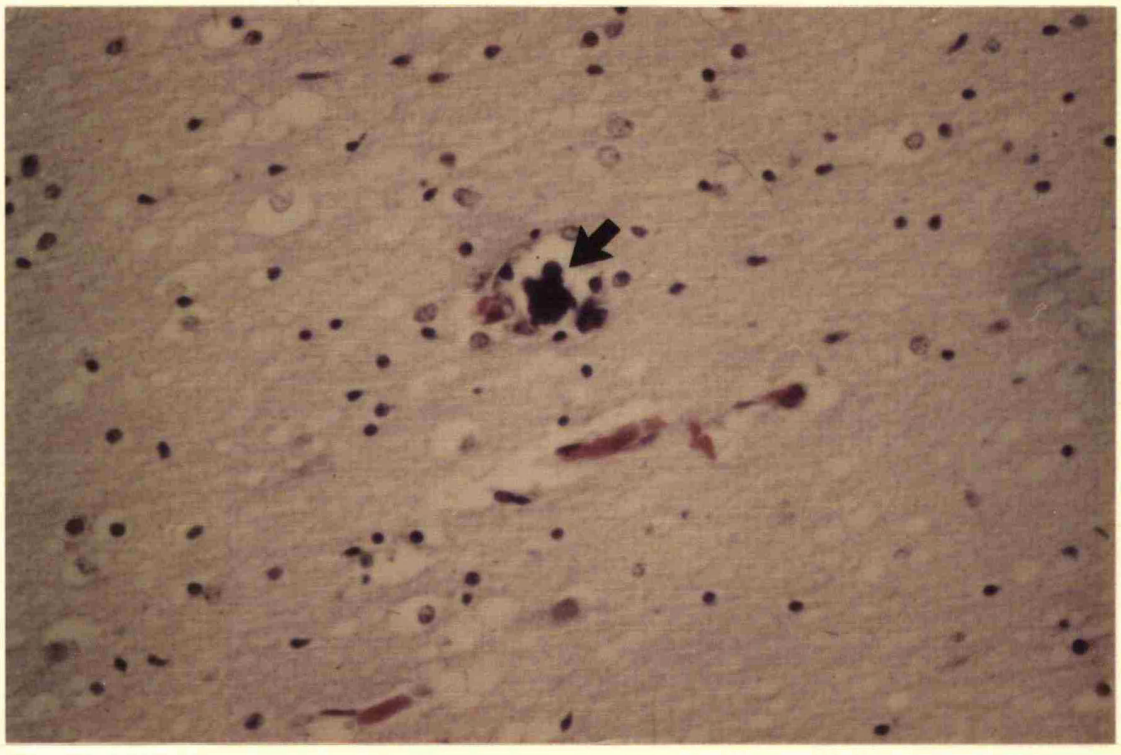


13. Coronal ultrasound scans of the same baby showing a right sided periventricular "flare" on day 3 (a) and a parenchymal haemorrhage in the corresponding site on day 6(b). There is ventricular dilatation in the second scan.

a)



b)



14. Haematoxylin and eosin stain showing generalised spongiosis (vacuolation) of the periventricular white matter (arrows) [a - magnification x400] and microcalcification (arrowhead) [b - magnification x1000].

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In addition, I should point out that the nucleus of this thesis (Chapters 4-7) lies in three publications:

Trounce JQ, Rutter N, Levene MI (1986) **Periventricular Leucomalacia and Intraventricular Haemorrhage in the Preterm Neonate.** *Arch. Dis. Child., 61, 1196-1202.*

Trounce JQ, Fagan D, Levene MI (1986) **Intraventricular Haemorrhage and Periventricular Leucomalacia: Ultrasound and Autopsy Correlation.** *Arch. Dis. Child., 61, 1203-1207.*

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