ASPHYXIA NEONATORUM IN A DEVELOPING WORLD SITUATION

A study of the impact of asphyxia neonatorum in term infants on the pattern of handicap in the Ciskei; an evaluation of its epidemiology and a trial of the efficacy of current therapy.

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THIS THESIS IS DEDICATED TO THE HANDICAPPED CHILDREN OF THE CISKEI AND THEIR CARETAKERS.

This study addresses the problem of asphyxia neonatorum in a developing African community in the Mdantsane region of Ciskei. It also documents asphyxia as a prominent cause of childhood handicap, examines aspects of its epidemiology and evaluates the effectiveness of a regimen of phenobarbitone and dexamethasone in limiting subsequent neurological deficit in asphyxiated neonates.

Analysis of neonatal deaths at Cecilia Makiwane Hospital over an 18 month period showed that aspyhxia accounted for one third of all neonatal deaths. In particular, asphyxia caused two thirds of deaths in infants over 2 Kg birth weight.

From a hospital register of handicapped children, 211 had cerebral palsy. Asphyxia was the cause of cerebral palsy in 33% of these children. Spastic quadriplegia, the type of cerebral palsy most often resulting from the cerebral damage associated with asphyxial hypoxic-ischaemic insults, was by far the largest diagnostic category (57%). Asphyxia therefore appears to be the single largest cause of significant handicap in Ciskei. In view of the underdeveloped support services to parents in most developing areas, the problem of asphyxia is of considerable importance.

In the study of the epidemiology of asphyxia , details

of pregnancy and labour were obtained for 163 asphyxiated term infants and 2758 non asphyxiated term infants whose mothers had delivered in the hospital. The factors positively associated with asphyxia were : low gravidity and parity, failure to book for antenatal care, the occurence of antenatal disorders, the occurence of fetal distress, a prolonged first stage of labour and delivery by caesarian section or vacuum extraction. Maternal age and the actual number of antenatal vists were not associated with asphyxia. The causes of asphyxia assigned by the specialist obstetrician in charge were : cephalopelvic disproportion (CPD) (39%), utero-placental pathologies (22%), other (8%), and "unknown" where he could find no abnormality in pregnancy and labour (27%).

From these findings it appears that the steps that need to be taken for prevention include : active recruitment of patients to book for antenatal care, more active detection and management of cephalopelvic disproportion and basic research to elucidate the causes of the "unknown" group whom it is speculated have undetected utero-placental pathology.

In a therapy trial 116 term infants were selected as being asphyxiated on the basis of having a 5 minute Apgar score of < 7 and/or having had signs of fetal distress in labour and having a placental arterial base

excess of > - 11. Patients were randomly assigned as cases or controls. Therapy was identical for both groups except that the cases received phenobarbitone and dexamethasone. At 48-72 hours of age blood was taken for electrolytes, urea and creatinine. In addition the neurological state was assessed. Infants were monitored in the nursery and then followed at home with visits at 6 weeks, 3, 6 and 9 months. At these visits they were weighed, measured and items of the Denver Developmental Screening Test (DDST) administered. At 12 months the infants were seen in hospital where DDST items plus a formal neurological assessment were carried out.

Taken as a single group the infants defined as being asphyxiated by these criteria experienced the following outcome : In the neonatal period 4/116 (3.4%) died. Of the 88 who completed follow-up to 12 months 21 (23.8%) children had some detectable neurodevelopmental problem, of whom 12 (13.6%) had significant neurological deficits, 9 of which were spastic quadriplegia.

The cases were significantly different to controls in the following respects : Lower neonatal mortality (0/64 vs 4/52), greater neurological depression at 48-72 hours of age, less neonatal jaundice and minor biochemical differences at 48-72 hours. There were no significant differences with respect to growth, items on the DDST or the occurence of neurological deficit.

It is concluded that the therapy regimen probably has some survival advantage to asphyxiated infants but it does not limit handicap in survivors. The supposition that spastic quadriparesis is the main form of cerebral palsy following asphyxia is supported.

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APPENDICES

CHAPTER 1

INTRODUCTION

1.1 THE HYPOTHESES.

The hypotheses advanced in this work are that asphyxia neonatorum is the leading ascertainable cause of cerebral palsy among handicapped children in developing communities in Southern Africa. Furthermore that data on the epidemiology of asphyxia neonatorum and on the efficacy of treatment regimens for the condition will be helpful in limiting the unduely harmful effects that it is having in such communities at present.

1.2. DEFINITION OF ASPHYXIA NEONATORUM.

In this study the term asphyxia neonatorum (or asphyxia) will be used to indicate the failure of adequate oxygenation of the fetus as reflected by clinical signs and biochemical abnormalities.

1.3. THE SETTING.

The work reported here was carried out in Mdantsane, the main urban area of the Ciskei which is one of the independent homelands in Southern Africa.

The Ciskei is located between the Transkei and the Eastern Cape border region and consists of 8 small towns and one major conurbation. In the rural areas the population is chiefly engaged in subsistence farming but the main economic support is from relatives working in the cities. The population of the Ciskei is appoximately 1 million of whom about 400,000 live in Mdantsane.

The people of the Ciskei are of Xhosa lineage. The Xhosa people traditionally occupied an area comprising the Ciskei and Transkei for several hundred years. With the advent industrialisation at the turn of the century many people left the Ciskei to seek work in cities such as Johannesberg and Cape Town. Subsequently in the 60's and 70's many ex-Ciskeians were forcebly returned to the Ciskei from the Western Cape and were resettled in Mdantsane.

Mdantsane is located some 25 kilometers inland from East London to which it is connected by rail and bus transport services. The building of Mdantsane began in the 60's and continues today. It is a township of small but well built houses, each with a municipal water supply and water borne sewerage. There are neighbourhood shops and schools as well a small downtown area but most people go to nearby East London for more sophisicated shopping or service requirements.

The majority of people in employment in Mdantsane commute to East London to work in factories, service industries and domestic service. There is a rapidly growing industrial area in Mdantsane itself. Despite this, unemployment is prevalent and the standard of living of most people is that of a poor working class. The possesion of consumer goods such as television sets, washing machines and motor cars are the privelige of a relatively small middle class.

1.3.1. Health Services.

The Ciskei has a health service infrastructure which divides the country into 6 health regions each with its own general hosptial. Each hospital is responsible for a network of clinics in its region. Each clinic is staffed by at least 2 resident registered nurses plus assistant nurses, domestics and a gardener. The clinic nurses render a comprehensive primary care service involving basic preventive work such as antenatal care and immunization as well as consulting sick patients of all ages who are referred to hospital if necessary. The clinics have either a telephone or radio link with the base hospital. Clinics are equipped to carry out normal deliveries and to resuscitate and transport sick neonates. A primary care training programme has been running over the last 4 years and over 300 clinic sisters have been trained. In this structure there are 6 hospitals and 109 permanent clinics as well as a large number of mobile clinic stops.

The Mdantsane region is served by the Cecilia Makiwane Hospital and 9 clinics. The hospital was built in 1976 and has 1400 beds. It is the only hospital in the Ciskei to have specialist departments and therefore is the hospital to which the other hospitals refer. Although provided with basic radiology and laboratory services, facilities for more advanced investigations such as computer assisted tomography (CT) and

electroencephalograms (EEG) are not available on the premesis. At the time of this study ultrasound facilities were also not available. Patients needing tertiary care are usually referred to the teaching hospitals in Cape Town.

1.3.2. Paediatric Service.

The hospital has 200 medical paediatric beds and a 50 bed neonatal nursery. The paediatric staff at present consists of 4 specialist paediatricians, 9 medical officers, 1 registrar and 4 interns, although during the earlier part of the study there were only 2 specialists.

The neonatal nursery is adjacent to the labour ward and caesarian theatre and is connected to them by an interleading door which makes communication very easy and quick.

The author has held the position of head of the paediatric department at the hospital since 1980.

1.4. THE PROBLEMS THAT INITIATED THE STUDY.

A paediatrician arriving in a developing area is immediately impressed by obvious clinical problems such as malnutrition, gastroenteritis and tuberculosis, as well as by organisational problems such as the absence of clear routines, poorly trained paediatric nursing staff and a shortage of basic equipment. These problems

are pressing but the solutions are fairly obvious given the will to solve them.

Two less immediately obvious problems were encountered by the author. These were handicap and the high mortality in term neonates from asphyxia. From the outset there was a strong suspicion that these phenomena were linked and it was the preliminary investigation of these two problems that lead the author into this study.

An investigation into the causes of death of neonates in the nursery for an 18 month period was carried out. The results are shown in Table 1.4.1. Of all neonatal deaths 34% could be attributed to asphyxia. Furthermore most of these deaths (83%) were in infants weighing >2000 Gm at birth.. Asphyxia was responsible for 65% of neonatal deaths in infants of birth weight >2000 Gm.

TABLE 1.4.1. DELIVERIES AND EARLY NEONATAL DEATHS :CECILIA MAKIWANE HOSPITAL

JULY 1981 - DECEMBER 1982

	BIRTH WEIGHT (Gms)							
	-1000	-1250	-1500	-1750	-2000	>2000	TOTAL	
DISCHARGED NEONATES	8	31	52	87	180	8140	8498	
DEATHS BY CAUSE :								%DEATHS
CONGENITAL ABNORMALITIES	1	-	-	-	1	11	13	7.6
PREMATURITY	42	16	9	5	7	-	79	46.1
ASPHYXIA	-	3	2	1	4	48	58	33.9
OTHER	-	-	-	1	5	15	21	12.3
ALL	43	19	11	7	17	74	171	100.0
TOTAL	51	50	63	94	197	8214	8669	
%DEATHS	25.1	11.1	6.4	4.1	9.9	43.2	100.0	

At the second conference on perinatal priorities in Southern Africa in 1983 the problem of asphyxial deaths at Cecilia Makiwane Hospital was presented by the author and the data were compared to those from other units in Southern Africa. It was clear that in units serving the economically disadvantaged areas a similar picture was seen with 40-60% of the deaths in neonates over 2000 Gm being due to asphyxia. In units serving more affluent communities the percentage was much lower. The problem of a high neonatal mortality from asphyxia was thus not just a local Ciskeian problem but a regional one as well. It was resolved that as much work as possible should be done by all units on this problem. The feeling was also expressed that if many infants were dying of asphyxia there would also be many handicapped survivors.

The problem of handicap was important in that it was prevalent, tended to be severe and that the social welfare, educational and other community facilities to deal with it were very limited. This will be explored further in Chapter 2.

1.5. AIMS OF THE STUDY.

1.5.1. To determine the aetiology of cerebral palsy as it presents in Ciskei.

1.5.2. To determine as far as possible, the epidemiolgical associations of asphyxia neonatorum in Ciskei with particular reference to factors in pregnancy and labour.

1.5.3. To determine the efficacy or otherwise, of a regimen of phenobarbitone and dexamethasone on the survival and long term neurodevelopmental outcome of term asphyxiated neonates.

1.5.4. By using data gathered in the above studies to make recommendations for limiting the unduly harmful effects of asphyxia neonatorum on the children of Ciskei and similar areas.

1.6. OUTLINE OF THE THESIS.

The investigation starts by reporting the results of a study of handicapped children with a view to elucidating the aetiology. This is followed by a review of the literature on the pathophysiology of asphyxial cerebral injury in term infants. The next section deals with the problem as to which criterion or group of

criteria can reasonably be taken to indicate that a newborn infant has suffered a significant hypoxic-ischaemic cerebral insult. This is followed by a review of the literature on the epidemiology of asphyxia neonatorum. Next is a report on a study of the epidemiology of asphyxia in the Mdantsane region of Ciskei. This is followed by a review of the literature relating to the therapy of hypoxic-ischaemic insults in the newborn and the work concludes with a report on a controlled trial of the possible long term neurodevelopmental benefits of a phenobarbitone and dexamethasone regimen in term asphyxiated infants.

CHAPTER 2

HANDICAP IN CISKEI

2.1. INTRODUCTION.

A distressing feature of paediatrics in the developing world is the plight of handicapped children and their guardians. One gains the impression that there are many such children and further that they tend to be very severely affected. The doctor trying to assist their families quickly discovers that facilites in the community are inadequate and often simply non-existent.

In Ciskei, residential care for the very severely affected children is not available and such children have to be cared for at home. Houses in the urban areas tend to be small and often overcrowded. The presence of a severely handicapped child is inevitably a great trial to the family. There may be loss of income as a result of the guardian having to stay at home to care for the child. The limited availability of appliances such as wheel chairs leads to hardship when the children become too heavy to carry on public transport. Some day training facilities for the mentally retarded are provided in the urban area of Mdantsane, but they are not enough. Physiotherapy and occupational therapy are available to a limited extent in Mdantsane, but not in the other urban and rural areas. The state assists by awarding single care grants to the guardians of mentally retarded children over the age of 3 years who stay at home to care for the child. These grants are

subject to availability of state funds.

Commentators from the developed world have suggested that the problem of handicap is less burdensome in underdeveloped communities because the "extended family" supports the parents. Trudy Thomas (1973) has pointed out that in the Ciskei, the family structure in both rural and urban areas has become disorganized as a result of the socially disruptive effects of urbanization and the migrant labour system. The result is that elderly grandparents (usually grandmothers) are to be found in the rural areas caring for children while the young adults go to town to seek work and to send money home on an irregular basis. Thus, a normal family structure, extended or otherwise, is absent and ecomomic support very tenous. In this environment it is difficult enough to care for a normal child let alone a severely handicapped one.

The need to investigate this distressing problem was seen to be important. Effective prevention of the handicap is the most desirable approach, combined with efforts to improve the care and facilities for such children. A start has been made on the latter and will not be discussed further here. Before prevention can be embarked upon the problem needs to be clearly defined and the causes described as far as possible. It was for this reason that the following survey of handicapped children in the area was carried out.

2.2. PATIENTS AND METHODS.

During the period January 1981 to June 1986 a register was compiled of all handicapped children presenting to the paediatric department of the Cecilia Makiwane Hospital.

On registration patients entering the register were referred to 2 specially orientated community health nurses who interviewed the parents or escort and later carried out a home visit to find out more about the social situation and the specific medical and social needs of the handicapped child.

The patients were assessed medically either by the author or by a senior paediatric medical officer with an interest in handicap (J.W.). A full paediatric history was taken and a physical examination with special emphasis on the neurological aspects was carried out by the same pair. The assignment to each case of an aetiology for the handicap was in the majority of cases done on the basis of the history. The perinatal records were available for relatively few. Where any doubt existed as to the intellectual or developmental level of the child a more formal developmental assessment was carried out by the same medical officer (J.W.). The mental and physical evaluations were carried out by the same examiner at the same session. Every effort was made to prevent the

child's physical state from influencing objective assessment of the mental state. At the end of the evaluation each patient was categorised in terms of :

* Aetiology.
* Type of cerebral palsy, if present.
* Degree of mental retardation.
* Presence of seizures.
* Requirements for community facilities.

2.2.1. Definition of Handicap.

The handicapped child is one who suffers from any continuing disability of body, intellect or personality which is likely to interfere with normal growth, development and capacity to learn (Sheridan 1968).

2.2.2. Definition and Classifiction of Cerebral Palsy.

Cerebral palsy is the result of a lesion or maldevelopment of the brain, non-progressive in character and existing from earliest childhood (Bobath 1966).

The classification used here is as follows :

Spastic, in which spasticity is the dominant motor pattern.

Athetoid, in which dystonia and/or choreoathetosis predominate.

Mixed, in which spasticity and athetoid features are clearly found.

Hypotonic, an undifferentiated form found most often in young infants in whom hypotonia is the dominant feature.

Quadriparesis refers to the involvement of all four limbs with arms more affected than legs. In diplegia the legs are involved more than the arms which may be normal. In hemiplegia the motor disorder is limited to one side of the body.

2.2.3. Categories of Mental Retardation.

The following categories of mental retardation were used. (Steenkamp and Steenkamp 1981) :

Mild : The child shows poor scholastic progress. IQ 84-70.

Moderate : The child needs special education to make any progress. IQ 69-50.

Severe : The child is able to cope with simple activities of daily living but unable to benefit from any form of academic schooling. IQ 49-25.

Profound : Totally Dependent on others for most routine functions. IQ less than 25.

2.2.4. Community facilities for handicap.

The following terms are used below and need some explanation in the local context :

Day Training : This is form of care is provided at a suitable centre which the child attends on a daily basis. The programme involves activities of daily living and adaption to everyday life in the community. It does not involve academic work of any kind. Normally children in the severe category who are older than 5 years and who are largely "clean and dry" , are suitable for this type of care.

In Ciskei there are at present no educational facilites for children in the the mild and moderate categories in the educational system. These children have either to attend a normal school which poses many difficulties for them socially and educationally or to attend a day training centre whose programme is also not suitable for them but less difficult socially.

Institutional care : This refers to residential, hospital type care which is suitable for those whose physical or mental state makes it impossible for the parents to care for them at home. It is also suitable for less severely handicapped children who have no-one in the community to care for them.

In this study the above local conditions as well as the

social position of the child were taken into account before deciding on which community facilites would be suitable for the child.

2.3 RESULTS :

2.3.1. CEREBRAL PALSY :

A total of 350 children were entered in the register at the time of analysis. Table 2.3.1. sets out the categories of cerebral palsy and mental retardation.

TABLE 2.3.1. CEREBRAL PALSY AND MENTAL RETARDATION. FROM HANDICAP REGISTER.

	NO MENTAL RETARDATION	MENTAL RETARDATION	TOTAL
NO CEREBRAL PALSY	10	129	139
CEREBRAL PALSY	18	193	211
TOTAL	28	322	350

2.3.2. CEREBRAL PALSY : AETIOLOGY AND TYPES :

The aetiology of cerebral palsy by type is set out in Table 2.3.2. The spastic group is subdivided into quadriplegia, diplegia and hemiplegia. The other categories are athetoid, mixed (having features of both spasticity and choreoathetosis), hypotonic and other, which consisted of patients difficult to categorise.

TABLE 2.3.2. AETIOLOGY OF CEREBRAL PALSY BY TYPE.

	PRE-NATAL		PERI-NATAL			POST-NATAL					UKN	TOT
TYPE	HYD	MS	ASP	PRM	OTH	TBM	BCM	ENC	CVT	OTH		
SPASTIC												
QUADRIPLEGIA	1	-	52	7	7	5	6	2	2	1	37	120
DIPLEGIA	1	-	1	4	-	-	-	-	1	-	4	11
HEMIPLEGIA	1	-	8	2	2	10	2	-	3	1	16	45
MIXED	-	-	6	-	3	-	-	-	-	-	6	15
ATHETOID	-	-	-	1	1	1	-	1	-	-	2	6
HYPOTONIC	-	1	3	1	-	-	1	2	2	-	1	12
OTHER	-	-	-	-	-	-	-	-	-	-	2	2
TOTAL	3	1	70	15	13	16	9	5	8	2	69	211

Key : HYD = Hydrocephalus
MS = Morphological syndrome
ASP = Asphyxia
PRM = Prematurity
OTH = Other
TBM = TB meningitis
BCM = Bacterial meningitis
ENC = Encephalitis
CVT = Cerebral vein thrombosis
UKN = Unknown

TABLE 2.3.3. CEREBRAL PALSY : COINCIDENTAL MENTAL RETARDATION.

	MENTAL RETARDATION						
TYPE OF CP	NONE	MILD	MODERATE	SEVERE	PROFOUND	TOTAL	% MR
SPASTIC							
QUADRIPLEGIA	7	6	15	36	56	120	94
DIPLEGIA	5	-	4	1	1	11	45
HEMI PLEGIA	4	8	19	10	3	44	9
MIXED	-	-	3	8	4	15	100
ATHETOID	2	-	1	2	1	6	67
HYPOTONIC	-	2	1	6	3	12	100
OTHER	-	1	-	-	1	2	100
TOTAL	18	17	43	63	69	210	91
%	8.6	8.1	20.5	30.0	32.8	100	%

TABLE 2.3.4. DEGREE OF MENTAL RETARDATION IN NON- CEREBRAL PALSY CASES.

	NONE	MILD	MODERATE	SEVERE	PROFOUND	UNKNOWN	TOTAL
NO CP	10	20	49	52	7	1	139

The aetiology is divided into pre-natal, peri-natal and post-natal. The various sub- headings are indicated in the table.

The most noteworthy features are that spastic quadriplegia was by far the largest single group by type and that asphyxia is the dominant aetiological category. Fifty two cases (25%) were spastic quadriplegics caused by asphyxia. The next largest aetiological category was TB meningitis which is less than a quarter of the number in the asphyxia category.

2.3.3. MENTAL RETARDATION.

The distribution of mental retardation among the cerebral palsy patients is set out in TABLE 2.3.3. Only 8% of cases had no mental retardation and the single largest category (33%) was "profound". It is of note that the modal category of retardation for spastic quadriplegics was "profound" whereas that for hemiplegics was "moderate". Further the largest single cell in the table is that of profoudly retarded spastic quadriplegia. The spastic quadriplegics tend to be the most severely retarded.

The degree of mental retardation in non-cerebral palsy cases is set out in Table 2.3.4.

2.3.4. CEREBRAL PALSY AND SEIZURES.

The proportions of each category of cerebral palsy experiencing seizures is set out in TABLE 2.3.5. The

overall rate of occurence was 35% with the athetoid group having the highest rate (66%) although the numbers in this category are small.

TABLE 2.3.5. SEIZURES BY TYPE OF CEREBRAL PALSY

TYPE OF CEREBRAL PALSY	N	No. WITH FITS	% WITH FITS	% ON TREATMENT
SPASTIC			%	%
QUADRIPLEGIA	120	37	31	73
DIPLEGIA	11	1	10	100
HEMIPLEGIA	45	20	44	65
MIXED	15	5	33	80
ATHETOID	6	4	66	50
HYPOTONIC	12	7	54	58
OTHER	2	-	-	-
TOTALS	211	74	35%	69%

2.3.5. PROVISION OF COMMUNITY FACILITIES FOR HANDICAP.

2.3.5.1. Institutional Care :

Of the total of 350 patients in the handicap register 136 (39%) were regarded by the medical assessor as being most suitably placed in residential institutional care which is felt to be appropriate for only the most severely affected patients taking the social circumstances into account. To indicate the severity of those considered suitable, the percentage of those in each age category who were both non-ambulant and

incontinent is set out in TABLE 2.3.6. It must be noted that in the situation studied no child was actually in institutional care as no such facility is provided in the region.

TABLE 2.3.6. PATIENTS ASSESSED AS NEEDING INSTITUTIONAL CARE.

	ALL IN AGE GROUP	% NON AMBULANT & INCONTINENT
UNDER 6 YEARS	80	87
6-10 YEARS	33	79
10 + YEARS	23	52
TOTAL	136	

2.3.5.2. Day Care for Suitable Children with Mental retardation.

In the group of handicapped children studied 124 were assessed as being best placed in day training taking local conditions and their social position into account. The extent to which they were receiving it are set out in TABLE 2.3.7. Only 49% of children qualifying for such day care were actually receiving it. This was because either the parents were working and so could not take a child to a centre every day or that the 2 centres providing such care were too far away from their place of residence.

TABLE 2.3.7. PROVISION OF DAY TRAINING FOR SUITABLE MENTALLY RETARDED CHILDREN.

	MDANTSANE	OTHER CISKEI	TOTAL
ATTENDING DAY CARE	55 (5)	6 (5)	61 (10)
NOT ATTENDING DAY CARE	40	23	63
TOTAL	95	29	124

( ) = Those mentally retarded children suitable for day care but attending normal schools.

2.3.6. SUMMARY OF RESULTS :

2.3.6.1 Spastic quadriplegia is the commonest category of cerebral palsy encountered.

2.3.6.2. Asphyxia is the major acertainable cause of spastic quadriplegia.

2.3.6.3. Severe and profound mental retardation and seizures are frequent accompaniments of spastic quadriplegia.

2.3.6.4. In a developing world setting the facilities for coping with the problem of severe handicap are very inadequate.

2.4. DISCUSSION.

2.4.1.Type of Cerebral palsy :

The distribution of the types of cerebral palsy in this survey was very striking with 83% being spastic of which 57% were quadriplegics. Less common were the hemiplegics (21%) with the diplegic (5%) and athetoid (3%) groups being surprisingly small.

The difficulties inherent in this type of study have been emphasised by Pharoah and McKinlay (1986). They note that even in developed countries the detection or ascertainment of cases of cerebral palsy is often incomplete. This is evidenced by the apparent increase in prevalence with age. This occurs because with time more handicapped children come forward for help and are so identified.

A lack of uniformity in classifying types of cerebral palsy also leads to difficulties in making comparisons. These problems are compounded by the frequent difficulty in making a clear clinical distincton between quadriplegia and diplegia. This subjectivity has been emphasised by Jarvis et al (1985). In a study of cerebral palsy in Newcastle they avoid the term diplegia and use quadriplegia when all 4 limbs are affected and paraplegia when only the legs are affected. Rantakillio and Von Wendt (1986) also avoid the term diplegia.

The types of cerebral palsy from a number of published studies including the present report are compared in Table 2.4.1.

The present study is striking in having the highest proportion of spastic quadriplegia (57%) of these studies. The reports from Nigeria (Izuora and Oroko 1981), Newcastle (Jarvis et al 1985) and Finland (Rantakillio and Von Wendt 1986) also have relatively high proportions of quadriplegics. However both Rantakillio and Jarvis avoid using the category diplegia and in doing so possibly overload the quadriplegic group. Furthermore Rantakillio and Von Wendt used small numbers (47). Although the study from Tanzania has a particularly low percentage of quadriplegics, it has the highest proportion (74%) of diplegics and quadriplegics combined of any study. This may reflect the diagnostic difficulty referred to above.

There are possible explanations for the high proportion of quadriplegia in the present study. Diagnostic error may have occured with some diplegics being assigned as quadriplegics. The level of experience and expertise of the two doctors carrying out the assessments would make large scale errors of this sort unlikely. Furthermore wrong assignment of dyskinetics as spastic quadriplegics is extremely unlikely due to the striking clinical features.

TABLE 2.4.1. TYPES OF CEREBRAL PALSY IN PUBLISHED STUDIES

TYPES OF CEREBRAL PALSY : COMPARATIVE STUDIES.

Place	PRESENT	FINLND	SEATTLE	SWEDEN	CAPE TOWN	FINLND	W.AUSTRALIA	NIGERIA	TANZANIA	NEWCASTLE
Date	81-86	85	82	54-70	80	66-83		78-79	83	60-75
No.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
SPASTIC	%	%	%	%	%	%	%	%	%	%
QUADRPLEGIA	57	36	17	3	14	40	24	37	10	52
DIPLEGIA	5	16	19	33	25		25	11	64	
HEMIPLEGIA	21	30	17	36	29	34	24	20	6	32
MIXED	7	-	-	11	10	-	5	16	4	2
ATHETOID	3	12	10	4	18	26	5	2	12	4
HYPOTONIC	6	-	16	6	1	-	7	13	4	-
OTHER	1	7	3	8	3	-	10	1		10
N =	211	69	142	560	389	47	899	104	50	325

Key:

1. Present Study
2. Von Wendt et al 1985
3. Holm 1982
4. Hagberg et al 1975
5. Molteno & Arens 1980
6. Rantakillio & Von Wendt 1986
7. Blair & Stanley 1982
8. Izuora & Oroko 1981
9. Makwabe and Mgone 1984
10. Jarvis et al 1985

With such a hospital based survey a certain bias could operate in selecting more severely affected cases. The disproportionate number of mentally retarded children amongst the cerebral palsy patients is very suggestive of this bias. The parents of handicapped children attend hospital in order to receive physical therapy and to be put in touch with social services, particularly single care grants. Spastic quadriplegics tend to be much more disabled than diplegics or dyskinetics and as such are more likely to attend hospital and so be over-represented. On the other hand the organisation of health and welfare services in the area is such that the hospital is the only satisfactory point of first contact with the supporting services. Parents in seeking help for their handicapped child, will first attend hospital and then be referred to other health and welfare services as necessary. Thus a hospital survey should identify most handicapped children who seek help and only miss those who need no help. Studies from developed countries rely on domicilliary follow up which excludes this type of bias. The clinical impression of the author is that spastic quadriparesis is very strongly represented amongst the handicapped children attending the health services.

It remains a strong possibility that together with Nigeria and possibly Tanzania the study area does in fact have an unusually high prevalence of spastic

quadriplegia.

A further perspective on this problem is to be gained from Table 2.4.2. which summarises the types of cerebral palsy diagnosed at follow up in studies of the neurodevelopmental sequelae of asphyxia associated with consequent hypoxic-ischaemic encephalopathy (HIE). The leading category was spastic quadriparesis with others being much smaller. This high ratio is to be compared to the much smaller proportion in the general cerebral palsy population as set out in Table 2.4.1. Thus it might be expected that in a community where asphyxia is prevalent the pattern of cerebral palsy would be biased toward spastic quadriparesis.

TABLE 2.4.2. TYPE OF CEREBRAL PALSY AFTER DOCUMENTED HYPOXIC-ISCHAEMIC ENCEPHALOPATHY

AUTHORS	GA	N	TYPES OF CP (%)					
			SPASTIC			ATHETOID	MIXED	ATAXIC
			Quadriplegia	Diplegia	Hemiplegia			
Brown el al 1974	All	22	36	22	18	9	14	-
Mulligan et al 1980	All	10	20	30	10	10	30	-
Ziegler et al 1976	36+W	13	30.5	7.7	15.4	15.4	7.7	15.4
Robertson & Finer 1985	Term	20	70	-	15	5	10	-
Levene et al 1986	Term	6	50	-	-	33	16	-
Fitzhardinge et al 1981	Term	26	65	3.8	27	-	-	4
Mulligan et al 1980	Term	5	40	20	-	20	20	-

2.4.2. Aetiology of Cerebral Palsy :

It is recognised that the method of determining the aetiology by history, used in this study cannot be as accurate as the perusal of detailed perinatal records. Due to the situation in which this study was conducted this was not at all possible. Nevertheless it was usually possible to piece together the broad nature of the perinatal or post natal insult.

The leading aetiological category in the present survey was asphyxia (33%), the second, a large "unknown" category (32%), the third TB meningitis (7.6%) and close thereafter prematurity (7.1%) followed by lesser perinatal and postnatal causes. The presence of a large "unknown" category may be attributed to two factors. Firstly, the guardian of the child was sometimes not the mother, as in rural Xhosa society young children are frequently left in the care of elderly grandmothers. Very often these caretakers knew about the perinatal events, having been present themselves at delivery, but this was not always so. Their knowlege of postnatal events on the other hand was nearly always very good. The second possibility is that the cause is truly occult.

Despite these possible sources of error the broad picture emerges that asphyxia is the leading cause of cerebral palsy in the survey area.

In this discussion it is freely assumed that the connection between perinatal asphyxia and later cerebral palsy is very frequently causative. It is however possible that infants with congenital cerebral abnormalities could suffer both perinatal asphyxia and later cerebral palsy as parallel features rather than one being causative of the other. Nevertheless the review of the connection between asphyxia and cerebral injury in Chapter 3 provides evidence for a strong but not exclusive causative link between these two phenomena.

It is of interest to speculate that the preconception of many health personnel as to the leading cause of severe handicap in such a developing community would be that TB meningitis, polio, cerebral vein thrombosis as result of dehydration and prematurity are the main culprits. Asphyxia in the term infant is unlikely to be perceived as a leading cause.

Comparisons of causes of cerebral palsy from published studies are difficult in that diagnostic categories chosen by authors tend to be different. In Table 2.4.3. an attempt has been made to compare studies but some grouping of categories has had to be used. No other survey has shown such a high proportion of asphyxia (33%) as the present one. Izuora and Oroko (1981) from Nigeria report 31% and Makwabe and Mgone (1984) from

Tanzania state that 24% of cases of cerebral palsy were due to asphyxia. Their figures are unusual in that the proportion of post natal cases is much higher than in other studies which they attribute to prolonged seizues in children caused by cerebral malaria. If their postnatal group were excluded the proportion due to asphyxia would be large. Molteno et al (1980) in their report from Cape Town give a figure of 15% due to asphyxia but the community served by their group is considerably more affluent than that of the Ciskei. The large survey from Seattle by Holm (1982) used comparable diagnostic categories and found only 13% attributable to asphyxia. Noteworthy was the high proportion assigned by him to prenatal causes.

There is a body of evidence and speculation that finds it difficult to accept asphyxia as a cause of cerebral palsy at all. This debate which is partly semantic will be reviewed in Chapter 5 (section 5.4.).

The picture emerges in which asphyxia is an important association of cerebral palsy in Ciskei. Furthermore spastic quadriparesis is particularly common and is most usually caused by asphyxia.

The implications of this are many. Firstly reference to Table 2.3.3. will show that the children with spastic quadriparesis tend to have the most severe degrees of associated mental retardation, with 47% being

TABLE 2.4.3. COMPARATIVE AETIOLOGY OF CEREBRAL PALSY.

	PRE-	PERI-NATAL				POST-NATAL					UKN	TOTAL
TYPE	NATAL	ASP	PRM	OTH	NNJ	TBM	BCM	ENC	CVT	OTH		
	%	%	%	%	%	%	%	%	%	%	%	N
1. CISKEI	2	33	7	6	1	8	6	2	4	1	33	211
6. CAPE TOWN	19	15	18	1	3	------22--------					20	331
7. NIGERIA	16	31	3	-	23	------17--------					10	104
8. NIGERIA	4	-	-	7	49	--5---	8	-	-		28	196
4. SWEDEN	25	------48-----				-------6--------					21	560
2. FINLAND	32	------36-----				------19--------					13	69
3. SEATTLE	27	13	33	1	-	-------9--------					23	142
9.TANZANIA	-	24	-	-	12	-	-	-	-	60	4	50

Key:

1. Present Study
2. Von Wendt et al 1985
3. Holm 1982
4. Hagberg et al 1975
5. Molteno & Arens 1980
6. Rantakillio & Von Wendt 1986
7. Woods 1983
8. Animashaun 1971
9. Makwabe and Mgone 1984.

ASP = Asphyxia
PRM = Prematurity
OTH = Other
NNJ = Neonatal Jaundice
UKN = Unknown

TBM = Tuberculous meningitis
BCM = Bacterial meningitis
ENC = Encephalitis
CVT = Cerebral vein thrombosis

profoundly retarded.

The community facilities available for such severely handicapped children and their parents in such a developing community are scanty. In the handicap survey 136 children were assessed as being so severely physically, mentally and or socially disabled as to need residential care. None were in such care due to lack of facilities. Only 49% of those mentally handicapped children assessed as needing day care training were recieving it.

Even in more affluent parts of the region, facilities may not be adequate. The author, in 2 studies of facilities in Cape Town for mentally retarded children found that while residential care was adequate that for day training was not. (Power 1977 and Friedlander and Power 1982). It must be stated that the community surveyed in Cape Town was at a higher socioeconomic level than that in Ciskei.

2.5. CONCLUSIONS :

2.5.1. In a developing world situation handicap in children causes a disproportionate degree of distress to the guardians.

2.5.2. The leading form of cerebral palsy is spastic quadriparesis with a high prevalence of coexisting mental retardation which tends to be profound.

2.5.3. The social facilites to deal with the problem are scanty.

2.5.4. The leading acertainable cause of cerebral palsy in this area is asphyxia.

2.5.5. Efforts to prevent cerebral palsy in the developing world should centre on asphyxia.

2.5.6. The relationship between asphyxia and cerebral palsy will be further explored in Chapter 3.

CHAPTER 3

ASPHYXIA AND CEREBRAL INJURY

3.1. INTRODUCTION.

In the last chapter the importance of asphyxia as a cause of cerebral palsy in developing communities was noted. This chapter reviews the pathophysiological aspects of this association. The epidemiological aspects will be dealt with in Chapter 5.

The distribution and type of cerebral injury after asphyxial insults is reviewed starting with the effect of hypoxia on the rate and distribution of cerebral blood flow and how this may affect injury. Thereafter the possible effects of regional differences in cerebral metabolism on injury patterns are considered. Finally the actual patterns of cerebral injury as seen in both experimental animals and human asphyxiated infants will be reviewed.

3.2. EFFECT OF CEREBRAL BLOOD FLOW AND METABOLISM ON INJURY PATTERNS.

3.2.1. Hypoxia and cerebral blood flow :

Mild to moderate hypoxia is known to cause increased cerebral blood flow, possibly as a protective mechanism. This has been demonstrated in fetal lambs by Purves and James (1969) and in puppies by Duffy et al (1982). These changes were quantified in puppies by Casciotti et al (1979) who found that the increase began when arterial pO2 fell below 35mm Hg.

More severe hypoxia causes myocardial depression with a consequent fall in cerebral blood flow. (Gardiner 1980). As a result, ischaemia is added to hypoxia and the products of anaerobic metabolism accumulate rapidly in the form of brain adenosine monophosphate (AMP) and inorganic phosphate. This was shown by Lowry et al (1964) in mice after decapitation and by Hope et al (1984) and Younkin et al (1984) in asphyxiated human infants both using phosphorous nuclear magnetic resonance spectroscopy. Increasing proportions of anaerobic metabolites correlated well with poor survival and adverse neurodevelopmental outcome.

3.2.1.1. Failure of cerebral autoregulation.

Hernandez and Brennan (1978) have described the autoregulatory plateau of cerebral blood flow in newborn puppies in whom the cerebral blood flow remains fairly constant over a range of mean arterial blood pressures from 27 - 97 mm Hg. Lou et al (1979) and Lou (1980) carried out similar studies in human neonates and found that in the normal infant, as blood pressure falls cerebral arteriolar dilatation occurs maintaining cerebral perfusion. They found that in the asphyxiated infant this does not occur resulting in a situation where cerebral blood flow is directly dependant on blood pressure. The infant is thus prone to cerebral ischaemia with even small falls in blood pressure.

3.2.2. Consequences of a severely reduced cerebral blood flow :

3.2.2.2. Alteration in cerebral blood flow and neurodevelopmental outcome.

Lou et al (1977, 1978, 1979) studied the cerebral blood flow of the human neonate using the 133-Xenon technique. They reported on 19 infants of whom 10 had been asphyxiated. The least severely affected infants had a mean cerebral blood flow of 40ml/100gm/min shortly after birth and the most severely affected had flows of < 20 ml/100gm/min. At follow up Lou et al (1979) found that 6 of the 10 infants who had had cerebral blood flows of less than 20 had cerebral atrophy on computed tomography (CT) scan or post mortem examination, whereas none of 9 infants who had had flows above 20 had cerebral atrophy. He found that only one infant who had a low flow developed normally while the majority of infants who had had higher flows were normal at follow up. He concluded that a cerebral blood flow of < 20 ml /100 gm /min places the infant at high risk of hypoxic-ischaemic brain damage.

Skov, Lou and Pedersen (1984) re-evaluated the 15 survivors of the above study at 4 years of age and found that the 5 survivors who had had low cerebral blood flow had significantly more abnormal neurological

signs as well as lower I.Q. They speculate that neonatal cerebral ischaemia may be the most important single factor contributing to the development of neurological handicap.

Another study of cerebral blood flow on asphyxiated term infants showed a persistence of low cerebral blood flow for up to 4 days after the asphyxial insult (Sankaran, Peters and Finer 1981). The method used was unusual in that cerebral blood flow was derived from data on the change in intra-cranial pressure and head circumference during a brief period of occlusion of both jugular veins.

A fall in cerebral blood flow is a consistent finding in studies of severely asphyxiated human infants. With a falling cerebral blood flow the brain is likely to be injured and the pattern of injury will depend on the following factors :

3.2.2.2. Cerebral vascular anatomy.

The anatomical development of the cerebral circulation in the fetus has been studied by Wigglesworth and Pape (1978). They studied cleared barium-gelatine injected preparations of fetal brains of various ages to establish the pattern of development of the cerebral vasculature.

Initially the blood supply of the brain is dominantly

to the brain stem/basal ganglia. With advancing gestation this changes to a cortically orientated arrangement. The zone between the cortex, (supplied ventriculopetally by the cortical vessels), and the underlying white matter, (supplied ventriculofugally), remains as a boundary or watershed zone and as such is vulnerable to episodes of hypotension. During this same gestational period the degrees of anastomosis between the territories of supply of the 3 major cerebral arteries becomes more and more attenuated so that in the term fetus the vulnerable or "watershed" zones between their areas of supply are well established. Cerebral ischaemia will clearly exert its maximal adverse effect in these watershed zones.

3.2.2.3. Areas of brain prone to reduction in blood flow in hypoxia-ischaemia.

To study the pattern of alteration in cerebral blood flow in asphyxia, Vannucci and Duffy (1977) injected colloidal carbon black intravenously into neonatal dogs at various intervals after the onset of respiratory arrest. They found that the degree of reduction in cerebral blood flow increased with the duration of asphyxia and was greatest in the cerebral cortex and least in the brain stem. Myers (1972) in primate animal studies of prolonged partial asphyxia, using the 14c labelled antipyrine method of determining cerebral

blood flow, also found that the hemispheres of the brain rather than the brainstem structures, are more affected by alterations of blood flow. The areas of supply of the posterior cerebral arteries seem to be affected later and to a lesser extent than those supplied by the anterior and middle cerebral vessels.

3.2.2.4. Differences in susceptibility to hypoxic-ischaemic injury between gray and white matter.

In the newborn infant the gray matter has a much higher blood flow than the white matter. In mild hypoxia Purvis and James (1969), found that the increase in cerebral blood flow was much more marked in the gray as compared to the white matter. Not surprisingly, when cerebral blood flow falls in more severe hypoxia it is the white matter that suffers the more severe reduction in flow. Ment et al (1985) used the 14c iodoantipyrine method to asses cerebral blood flow in Beagle puppies subjected to hypotension and found that the dominant reduction in blood flow was to the white matter particularly of the parietal and temporal areas.

The difference between white and gray matter in adaption of blood flow to hypoxia may partly explain the known susceptibility of white matter to hypoxic insult in the perinatal period.

3.2.2.5. Studies of human neonatal cerebral blood flow in response to hypoxia.

There have been a number of studies trying to establish the pattern of alteration of cerebral blood flow in term asphyxiated human infants. Volpe et al (1985) used positron emission tomography which makes tomographic cuts after an I.V. bolus of radioisotopic (O 15) water. They found that in infants only very mildly affected, blood flow to the caudate nucleus and thalamus was similar to that to the cortical areas. Furthermore the blood flow to the gray matter of the cortex was double that to the white matter. The cortical area with the highest flow was the Sylvian area. In severely asphyxiated infants there was a decrease in the blood flow to the parasaggital regions of the cortex, which was usually symmetrical and more noticable posteriorly. The caudate nucleus, ventral pons and Purkinje cell layers of the cerebellar cortex were also markedly affected. One infant died and at post mortem examination showed a bilateral parasagital softening of the parietal lobes. These findings are similar to those of Amiel-Tison (1973) with regard to the distribution of the neuropathological lesions at post mortem.

The balance of evidence from animal and human studies is that in hypoxic-ischaemic insults in the term infant

the areas of the brain that suffer the greatest reduction in blood flow are those of the cerebral cortex and particularly the associated white matter.

3.2.3. The effect of regional differences in brain metabolism on the pattern of hypoxic ischaemic cerebral injury.

The distribution of asphyxial injury to the neonatal brain is related not only to the pattern of blood supply but also to the pattern of metabolic activity of various parts of the brain.

Hopkins et al (1980) in histochemical studies have demonstrated a lower density of the enzymes of oxidative phosphorylation, such as succinic dehydrogenase, in immature as compared to mature brains. They also showed that these enzymes display regional differences within the brain in that the phylogenetically older parts of the brain have higher levels than the phylogenetically newer parts. Thus the vermis of the cerebellum has higher levels than the lateral lobes and the basal ganglia have higher levels than the neocortex.

Duffy et al (1982) have studied regional brain metabolism and found that gray matter consumes more glucose than white matter and that "caudal" (mainly basal ganglia) gray matter consumes more glucose than cortical gray matter.

It would be expected for example that the higher the glucose consumption of an area of the brain, the more vulnerable it would be to hypoxia-ischaemia in which the utilization of substrate is accelerated and its delivery curtailed. The pattern of injury that could be expected in hypoxia-ischaemia on the basis of these metabolic differences would mainly be to the gray matter of the basal ganglia and brain-stem rather than to the cortex, and different to that attributable to the accompanying reduction in cerebral blood flow. As will be seen in the next section the actual pattern of neuropathological injury is usually a combination of the patterns predictable from blood flow changes and from metabolic differences.

3.3. NEUROPATHOLOGICAL APPEARANCES OF HYPOXIC-ISCHAEMIC CEREBRAL INJURY.

The actual pattern of cerebral injury seen neuropathologically in neonates who have experienced asphyxia has been examined in a number of ways. Several primate models have been used by Myers and his co-workers (Myers et al 1969, Myers 1972) while the clinical and neurohistological findings in human aphyxiated neonates have been examined by a number of authors.

3.3.1. Neuropathology in animal models of perinatal hypoxic-ischaemic injury.

Myers (1972) compared two models of asphyxia, namely total aspyhyxia and prolonged partial asphyxia. In total asphyxia the cord of newborn monkeys was clamped and effective breathing prevented by placing a saline filled rubber bag over the infant's head. In prolonged partial asphyxia the intrauterine fetus was subjected to hypoxia-ischaemia by obstructing the maternal arterial blood supply to the uterus and hence to the placenta by means of abdominal aortic banding. Further details of these models are given in Chapter 4.

3.3.1.1. Total asphyxia.

The pattern of neuropathological damage reported by Myers in fetuses which had experienced periods of total asphyxia was consistent. The following structures were involved in order of frequency after asphyxial periods lasting from 10-13 minutes :

Inferior colliculi.
Superior olives.
Sensory nuclei of V.
Gracile and cuneate nuclei.
Medial and spinal vestibular nuclei.
Posterior and lateral ventral thalamic nuclei.

When the asphyxial period was greater than 16 minutes the neurohistological damage extended as follows :

Thalamus.
Lateral brainstem tegmentum.
Brainstem motor nuclei.
Spinal cord.

It is very striking that the cerebral cortex is virtually not involved in the damage caused by this type of asphyxia.

He showed that the most vulnerable areas are those with the highest blood flow as determined by 14C antipyrine emission studies.

3.3.1.2. Partial asphyxia.

Myers found that partial asphyxia on the other hand produced a very different pattern of neuropathological damage. The brunt of damage fell on the cortex and basal ganglia and with very little brainstem involvement.

He reported a spectrum of injury which ranged from total necrosis of both hemisheres to limited damage of the middle third of the precentral gyrus. The former is usually associated with early death and the latter with adult survival and mild cerebral palsy. Involvement of the basal ganglia may occur alone or more usually together with cortical injury. Myers reports that the brain stem involvement is uncommon but may occur if episodes of total asphyxia are superimposed upon episodes of partial asphyxia.

The group of Bondareff et al (1970) and Brann and Myers (1975) using a different model of prolonged partial

asphyxia produced asphyxia in 8 pregnant Rhesus monkeys at the 157-162 day stage of gestation. Maternal hypotension of < 75 mm Hg was produced by means of halothane anaesthesia and maintained for 1-5 hours. The infants were then delivered by caesarian section. The infants required active resuscitation with artificial ventilation. They all developed evidence of encephalopathy and the mean survival time was 46.7 hours. At post mortem they exhibited cerebral swelling of various degrees of severity. Six had areas of cortical softening which in every case involved the middle third of the paracentral region. Four additionally had softening in the posterior parietal and occipital regions.

The basal ganglia, especially the head of the caudate nucleus, were affected in all cases, whilst the thalamus and cerebellum was affected in 5 of the 8 infants. The brain stem, medial uncus and hippocampus and the medial portions of the temporal and occipital lobes were not affected.

Conclusion : Primate studies of asphyxia show two different patterns of brain injury depending on the type of insult. Total asphyxia produces injury mainly to the brain stem whilst prolonged partial asphyxia produces injury primarily to the cortex and basal ganglia.

3.3.2. Neuropathology after asphyxial injury in human infants. :

Amiel-Tison (1973) found that the gross pathological appearance of the brain after asphyxial death in term neonates was of brain swelling with consequent flattening of the convolutions, narrowing of the sulci as well as uncal and tonsillar herniation. Pryse-Davies and Beard (1972) found similar gross appearances.

Amiel-Tison (1973) noted that histologically the brainstem, basal ganglia and cerebellum were nearly always involved while the cortex was affected to a progressively greater degree with increasing severity. She noticed that cortical damage was worst in the depths of the sulci, that the hippocampal area was always the most severely affected part of the brain. The affected tissue showed swelling of the cytoplasm of the neurones with pyknosis and variable karyorrhexis. At later stages there was dissolution and glial replacement.

Hill and Volpe (1981) have combined clinical, CT, isotope scan, and postmortem histological data from asphyxiated infants and suggest that the major cerebral lesions associated with hypoxic-ischaemic injury in the perinatal period are as follows :

3.3.2.1. Selective neuronal necrosis -

This involves the cerebral cortex, Purkinje cells of the cerebellar cortex, thalamus and brain stem. When examined some time after the acute episode, typically there is neuronal loss with astrocytosis and smooth gyral atrophy of the cortex (ulegyria). The long term clinical picture is of mental retardation, seizures, spastic motor defects and bulbar disorders such as poor sucking and difficulty with swallowing. Technetium brain scan shows increased uptake over the cerebral hemispheres.

3.3.2.2. Parasaggital cerebral necrosis -

This involves necrosis of cerebral cortex and adjacent subcortical white matter in the parasaggital areas of the cortex. The lesion seen later involves cortical atrophy and gliosis in the affected area. These are thought to be watershed lesions as a result of severe systemic hypotension. Technetium scans in the neonatal period show increased uptake in the parasaggital areas.

3.3.2.3. Status marmoratus -

This involves neuronal necrosis in the caudate nucleus, putamen and globus pallidus. The clinical picture is later development of rigidity and choreoathetosis. Technetium scan in the neonatal period shows increased uptake in the basal ganglia.

3.3.2.4. Periventricular leukomalacia -

The lesion is in the white matter adjacent to the external angle of the lateral ventricles. There is variable atrophy of tissue lateral to the ventricles leading to an appearance of ventricular dilatation. The lesion is thought to be a watershed phenomenon between the penetrating branches of the anterior and middle cerebral arteries. Hypotension and impaired autoregulation of the cerebral circulation seem to be the critical factors in its development. It is a particular feature of asphyxia in the preterm infant in whom the overlying cortex tends to be spared. The clinical correlate is spastic diplegia with relative sparing of the intellect. This type of lesion is not frequently seen in the term infant.

3.3.2.5. Focal ischaemic brain damage -

In term infants this involves the occlusion of single major arteries or their main branches with resulting cerebral infarction. The middle cerebral artery is most often involved. The common cause is embolization as a result of disseminated intravascular coagulation secondary to sepsis. The lesion seen later involves a focal cystic lesion with or without dilatation of the lateral ventricles. Porencephaly occurs if communication between a cyst and the lateral ventricle exists. Both the CT and Technetium scans show the lesions in the neonatal period. The late sequelae of

this type of lesion is mental retardation and/or focal motor defects such as hemiplegia.

3.3.3. Unifying models of neuropathological injury. :

Brann and Myers (1975) note the close similarity between the injury patterns in the brains of human infants dying of hypoxic-ischaemic injury and those of their primate model of prolonged partial asphyxia. They suggest it is likely that the pathogenetic mechanisms are similar.

3.4. PATHOLOGICAL APPEARANCE OF NEONATAL HYPOXIC-ISCHAEMIC BRAIN INJURY AS REVEALED BY NEWER IMAGING TECHNIQUES.

The new imaging techniques provide some information about pathological damage sustained by asphyxiated infants who do not come to post mortem.

3.4.1. Computed tomographic appearances :

The computed tomographic (CT) appearances following perinatal asphyxia in term infants have been studied by a number of authors including Flodmark et al (1980), Shewmon et al (1981), Fitzhardinge et al (1981), Lutschg et al (1983), Voorhies et al (1984) and more recently Lipp Zwahlen et al (1985). Initially the resolution of the instruments was poor and the importance of the timing of the scan was not fully appreciated. Once these problems were overcome a fairly

consistent pattern of CT appearances has been reported.

In an affected infant, scans done in the first few days after delivery show compressed ventricles and widespread decreased brain tissue density typical of cerebral oedema. Haemorrhages are seen in a minority. Periventricular hypodensities are sometimes seen at this early stage.

The greater value of scanning at 2-4 weeks after birth has been well demonstrated by Lipp Zwahlen et al (1985). They found that in infants later found to be neurologically normal, the periventricular densities of scans performed in the first few days cleared, whereas in those who were ultimately neurologically abnormal, the periventricular hypodensities became symmetrical in distribution and very clearly demarcated. The latter extended into the subdural white matter and often reached as far as the cortex.

These authors report that when the scans are repeated at 3 or more months after birth, the hypodensities seen at 2-4 weeks had either disappeared due to glial proliferation or transformed into permanent cystic lesions. At this stage dilation of the ventricles is often seen. The cystic lesions may seem to communicate with the ventricles. This loss of periventricular tissue is felt by Lutschg (1983) to be the equivalent of the pathological finding of periventricular

leukomalacia.

Earlier authors did not comment on basal ganglion or thalamic changes with CT scanning. However Lipp Zwahlen et al (1985) report that the basal ganglia may show areas of hypodensity in scans performed at 2-4 weeks of age. A scan done at 11 months of age showed high density in the thalamus which they felt was the radiographic equivalent of status marmoratus.

3.4.2. Ultra-sound (US) appearances :

Another recent tool for the assesment of brain injury in hypoxic-ischaemic encephalopathy is ultrasound (US). This has great advantages over CT scanning in that it is less invasive, more portable, quicker to obtain, less disturbing for the infant and the cost of the equipment much lower.

Siegel et al (1984), Martin (1983) and Slovis (1984) have reported consistent US appearances in aspyxiated infants. Firstly they report small or non-visualisable ventricles typical of cerebral oedema. Secondly they report diffuse cerebral echoes thought to be due to widespread ischaemic changes or cerebral oedema which US cannot easily discriminate. Thirdly they describe focal parenchymal echoes which are thought to be due to ischaemia resulting from single major vessel infarction. Fourthly they saw periventricular echoes.

Martin (1983) and Slovis (1984) found that over 2-4 weeks these echogenic areas tend to develop a cystic appearance equivalent to periventricular leukomalacia. It is of note that the cystic lesions are not seen as such on CT scanning; their equivalent being the ventricular diatation seen at 2-4 weeks on CT scan.

The US may have a disadvantage in that it tends to underestimate cerebral injury. The above authors report that in cases which later came to post mortem the US had underestimated the extent of cerebal damage. Siegel et al (1984) found that of 32 cases of hypoxic-ischaemic encephalopathy, all but 2 showed small or non-visualised ventricles, but only 20 showed abnormal echoes. Ten out of the 32 cases died of whom all had had abnormal US scans and only 10 out of 22 survivors had abnormal echoes on scan.

A further role for US scanning in asphyxia is to asses cerebral vessel pulsation in, and hence detect, infarcted areas of brain. Hill et al (1983) have described 4 asphyxiated infants with major focal ischaemic lesions on CT scan who had equivalent echodense areas on US performed at the same time. In these major lesions the pulsation of the major arteries could be seen and assesed in "real time". Within the echodense areas the vessel pulsation was visibly decreased. Voorhies et al (1984) also noted decreased

vessel pulsation bilaterally in the echodense areas associated with HIE.

3.4.3. Digital intravenous angiography :

Voorhies et al (1984) have described the use of digital intravenous angiography (DIVA) in the investigation of asphyxiated neonates. This is a new and relatively non-invasive technique which involves an intravenous injection of a contrast medium and the taking of rapid serial radiographs which are later subjected to computer analysis to produce images of the vessels. Both the arterial and venous phases can be visualized. They studied 6 severely asphyxiated term infants with hypoxic-ischaemic encephalopathy. The US and CT scans were typical of severe cerebral injury as described above. The DIVA was carried out in the first week of life and the significant finding was in the venous phase of the examination in which saggital sinus thrombosis was found in 5 infants. Of these, 3 also had straight sinus thrombosis and of these, one also had a transverse sinus thrombosis. In the arterial phase 2 had internal or common carotid artery thrombosis. It is known that in asphyxia the synthesis of prostacyclin (PG I2) is reduced and that of Thromboxane T2 increased (Farber 1981). The latter may lead to a state of hypercoagulability. The occurence of venous occlusion may mean that venous infarction may add to the

prexisting hypoxic and ischaemic damage. Voorhies et al (1984) postulate that the frequent finding of haemorrhagic cerebral infarcts at post mortem may be related to venous infarction as illustrated by DIVA. The group of infants studied were unusually severely affected as 5/6 died and the sole survivor was a severe spastic quadriplegic with mental retardation.

This technique has begun to reveal the contribution of venous infarction to asphyxial brain injury. This is an area that thus far has been little discussed.

3.4.4. Other Techniques

A number of other techniques have been used to characterize the cerebral state of the asphyxiated neonate. These include the electroencephalogram (Rosen 1967, 1973, and Archbald et al 1984) and visual evoked potential (Woods 1983). The use of these techniques may also be helpful.

3.5. CONCLUSIONS :

3.5.1. Hypoxic insults are associated with dramatic falls in cerebral blood flow leading to ischaemia which is exacerbated by subsequent cerebral oedema.

3.5.2. The impact of ischaemia on the brain varies with the type of insult. Total asphyxia results in damage predominantly to the brain stem whereas prolonged partial asphyxia results in damage mainly to the cerebral cortex and basal ganglia.

3.5.3. The white matter is more vulnerable to ischaemia than is the gray matter.

3.5.4. Metabolic differences also determine the injury pattern after hypoxic-ischaemic insults. The hind brain is more vulnerable metabolically than is the fore brain and the gray matter is more vulnerable in this sense than the white matter.

3.5.5. The final pattern of injury is a blend of these opposing tendencies with the length and type of insult determining the precise pattern in each case.

3.5.6. The pattern of cerebral injury seen in human asphyxiated infants is fairly well reproduced in animals by the model of prolonged partial asphyxia.

3.5.7. The neuropathological patterns of brain injury after hypoxic-ischaemic insults can be correlated with the clinical type of resulting neurological deficit, as well as with CT and ultra-sound findings.

3.5.8. When a community shows a high incidence of mentally retarded spastic quadriplegia it is reasonable to assume that in the absence of a common post natal cause the aetiology is perinatal hypoxic ischaemic insults. This would appear to be the case in Ciskei and probably in many similar areas. Further studies on the distribution of type and aetiology of cerebral palsy in developing areas are needed to confirm this.

CHAPTER 4

CLINICAL CRITERIA OF ASPHYXIA

4.1. CHANGING CONCEPTS OF ASPHYXIA.

A problem facing any proposed study relating to asphyxia is the lack of clarity as to which parameters should be used to define it. This stems in part from changing concepts of asphyxia. Previously it was felt that the term applied to any infant who failed to establish adequate spontaneous respiration at birth. It was recognised that there was a long and divergent list of possible causes for this. More recently the concept has narrowed down to include only the consequences of hypoxic and/or ischaemic insults in pregnancy and/or labour. This concept would not for instance, include an infant failing to establish respiration as a result of maternal sedation. The need to find valid markers of hypoxia/ischaemia for the purpose of defining populations of asphyxiated infants has lead to the use of an increasing number of such markers and more recently to the use of "packages" of criteria which include an ever growing list of new investigations.

This chapter aims to review the existing literature on the criteria used for defining neonatal asphyxia in the clinical situation. Such a review starts with consideration of the basic pathophysiology of fetal hypoxia-ischaemia and then goes on to consider individual and group measures of asphyxia.

4.2. PATHOPHYSIOLOGY OF FETAL HYPOXIA-ISCHAEMIA.

Most of the measures of fetal and neonatal well-being such as fetal heart rate, fetal pH and Apgar score for example are functions of the altered pathopyhsiological state of the fetus. Before considering their validity it is useful to look at the pathophysiological process as a whole. Animal models and human studies will be reviewed.

4.2.1. ANIMAL MODELS OF ASPHYXIA :

A good deal of experimental work has been done on animal models of asphyxia and while it is accepted that even the best is not an exact replica of human fetal asphyxia, a great deal has been learned from their use.

4.2.1.1. Total asphyxia :

A significant contribution to the knowlege of the pathophysiology of asphyxia was made by Myers et al (1972) who reported the cardiovascular, respiratory, metabolic and neuropathological consequences of total asphyxia in term monkey fetuses. In this model, as mentioned in Chapter 3, fetuses were prevented from breathing air at birth by placing a thin saline filled rubber sac over the fetal head. The placental circulation was stopped by immediate cord clamping. The newborn monkeys were subjected to various periods of total asphyxia before resuscitation was initiated. During this period the heart rate, blood pressure,

blood gases and respiratory efforts were monitored.

It was found that the blood pressure rose very briefly after cord clamping and then fell only to rise again at 2 minutes as a result of catecholamine release. This rise peaked at 3 minutes, and was followed by a gradual fall to a low of 2-3 mm Hg by about 13 minutes. At blood pressures of less than 5-10 mm Hg a state of severe cerebral and myocardial underperfusion exists. The heart rate mirrored the changes in blood pressure in that after a brief period of no change it fell sharply and subseqently rose with the catecholamine surge. It fell thereafter to a fixed value of 60 per minute in which state there was very little effective cardiac output but basal ECG activity continued for a long period.

The arterial pO2 fell precipitously to 4-7mm Hg by 1.5 minutes and remained as such until resuscitation. Such rapid change was not seen in the acid base parameters. The pH fell steadily at 0.04 units per minute to reach 6.7 at 13 minutes. The base excess rose to -15 to -20 in a steady linear fashion over the same period.

The normal respiratory efforts which were present for 1-2 minutes were followed by a period of primary apnoea lasting to the 6th minute when strong "terminal" gasping began. This continued until the 14th minute. It is noteworthy that terminal gasping continued even at a

time when the circulation had virtually ceased, the metabolites entirely anaerobic and the acid-base status grossly abnormal.

Neuropathological changes could be found in the brain in fetuses after 10 minutes of total asphyxia. Those fetuses who experienced more than 25 minutes of total asphyxia regularly died of intractable cardiac failure due to hypoxic myocardial injury.

4.2.1.2. Prolonged partial asphyxia :

Myers (1972) has used a another model of asphyxia which, as discussed in Chapter 3, he feels is more akin to the situation of the asphyxiated human infant. The fetus is exteriorised, cannulated and returned to the uterus. It is then subjected to the consequences of banding the maternal abdominal aorta to produce various mean aortic pressures distal to the banding. Myers (1972) , and Brann and Myers (1975) found that mean aortic pressures of between 70 and 50 mm Hg could be tolerated for prolonged periods with only minor evidence of fetal disturbance, while pressures below 40 mm Hg lead to progressively severe signs of fetal distess. These included falling fetal heart rate, blood pressure, pO2 and pH and a rising pCO2 and base excess.

4.2.1.3. Fetal heart patterns and acidosis in hypoxia-ischaemia :

In human subjects Caldeyro-Barcia et al (1952) described the relationship between uterine contractions and the associated variations in fetal heart rate. They categorized the fetal heart pattern as: Type 1 dips which are synchronous with the peak of uterine contraction and which are thought to be due to head compression altering cerebral blood flow. Slow waves are seen on electroencephalographic recording during this type of dip. These dips occur during 25-40% of uterine contractions after rupture of the membranes and cervical dilatation.

Type 2 dips consist of fetal bradycardia during uterine contraction but reaching a nadir 30-60 seconds after the contraction is completed. The delay represents the time needed for the depletion of intervillous space oxygen and for the hypoxic fetal blood to reach the myocardium.

Using his primate model of intrauterine hypoxia-ischaemia Myers found that the fetal bradycardia is accompanied by falls in the fetal blood pressure. As the severity of the dips increases with progressive maternal asphyxia the acid base status deteriorates, the blood pressure falls further and eventually the heart rate and fetal blood pressure even between dips

are lowered. During severe dips, perfusion of the fetal brain and myocardium is seriously impaired. Myers found that type 2 dips begin to appear at a fetal pH of 7.10-7.15 but that fetal brain damage does not occur at this pH level even after several hours exposure. On the other hand at pH levels below 7.00 fetal brain damage occurs regularly. The lower the pH and the longer the duration of the insult, the more likely brain damage is to occur.

Myers observes 3 possible outcomes for the experimentally asphyxiated infant :

Mild asphyxia - pH > 7.10 and fetal blood oxygen content >1.5 volumes per cent. There is no evidence of subsequent neurologial abnormality or of histological evidence of brain damage.

Intermediate asphyxia - pH 7.00-7.09. These infants have asphyxia that permits survival but with evidence of permanent brain injury.

Severe asphyxia - pH < 7.00 and fetal blood oxygen content < 0.4-0.8 % lasting for several hours. These infants all die even if they are initially resuscitated and live for a few hours or days. They are unable to maintain a normal blood pressure and die as a result of hypoperfusion. At post mortem the brains show swelling and hemispherical necrosis.

4.2.1.4. Conclusion :

Myers' animal work is entirely compatible with findings in human asphyxia and produces quantitative data unobtainable from human work.

4.2.2. HUMAN EQUIVALENTS OF ANIMAL MODELS :

Both Althabe et al (1967) and Kublik et al (1969) found that Type 2 dips are associated with fetal hypoxia as measured by fetal scalp samples of capillary blood and tissue oxygen electrodes.

4.2.2.1. Fetal Heart Patterns :

A number of authors have demonstrated a close association between the occurence of Type 2 dips and depression of the neonate (Hon 1959), Brady and James (1962), Kublik et al (1969) and Bissonnette (1975).

Painter et al (1978) found that in term infants the occurence of severe variable and late deceleration fetal heart patterns in labour showed significant association with abnormal neurodevelopmental outcome at 1 year.

There is a substantial basis for regarding severely abnormal fetal heart patterns as being highly suggestive of fetal hypoxia.

4.2.2.2. Fetal acidosis and neonatal depression :

Beard et al (1967) found a good relationship between fetal scalp pH sampling taken within 30 minutes of delivery and the subsequent Apgar score of the infant. A scalp pH of <7.16 was usually associated with a depressed infant and a pH of >7.25 with a vigorous infant. pH values between these two were unreliable predictors of outcome. Hon and Khazin (1969) had similar findings. Both groups found that the relationship was only valid if the scalp sample was taken no longer than 30 minutes before delivery.

4.2.3. CONCLUSION ON PATHOPHYSIOLOGY OF HYPOXIA-ISCHAEMIA :

The interrelationship between fetal scalp pH, fetal heart rate patterns and fetal outcome are well established. The pH reflects the state of fetoplacental gas exchange. Fetal hypoxia will be reflected as metabolic acidosis which is a consequence of increasing anaerobic metabolism. The ischaemic stress of each uterine contraction leads to hypoxia of the myocardium and the brain. In an already compromised infant the additional stress is not well tolerated. The result is significant fetal bradycardia and a reduced level of neurological drive at birth.

The clinical use of type 2 fetal bradycardia and fetal scalp acidosis to detect fetuses at risk of asphyxia is valid.

4.3. EVALUATION OF PARAMETERS CURRENTLY USED IN THE DEFINITION OF ASPHYXIA.

4.3.1. General problems :

An individual parameter of asphyxia has been considered useful if it correlates well with long term neurological outcome. Unfortunately the interpretation of studies evaluating these criteria have been bedevilled by a number of variables. These include :

Gestational age :

Some studies have limited themselves to term infants while others have included data for all gestational ages.

The neurodevelopmental criteria used to asses late outcome :

Established cerebral palsy, mental retardation, speech deficits, learning disabilities and a variety of other criteria have been used alone or in combination. Some studies have used very sophisticated intelligence and perceptual testing while others have not been clear as to what methods were used. Global statements such as "neurologically abnormal" have been used.

Mortality :

Some studies specifically refer to death in the neonatal period while others refer to 1 st year mortality. Others do not define the period to which their mortality refers.

Use of multiple criteria :

Many studies use a main parameter such as an Apgar score but also require one or more additional criteria such as encephalopathy or failure to achieve sustained respiration within a certain period. These additional criteria greatly alter the type of infant included in any study.

Lack of Uniformity :

Very many different criteria or combinations of criteria have been used in different studies.

Amiel-Tison and Ellison (1986) in their review of studies of asphyxia recognize problem of definition and suggest that any new study of asphyxia must describe variables from (1) labour and delivery - signs of fetal distress; (2) the immediate newborn period - Apgar and need for resuscitation and (3) the neonatal period - neurological features, including special investigations such as ultrasound, CT scan, nuclear magnetic resonance, EEG and brain stem auditory evoked response. To date studies have defined their cases in terms of only one or two of these criteria with resulting uncertainty as to what degree of insult the author is describing.

4.3.2. THE APGAR SCORE AS THE MAIN CRITERION OF ASPHYXIA :

Prior to 1953 the methods used to asses infants who had experienced pre- or intra-partum hypoxia were not uniform and the contribution of Apgar (1953) was to provide a practical routine method of recording the condition of such infants at birth. Subsequent follow-up studies have confirmed the usefulness of the Apgar score but have also pointed out its limitations.

Those studies which used the Apgar score as the only criterion of asphyxia are set out in Table 4.3.1. The studies have been sorted first by gestation and then by increasingly severe Apgar criteria. "Term" has been taken to include those specifying at least 37 weeks gestational age or of birth weight greater than 2.5Kg. Where available the figures for controls with "good" Apgar scores, ie 7-10, have been included in brackets.

It is noted that mortality and handicap ratios as compared to controls are high (X10-X50).

There is a crude agreement within these categories as to mortality and to the incidence of significant neurodevelopmental abnormalities in the survivors, but there are exceptions. The study by Dweck et al (1974) shows an overall mortality of 61% which is much higher than other studies in its group. This study included ventilation at resuscitation and the use of alkali as

TABLE 4.3.1. STUDIES USING APGAR SCORE AS ONLY CRITERION OF ASPHYXIA.

AUTHORS	N	GA	CRITERIA FOR SELECTION	MORTALITY %	OUTCOME % SEVERE	OTHER	NORMAL	FOLLOW UP MONTHS
Molteno 1976	126	ALL	APGAR 1 =< 3	13	5.5		83	12
Drage et al 1964	1123	ALL	APGAR 1 =< 3	11 (0.3)	-		-	1
Nelson and Ellenberg 1981	2764	ALL	APGAR 1 =< 3	17.6 (1.8)	1.8 (0.2)			84
Nelson and Ellenberg 1979	788	ALL	APGAR 5 =< 3	44	5.1		51	84
Drage et al 1966	148	ALL	APGAR 5 =< 3	**	7.4			12
Nelson And Ellenberg 1979	362	ALL	APGAR 10 =< 3	68	12.6		19	84
Drage et al 1964	878	BW >2.5	APGAR 1 =< 3	3.2 (0.3)	-	-	-	1
Nelson and Ellenberg 1981	2002	BW >2.5	APGAR 1 =< 3	5.6 (0.9)	1.5 (0.2)			84
Drage et al 1966	115	BW >2.5	APGAR 5 =< 3	**	4.3			12
Nelson and Ellenberg 1981	399	BW >2.5	APGAR 5 =< 3	15 (1.0)	4.7 (0.2)			84
Thomson et al 1977	86	TRM	APGAR 5 =< 3	50 (0.0)	2.3 (0.0)		48	96
Ergander et al 1983	76	TRM	APGAR 5 =< 3	21	1.7	4.0	58	24-48
Drage et al 1964	175	BW >2.5	APGAR 5 =< 3	15 (0.3)	-	-	-	1
Nelson and Ellenberg 1981	127	BW >2.5	APGAR 10 = < 3	34 (1.8)	16.7 (0.4)	-	-	84
Dweck et al 1974	51	ALL	APGAR 1 =< 3 +IPPV & Alkali	61	6	6	19	22-40

** = Neonatal survivors only. (n.n)= Figures for controls.

TRM = Term
SEVERE = Significant neurodevelopmental abnormality.
OTHER = Lesser degree of neurodevelopmental abnormality.
GA = Gestational age.
BW = Birth weight.
APGAR 1 = Apgar score at 1 minute

additional selection criteria which will select more severely affected infants. The numbers in the study are small and the period to which mortality refers is not specified. The study of Thomson et al (1977) also showed a very much higher mortality than comparable studies and the reasons for this are not clear.

Data from the US collaborative study (Drage et al 1964, Nelson and Ellenberg 1979 & 1981) had very large numbers, careful recording by outsiders of Apgar scores and high quality, long term follow-up. It is likely that this data will be used as standard reference material.

Conclusions on Apgar score :

Allowing for the factors mentioned above which make accurate numerical comparisons difficult, a few reasonable conclusions are possible from the data in these studies.

4.3.2.1. A low Apgar score (0-3) is associated with a very considerably increased risk of mortality and long term neurodevelopmental abnormality in groups of mixed gestation as well as in term infants.

4.3.2.2. The incorrect use of a low Apgar score as being synonymous with asphyxia has been the subject of a recent statement by the American Academy of Pediatrics (1986). They note that immaturity, maternal medication,

congenital malformation, cardiorespiratory disease and other non-asphyxial factors may affect the score. A low score is not necessarily due to fetal hypoxaemia which is the essence of asphyxia. They conclude that to substantiate a diagnosis of asphyxia, a low Apgar score must be accompanied by other markers of fetal hypoxaemia such as metabolic acidosis.

4.3.3. TIME TO SPONTANEOUS RESPIRATION AS A CRITERION OF ASPHYXIA.

Table 4.3.2. below gives the details of a number of studies in which the time to spontaneous respiration was used as the only criterion of asphyxia. The figures reflect a severely affected group of infants with mortality from 18 to 33 % and abnormal long term neurodevelopmental outcome of 15-25%. It is of note that the outcomes in the studies are similar despite widely differing times to spontaneous respiration.

It should be noted here that the need for endotracheal intubation with ventilation at birth is also not necessarily indicative of hypoxaemia. Lissauer and Steer (1986) found that 57% of infants requiring intubation at birth had had neither an abnormal cardiotochograph nor placental arterial acidosis. The reasons for intubation in this group were related to factors such as meconium stained liquor, operative delivery or anaesthetic agents given to the mother.

TABLE 4.3.2. STUDIES USING TIME TO SPONTANEOUS RESPIRATION AS THE CRITERION FOR ASPHYXIA.

AUTHORS	N	GA	CRITERIA FOR SELECTION	MORTALITY	NEURODEVELOPMENTAL OUTCOME %			FOLLLOW UP
				%	SEVERE	OTHER	NORMAL	MONTHS
Scott 1976	20	All	NO RESP OR HEART BEAT AT 1MIN OR TSR >20 MIN	30	25		45	36-84
DeSouza et al 1981	26	All	TSR > 10 MIN	**	16	23	61	24-60
Mulligan et al 1980	48	Term	IPPV FOR >1 MIN BEFORE SPONT. RESP.	18	15		67	60
Svenningsen et al 1982	30	Term	TSR > 30 MIN.	33	20		46	18
Koppe and Kleiverda 1985	20	Term	TSR > 15 MIN.	60	20		20	60

** = Neonatal survivors only.

Key :

IPPV = Intermittent positive pressure ventilation.
TSR = Time to spontaneous respiration.
GA = Gestational age.

Note : Neurodevelopmental outcome % - refers to the percentage of the whole group with that category of abnormal neurodevelomental outcome.

4.3.4. ENCEPHALOPATHY AS A CRITERION OF ASPHYXIA :

The development of encephalopathy in an infant who has been at risk for asphyxia during pregnancy and labour is a fairly easily defined event and worth evaluating as a criterion of asphyxia. There have been a number of studies that have looked at the mortality and neurodevelopmental outcome of infants who have had an asphyxia related encephalopathic episode in the early neonatal period. Associated features have been used to assign the encepalopathy as asphyxial. These features have included abnormal fetal heart patterns, meconium stained liquor, low Apgar scores, the need for ventilatory assistance or acidosis at birth. The details of these studies are set out in Table 4.3.3.

Two of these studies refer to infants of all gestational categories and the rest refer to term infants. While the immediate mortality and long term neurodevelopmental abnormality rates are relatively high, the wide range (6.7-37% and 6-47%) points to the lack of uniformity in the selection criteria. Nevertheless one can draw some broad conclusions. It seems that an encephalopathic state associated with other asphyxial markers reflects a severely affected infant with an appreciable risk of unfavourable outcome.

TABLE 4.3.3. STUDIES USING HYPOXIC-ISCHAEMIC ENCEPHALOPATHY PLUS OTHER FACTORS AS CRITERIA FOR ASPHYXIA.

AUTHOR	N	GA	CRITERIA FOR SELECTION IN ADDITION TO HIE	MORTALITY %	NEURODEVELOPMENTAL OUTCOME %			FOL UP
					SEVERE	OTHER	NORMAL	MNTHS
Brown et al 1974	94	All	AP 1 < 3 OR AP 5 <5 FET DIS,IPPV ACIDOSIS SEVERE RDS, CERTAIN ANTE PARTUM DISORDERS	22	12	30	36	21
Volpe 1976	93	All	AP 1 < 3 OR AP 5 < 5 IPPV, MSL, FETAL HRT ABN,	20	30	15	35	NOT STATED
Ziegler et al 1976	90	Term	MSL,FH ABN, AS 1 < 4 AS 5 < 6, ACIDOSIS, SIG PREG OR DELIVERY COMPLICATIONS.	37	18	10	35	31-90
Sarnat and Sarnat 1976	21	36+	AP 1 =<5 OR AP 5 =<5 FETAL DISTRESS	10	33	---	57	6-12
Finer et al 1981	95	Term	AP 1 < 5 OR AP 5 < 5 IPPV, MSL, FET HT ABN.	6.7	14.6	28	49	96
Fitzhardinge et al 1981	65	Term	AP 5 < 6, MSL, FET HT ABN, IPPV > 2 MIN.,	***	47	8	45	24
Finer et al 1983	82	Term	AP 1 OR 5 < 5, IPPV MSL, FETAL HT ABN.	11	6	16	67	27
Siegel et al 1984	32	Term	AP 1 OR 5 =<4, IPPV, + FETAL DISTRESS	31	22	6	31	6-24
Robertson and Finer 1985	226	Term	AP 1 OR 5 < 5, IPPV, FETAL DISTRESS	12	19		73	36-60
Adsett et al 1985	43	Term	AP 5 < 6, IPPV, FETAL DISTRESS, pH<7.2 WITHIN 2 HRS OF BIRTH	19	46.5	9.3	26	12-23
Levene et al 1986	122	Term	---	11	7	11	71	30
DeSouza and Richards 1978	53	Term	FETAL DISTRESS	***	6	14	78	24-60

*** = NEONATAL PERIOD SURVIVORS ONLY.

Key :

HIE = Hypoxic-ischaemic encephalopathy
IPPV = Intermittent positive pressure ventilation
MSL = Meconium stained liquor
FET HT ABN = Fetal heart abnormality

4.3.4.1. Severity of encephalopathy :

A number of authors have attempted to refine the use of encephalopathy as a marker by looking at how the severity of the encephalopathy affects outcome.

A number of schemes to grade the severity of encephalopathy have been devised by Sarnat and Sarnat (1976), Fenichiel (1983), Brown et al (1974) and Amiel -Tison and Ellison (1986). Details of these are given in Appendix I.

Set out in Table 4.3.4. are studies which have looked at the outcome of HIE in relation to its severity. They stress that outcome correlated with severity of the encephaloapthy. As illustration of how various studies have done this an analysis of 3 studies which use the Sarnat scheme is presented in Table 4.3.5.

TABLE 4.3.4. STUDIES RELATING THE SEVERITY OF HYPOXIC-ISCHAEMIC ENCEPHALOPATHY TO OUTCOME.

AUTHORS	N	GA	OUTCOME %				Grading scheme	Correlation Grade of Severity	Follow up Months
			Dead	Neurodevelopmental					
				Severe	Mild	Normal			
Finer et al 1981	89	Term	8	--27--		65	Sarnat	Sig c LTF	19
Finer et al 1983	49	Term	0	16	26	57	Sarnat	Sig c LTF	27
Sarnat and Sarnat 1976	21	36+	9.5	--33--		57	Sarnat	Sig c LTF	12
Levene et al 1986	122	Term	11	---7---		82	Fenichiel	Sig c LTF	30
Robertson and Finer 1985	200	Term	13	--15--		73	Fenichiel	Sig c LTF	40
Brown et al 1974	93	All	22	12	14	36	Brown	Sig c LTF	21
DeSouza and Richards 1978	53	Term	***	6	14	78	Own	Sig C LTF	24-60
Cyr et al 1984	21	All	*	--24---		76	Own	Sig c LTF	22

Key :

LTF = Long Term Follow-up from a neurodevelopmental point of view.
GA = Gestational ages included in the study.
Sig c LTF = Significantly correlates with long term follow-up.

Note : Neurodevelopmental outcome % - refers to the percentage of the whole group with that category of abnormal neurodevelomental outcome.

TABLE 4.3.5. POOLED DATA FROM 3 STUDIES USING SARNAT SCHEME

Sarnat Grading	Died	Categories of Outcome Degree of handicap				Totals	%
		Severe	Mod	Mild	Normal		
1	1	0	0	6	26	33	21
2	2	16	16	20	50	104	67
3	6	10	2	0	0	18	12
Totals	9	17	18	26	76	155	100

Chi-square = 58.24 DF = 8 p = < 0.001

From Finer et al (1981 & 1983), and Sarnat and Sarnat (1976).

The fairly close correlation between outcome and severity of encephalopathy suggests that grading of hypoxic ischaemic encephalopathy should become a routine clinical practice which will assist in prognostication.

Recently a 17 point scoring scheme of the neurological state of the asphyxiated newborn has been proposed by Lipper et al (1986). In a group of 34 term asphyxiated infants it was found that the score correlated well with neurodevelopmental outcome at 1 year of age. This would seem to be a more practical scheme for routine purposes than the Prechtl method which is very time consuming.

4.3.5. FETAL ACIDOSIS AS A CRITERION OF ASPHYXIA.

The idea that fetal metabolic acidosis consequent upon anaerobic metabolism might be a good marker of intrauterine hypoxia was favourably regarded as it is easy to measure and the results objective.

Initially attempts were made to correlate umbilical arterial acidosis with Apgar score. Bolton (1985) found a poor correlation between the Apgar score at 1 minute and umbilical placental arterial pH. Sykes et al (1982) in a study of umbilical arterial acid-base status and Apgar scores in a large group of normal deliveries found that while there was a statisically significant inverse correlation of Apgar score with increasing acidosis, the relationship was not close. In fact many acidotic infants were born very vigorous and many depressed infants were not acidotic. They found the incidence of 1 minute Apgar score < 3 to be 3.8% of their sample and that of base excess of > 12 mmol/l was 12.9%.

Low et al (1983) found that a group of term infants with umbilical arterial metabolic acidosis at birth had significantly lower Apgar scores at birth than a non acidotic control group, but did not have any higher neonatal mortality or different long term neurodevelopmental outcome. (See Table 4.3.6.)

TABLE 4.3.6. METABOLIC ACIDOSIS AS SOLE CRITERION OF ASPHYXIA.

N	GA	CRITERIA FOR SELECTION	MOR %	OUTCOME % SEV	OTH	NOR	F/U MTHS
37	TRM	Cases had umbilical arterial b.base < 34 meq/l	-	3 (2)	16 (18)	77 (76)	72

* 3/37 CASES DEVELOPED ENCEPHALOPATHY.

( ) = Figures for 59 controls with buffer base >34 meq/l. From Low et al (1983).

Lauener et al (1983) found that while only 10.7% of infants with an umbilical artery pH of < 7.15 had a 1 minute Apgar score of < 5 the proportion of non-acidotic infants with a similar Apgar score was lower (1.2%). They found that of 98 infants who had this degree of acidosis at birth, 2 had significant neurodevelopmental problems at 2 years of age. Unfortunately no controls were used so that the relative risk associated with the acidosis could not be determined.

Acidosis probably represents recent fetal hypoxia and when used alone as a marker, the level of acidosis used by Low et al for example is not a sensitive indicator of asphyxia.

4.3.6. COMBINATIONS OF PARAMETERS IN CHARACTERISING ASPHYXIA.

Given the limitations of individual items, several authors have put together combinations of criteria in an attempt to avoid the disadvantages of single parameters.

The important idea that a combination of Apgar score and pH might be a better marker of infants at neurological risk came from De Souza et al (1983). They found that of 24 infants who were depressed at birth (modified Apgar 0-2), only those 3 infants who also had a low umbilical venous pH were neurologically abnormal in the neonatal period. The 40 infants who had acidosis but were not depressed at birth were all neurologically normal.

Although these numbers are small they suggest that a combination of criteria may be more predictive than either alone.

Low et al (1983) and Rothberg (1986) have each produced a scheme of classifying perinatal asphyxia which incorporate a variety of parameters to provide a progressive staging from mild to severe. Details of these are given in Appendix II. It may well be that these or similar combination schemes will eventually be used to characterize the insult experienced by an individual infant. If the above 2 schemes become widely accepted and used it will be important to obtain reliable prognostic data for each stage/grade.

Van der Elst and Malan (1986) found that when they used Rothberg's scheme about 40% of patients in the milder grades 1 and 2 had encephalopathy. This highlights the need to agree on a standard definition and grading of encephalopathy.

4.3.7. OTHER MARKERS OF ASPHYXIA :

In an attempt to delineate asphyxia in a more physically measurable way, ultrasound, EEG, and CT scan have been evaluated as markers of asphyxia.

4.3.7.1. Electroencephalography as a marker of asphyxia :

Finer et al (1981) and Sarnat and Sarnat (1976) have both described EEG findings in groups of term infants

who had suffered asphyxia related encephalopathy. They found that 69% (N=51) and 85% (N=46) respectively had abnormal EEGs in the first few days of life. The changes were low voltage or supression patterns. They both found a correlation between early EEG abnormalities and long term neurodevelopmental abnormalities. Finer (1983) in a later study of a similar group of infants could find no such correlation. The position of EEG in this situation remains unclear.

4.3.7.2. Ultrasound as a marker of asphyxia :

Siegel et al. (1984) in a controlled study found 62% of 32 term infants suffering from hypoxic-ischaemic encephalopathy (HIE) to have abnormal ultrasound appearances. These findings were associated with a significantly higher immediate mortality as well as with a higher incidence of long term neurodevelopmental abnormalities. The method was specific in that only 2/10 had an abnormal outcome after a normal scan and sensitive in that only 1/19 with abnormal outcomes had had a normal scan. Babcock et al (1983) found it to have a sensitvity of 86% and a specificity of 100% in a similar study.

Ultrasound has also been used to study cerebral blood flow in infants with HIE. Archer et al (1986) found that in 43 term asphyxiated infants who survived for more than 2 days, an abnormal cerebral artery Doppler waveform predicted an abnormal neurodevelopmental

outcome at a median age of 18 months with a sensitivity of 100% and a specificity of 81%. Den Ouden et al (1987) found very similar results with this method but found a somewhat lower specificity.

4.3.7.3. Computed tomography as a marker of asphyxia :

It is becoming clear that CT scans can be effectively used in neurodevelopmental prognostication in an asphyxiated infant.

Finer et al (1983) found 46% of 43 CT scans, done in the first 7 days of life, to be abnormal in a group of term infants with HIE. The typical appearances have already been discussed in Chapter 3. However they could find no association between the mere presence of CT scan abnormalities and long term neurodevelopmental outcome.

On the other hand the severity of CT changes seems to correlate well with neurodevelopmental outcome. Fitzhardinge et al (1981) studied 65 term infants with HIE and showed a a strong correlation with adverse neurodevelopmental outcome at 2 years. Adsett et al (1985) also studied term infants with HIE and found an association between the severity and extent of hypodensities in the brain parenchyma on CT scan and poor neurodevelopmental outcome at 18 months. In neither of the above studies was the exact timing of the scan stated and it is likely that scans done at 1-4 weeks

when the appearances are more definite would have given a stronger association.

Lipper et al (1986) have developed a "low density index" for quantifying the low density areas on CT scans produced by hypoxia-ischaemia. They performed CT scans on 21 term asphyxiated infants within the first 48 hours of life and found that the low density index was strongly associated with mortality and adverse neurodevelopmental outcome.

It is clear that CT scanning is a very valuable prognostic tool in infants with HIE but the timing is important.

4.3.7.4. Computed tomography Vs Ultra-sound in prognostication :

Babcock et al (1983) compared US and CT scanning as to their ability to predict abnormal neurodevelopmental outcome at 4 months of age following asphyxia (Apgar at 5 minutes =<6) in 27 term infants. Eight had abnormal US appearances, all of whom had abnormal neurodevelopmental outcomes. US was designated as "early" if done at 7 days of age or less and as "late" if done after 7 days of age. The result for accuracy, sensitivity and specificity are tabulated below.

TABLE 4.3.7. COMPUTED TOMOGRAPGY AND ULTRASOUND IN ASPHYXIA

	US		CT
	Early	Late	
	%	%	%
Accuracy	71	89	100
Sensitivity	46	86	100
Specificity	100	100	-

From : Babock et al (1983).

Note : CT scan was performed after the 7th day.

4.3.7.5. Chemical markers of asphyxia :

Not surprisingly severe hypoxia induces changes in many organs other than the brain and induces chemical alterations that are becoming recognised and being assesed as markers of asphyxia. None have yet become widely used in clinical practice. These include :

Arginine vasopressin (Speer et al 1984, Wiriyathian et al 1986, De Vane and Porter 1980), Hypoxanthine (Swanstrom and Bratteby 1982, Thiringer 1983), thyroid hormone (Borges et al 1985), liver enzymes (Zanardo et al 1985, Fitzsimons et al 1984) catecholamines (Cheek et.al 1963), creatine phosphokinase (Rossi et al 1986, Amato et al 1986) and CSF lactate dehydrogenase (Fernandez 1986). These interesting aspects unfortunately cannot be persued in detail here.

4.4. CONCLUSIONS :

It is clear that no one criterion is absolute. A range of criteria of increasing severity may be used and as more data accumulate the prognostic equivalent for each set of criteria emerges.

4.4.1. The Apgar score is well documented in terms of outcome but it has low specificity in that a significant proportion of those with the lowest scores have a normal outcome.

4.4.2. The time to spontaneous respiration is a useful measure but thus far the studies on its outcome are few and have used a variety of times as criteria. It tends to select severely affected infants.

4.4.3. Encephalopathy seems to be a marker that is easy to establish and to grade clinically and which correlates well with outcome. It is however a marker at the more severe end of the spectrum.

4.4.4. Placental acidosis when taken alone would seen to represent one of the mildest criteria of asphyxia and should not be used alone but rather in combination with others. De Souza et al (1983) remark that the Apgar score and fetal pH individually are "blunt instruments" in representing fetal compromise and that to use them in combination would result in a more effective measure. Placental acidosis is however an objective marker that

an infant has recently been subjected to an hypoxic insult of whatever severity.

4.4.5. **Ultrasound and CT scanning** allow visualisation of the cerebral injury itself and have been shown to be sensitive and specific when judged against neurodevelopmental outcome. Their disadvantage is that the changes are not reliably visualised for some days and so would not be suitable for deciding soon after birth which infants had experienced a sufficiently great hypoxic-ischaemic insult to necessitate therapeutic measures being instituted.

CHAPTER 5

EPIDEMIOLOGY OF ASPHYXIA NEONATORUM

The literature on the epidemiology of asphyxia neonatorum will be reviewed beginning with the incidence, proceeding to its significance as a cause of perinatal death and then dealing with its antecedents in pregnancy and labour. Finally the relationship between asphyxia and cerebral palsy will be reviewed.

5.1.1. INCIDENCE :

The incidence of asphyxia as quoted by a number of studies is summarised in Table 5.1.1. The rates given vary from 12.9 to 0.48 %. This wide range relects the differing selection criteria of the studies. For example Sykes et al (1982) found a high incidence of 12.9% when umbilical arterial metabolic acidosis was used as the sole criterion. This selected a large group of very mildly affected infants. In contrast, in the same study the incidence as defined by an Apgar score at 1 minute of <3, was only 3.8%. Studies using more stringent criteria indicate an incidence of about 1%. The figure for groups of term infants is between 0.17 and 0.9%. One of the few studies from the developing world situation is that by Molteno (1976) which showed an incidence of 1.4% which is very similar to studies from the developed world. Unfortunately the incidence for term infants was not quoted separately.

TABLE 5.1.1. STUDIES OF THE INCIDENCE OF NEONATAL ASPHYXIA :

AUTHORS	GA	N	No.Del	Definition of Asphyxia	Incidence % All	Term	Prem	Country
Sykes et al 1982	All	116	895	Base Excess >12 mmol/l	12.9	-	-	UK
Nelson and Ellenberg 1981	All	2764	49000	Apgar 1 =< 3	5.6	-	-	USA
Brown et al 1974	All	760	14020	Wide criteria. See note.	5.4	-	-	UK
Sykes et al 1982	All	34	895	Apgar 1 < 3	3.8	-	-	UK
Nelson and Ellenberg 1981	All	-	49498	Apgar 5 =< 3	1.5	0.89	7.6 <2.5k	USA Coll
Molteno 1976	All	-	3167	Apgar 5 =< 3	1.4	-	-	SA
MacDonald et al 1980	All	447	38405	IPPV > 1 min to spont. respiration.	1.16	0.4 >38w	62.3 <27w	USA
Cyr et al 1984	All	103	9901	IPPV >1 min before spont respn. +-HIE	1.04	0.9	59.5 <1 Kg	CANADA
Mulligan et al 1980	All	133	13221	Time to spont Respn. >1 min	1.0	-	-	USA
Ergander et al 1983	All	116	19969	Apgar 5 =< 3	0.48	0.17	1.6 <38w	SWEDEN
Finer et al 1981	Trm	95	20155	Significant Encephalopthy	-	0.36	-	CANADA
Levene et al 1985	Trm	126	20975	Post asphyxia encephalopthy	-	0.6	-	UK

GA = Gestational age No. Del = Number of deliveries

The USA collaborative study reported by Nelson and Ellenberg (1981) involved a very large group of neonates in which Apgar scores were well documented and as such may well provide the best reference data on this topic. They found the incidence overall to be 1.8%, in deliveries at term 0.89% and for infants < 2.5 Kg, 7.6%.

5.1.2. Relative causes of neonatal death :

An indirect way of looking at the incidence of asphyxia is to look at its importance as a cause of neonatal death. Its importance as a problem in the developing world is clearly shown by reference to the Table 5.1.2. in which causes of neonatal death from a number of South African neonatal units have been categorised in a standard way. All the units serve communities of largely low socioeconomic status except that of Cooper et al (1984) which serves a much more affluent population in Johannesburg. The striking feature is that asphyxia is by far the largest single cause of neonatal death among term infants in all units except that of Cooper et al.

TABLE 5.1.2. CASES OF NEONATAL DEATH IN SOUTHERN AFRICAN NEONATAL UNITS.

AUTHORS	B.W.	No.	% Cause of Death					Unit
			Prem	Inf	Cong	Asphyx	Other	
Cooper et al (1984)	All	57	34	18	38	10	-	Johannesburg Hospital
Henning and Beyers (1984)	All	166	60	16	7	10	7	Tygerberg Hospital Cape Town
Hay et al (1984)	All	135	30	38	7	13	12	Garankua Hospital Pretoria
Rissik (1983)	All	363	30	17	9	35	9	Baragwaneth Hospital JHB
Power and Bok (1983)	All	171	46	-	8	34	12	Cecilia Makiwane Hospital Ciskei
Cooper et al (1984)	>2.5	20	-	15	65	15	5	Johannesburg Hospital
Henning and Beyers (1984)	>2.5	18	-	17	17	44	22	Tygerberg Hospital Cape Town
Rissik (1983)	>2.5	89	-	8	17	59	16	Baragwaneth Hospital JHB
Power and Bok (1983)	>2.0	74	-	-	15	65	20	Cecilia Makiwane Hospital Ciskei

Prem = Preterm
Inf = Infection
Cong = Congenital
Asphyx = Asphyxia

5.2. ANTECEDENT FACTORS IN PREGNANCY AND LABOUR :

There are a number of studies which investigate the factors in pregnancy and labour which precede asphyxia but with few exceptions they lack non asphyxiated control groups. Table 5.2.1. details 6 controlled studies. Unfortunately even these suffer from the problems of varying definitions of asphyxia, differing criteria of gestation and small numbers. Firm conclusions are thus difficult to arrive at. The studies by MacDonald et al (1980) and Cyr et al (1984) avoid these difficulties more than the others and examine a wide range of factors.

In all the studies in which it was included gestational age was highly associated with asphyxia, especially in preterm infants. In the studies where the numbers of cases were large and many factors examined, fetal distress, abruptio/ante-partum haemorrhage, malpresentations, non-elective caesarian section, and hypertension were found to be regularly associated with asphyxia. In the very large study by Macdonald et al (1980) several other factors were also found to be significantly associated.

From the nature of these positive associations it is tempting to infer that asphyxia tends to occur with conditions associated with uterine vascular pathology such as hypertension and abruptio or with prolonged

TABLE 5.2.1. CONTROLLED STUDIES RELATING ANTENATAL FACTORS TO INCIDENCE OF ASPHYXIA AND OR HYPOXIC-ISCHAEMIC ENCEPHALOPATHY.

AUTHORS	GA	N	CRITERIA FOR ASPHYXIA	PARAMETERS SHOWING SIGNIFICANT ASSOCIATION.
Dweck et al (1974)	ALL	15	AS 1 =< 3 + IPPV & IV Buffer.	Gestational age, Birth Weight, Incidence of pregnancy and delivery abnormalities.* (Nos. too small for individual factors to be analysed. factors to be analysed).
MacDonald et al (1980)	ALL	447	IPPV > 1 min before spont. respiration.	Race, marital status, diabetes,toxaemia,breech, growth retardation. Low social status. Caesarian Section for: Fetal distress, prolapsed cord, abruptio, placenta previa, prolonged rupture of membranes, isoimmunization, small for gestational age, gestational age.
Thomson et al (1977)	TRM	31	AS 1 min < 0 or AS 5 min < 5	Caesarian section, Intrapartum haemorrhage, fetal distress.
Cyr et al (1984)	ALL	93	IPPV >3 min before spontaneous respiration +- Encephalopathy.	Fetal distress, APH, prolapsed cord, hypertension, prolonged trial of labour, shoulder dystocia, malpresentation, breech, mid-forceps, large for gestational age, non- elective caesarian section, birth weight and gestational age.
Grauz et al (1983)	TRM	187	Fetal distress and neonatal acidosis.	Gestational age. (Only factor examined).
Rothberg et al (1986)	TRM	13	Chorionic acidosis	No significant associations.
Bolton (1985)	TRM	29	Apgar 1 min < 7	Maternal age & parity. (Antenatal clinic visits not significant).

* These factors included pre-eclampsia, antepartum haemorrhage, fetal distress, outlet dystocia, prolonged rupture of membranes and malpresentation.

GA = Gestational age
AS = Apgar score
TRM = Term

placental compression as in prolonged labour with a malpresentation.

Two other studies did not use controls and related factors in pregnancy and labour to the severity of encephalopathy in one and to long term neurodevelopmental outcome in the other. Details are given in Table 5.2.2. below. Neither study found significant associations. In as much as the contrast in variables between patients with different grades of HIE for example will not be as great as that between patients with HIE and controls, greater numbers may be needed in this type of study to show significant differences between variables than in controlled studies.

TABLE 5.2.2. STUDIES RELATING ANTENATAL EVENTS TO INCIDENCE OF ASPHYXIA AND/OR HYPOXIC-ISCHAEMIC ENCEPHALOPATHY.

No.	YR	GA	N	PREGNANCY & LABOUR w.r.t.	PARAMETERS SHOWING SIGNIFICANT ASSOCIATION.
1	81	TRM	95	STAGES OF HIE & SEVERITY OF LONG TERM CNS OUTCOME	No significant associations.
2	85	TRM	226	STAGES OF HIE & SEVERITY OF LONG TERM CNS OUTCOME.	Race was only significant association found.

Key :

1. Finer et al (1981).

2. Robertson and Finer (1985).

Finally in this discussion of the epidemiology of asphyxia it is necessary to consider the relationship between asphyxia and cerebral palsy which has traditionally been taken as the ultimate outcome of severe asphyxia.

5.3. ROLE OF ASPHYXIA IN CEREBRAL PALSY :

The classical view of the aetiology of cerebral palsy originating in the perinatal period is that the infant's brain suffered either a mechanical injury or a damaging hypoxic-ischaemic insult leading to cerebral infarction, haemorrhage or both or that there was a congenital abnormality of the brain. The view of Little (1862), recently reviewed by Paneth (1986), was that these injuries occured during labour and were manifest as CNS depression at birth. This depression was observed clinically as intra-partum asphyxia or failure to establish respiration. It was for this reason that for many years asphyxia was seen as central in the aetiology of cerebral palsy.

Certain paradoxes have been pointed out recently by authors such as Niswander (1985). Firstly there are many children with cerebral palsy who were not asphyxiated at birth. Nelson and Ellenberg (1986) reporting from the Collaborative study note that only 21% of 189 children aged 7 years with cerebral palsy had had any marker of intrapartum asphyxia. In their review Paneth and Stark

(1983) state that 50% of cases of cerebral palsy have no documented depression at birth.

Studies of the pre- and peri- natal antecedents of cerebral palsy are set out in Table 5.3.1. In all of these studies children with cerebral palsy were compared with controls. A large variety of significant associations were found in the studies but there were a few that recurred. In 7 studies the following factors were frequently quoted : Fetal distress (5), gestational age/birth weight (4), hypertension/pre-eclampsia (4), antepartum haemorrage (3), small for gestational age (2), social status (2), multiple pregnancy (2) breech (2).

It appears that it is factors related to fetal well being in utero rather than aspects of labour or the condition of the baby at birth that seem to relate to cerebral palsy.

The second paradox is that the majority of infants asphyxiated at birth do not exhibit cerebral palsy later on. In Tables 4.3.1.- 4.3.4. it was seen that between 50 and 95 % of infants with asphyxial markers at birth have normal outcomes in infancy and childhood. The proportion depends on the severity of the criteria for defining asphyxia.

TABLE 5.3.1. THE OBSTETRIC ANTECEDENTS OF LONG TERM ABNORMAL NEUROLOGICAL OUTCOME PARTICULARLY CEREBRAL PALSY.

AUTHORS	GA	N CASES	CASES	PARAMETERS SHOWING SIGNIFICANT ASSOCIATION.
Milligan et al (1980)	ALL	65	Abnormal neurological outcome.	"Prolonged" and "Acute" stress,birth weight gestational age, sex, social status.
Taylor et al (1985)	ALL	300	Abnormal neurological outcome.	Pregnancy : severe hypertension, primiparity previous neonatal death, APH, premature uterine activity, premature delivery, SGA, fetal tachycardia.
Dale and Stanley (1980)	ALL	315	Abnormal neurological outcome.	Previous abortion, threatened abortion, APH, prolonged rupture of membranes, PET, multiple pregnancy, breech, fetal distress *, failed obstetric proceedure *, birth weight *, gestational age *, SGA. * = significant on multivariate analysis.
Hagberg et al (1976)	ALL	560	Cerebral palsy.	Birth weight, PV bleeding in pregnancy, toxaemia, multiple births.
Niswander (1985)	ALL	34	Cerebral palsy at 18 months of age.	No difference in sub-standard obstetric care.
Nelson and Broman (1977)	ALL	50	Cerebral palsy and mental retardation at 7 years of age.	Fetal bradycardia in 2nd stage. Use of mid cavity forceps. (Wide range of social and obstetric factors examined). BW and OFC.
Nelson and Ellenberg (1986)	ALL	189	Cerebral palsy at 7 years of age.	Maternal mental retardation, severe proteinuria maternal seizures, maternal hyperthyroidism breech presentation.

A final paradox is that not every infant who develops hypoxic-ischaemic encephalopathy is depressed at birth. Neonatologists are familiar with the infant who, after having shown signs of fetal distress, is vigorous at birth but goes on to have seizures at 8-12 hours of age. For example in the study reported in Chapter 6, 22/47 (47%) infants who later developed HIE had 1 minute Apager scores of 4 or more.

These paradoxes have lead authors such as Niswander (1985) and Paneth (1986) to question the role of asphyxia in the aetiology of cerebral palsy.

On the other hand a great deal of evidence links intra-partum asphyxia with cerbral palsy. Studies concerned with the neurodevelopmental sequelae of intra-partum asphyxia are set out in Tables 4.3.1-4.3.4. They show that with increasing severity of asphyxia there is a rising proportion of neurodevelopmentally abnormal outcomes in childhood.

These studies include follow-up studies of infants with hypoxic-ischaemic encephalopathy which indicate that some 20-40% of such infants have neurological abnormalities in later childhood. Furthermore in cases of cerebral palsy following hypoxic-ischaemic encephalopathy there is a shift in the type of cerebral palsy in favour of spastic quadriparesis which is a pattern of brain damage seen in the experimental animal

work quoted above. The weight of experimental animal evidence indicates that hypoxic-ischemic insults produce neuropathological lesions that correspond to the picture seen in human spastic cerebral palsy.

A unifying theory that would explain most of the disparate findings about asphyxia and cerebral palsy is suggested :

(a) Many infants who later have cerebral palsy suffer hypoxic-ischaemic insults in utero. The fact that the timing and the severity of these insults varies accounts for the variablility of associated findings such as the occurence of depression at birth and/or encephalopathy.

(b) Severity of insult : An insult severe enough to produce cerebral palsy will always also produce temporary central nervous system depression and later encephalopathy. A somewhat lesser insult might produce temporary central nervous system depression and encephalopathy but not later cerebral palsy. A still lesser insult will produce temporary central nervous system depression followed by rapid recovery and not lead to encephalopathy or to later cerebral palsy.

(c) Timing : When the insult occurs long before birth the fetus will have recovered from the acute insult by the time of birth and thus be neither depressed at birth nor encephalopathic in the neonatal period. An insult

some hours before birth will allow time for the infant to recover from the immediate effects. There will be no depression at birth but encephalopathy will develop some hours later. If an insult occurs very close to birth itself the infant will still be depressed from the acute insult and will manifest a low Apgar score and other signs of acute asphyxia. Such an infant may or may not go on to develop encephalopathy depending on the severity.

This theory would explain the paradoxes that not all cases of cerebral palsy have had depression at birth nor HIE in the neonatal period, and that not all infants suffering from asphyxia or HIE will go on to have cerebral palsy.

Difficulty in initiating respiration at birth may well not be a cause of cerebral palsy in itself. It may be better to think of it as one of a number of markers of a cerebral insult in utero. Similarly HIE and cerebral palsy may be seen as markers of increasing severity.

From this theory one could predict that antenatal disorders relating to placental well being such as antepartum haemorrhage, pre-eclampsia, poor fetal growth etc are associated with cerebral palsy as they would predispose a fetus to intra-uterine hypoxic-ischaemic insults.

The intrauterine insult may not always be hypoxic-ischaemic. Nelson and Ellenberg (1986) have shown that a considerable number of their cerebral palsy cases in a community survey had developmental anomalies of the CNS. The authors do not state the types of cerebral palsy associated with the CNS anomalies but from animal experimental work it would be surprising if they produced the same pattern of disorder as does hypoxia-ischaemia.

5.4. SUMMARY : :

This review has attempted to examine the literature with a number of questions in mind :

5.4.1. What is the incidence of asphyxia neonatorum ?

The incidence as found in a variety of recent studies is given. It is a great defect in the literature that studies from the developing world are missing. This is not surprising in view of the fact that details of a very large number of deliveries are needed. This type of data base is infrequently kept in the developing world situation. More data in this area is needed.

Is the raised incidence of asphyxia in socially deprived communities merely a matter of poor access to obstetric care or is there an underlying (possibly placental) condition whose nature we do not understand and which disappears with economic advancement ?

5.4.2. What clinical or biochemical markers in pregnancy and labour are regularly associated with an increased risk of asphyxia ?

A number of studies have attempted to look at the contribution of a large range of factors in pregnancy and labour to the occurence of asphyxia. There are surprisingly few consistent associations in well contolled trials. Such associations include fetal distress, abrubtio and other antepartum haemorrage, malpresentations, non elective caesarian sections, and hypertension. None of the quoted controlled studies found that socioeconomoic status was associated with the occurence of asphyxia. Nevertheless studies of comparative neonatal mortality from developed and underdeveloped communities clearly show that whereas asphyxia in term infants is a major problem in the underdeveloped world it is much less so in more economically advanced communities. Socioeconomic status is thus associated with asphyxia when viewed on a global scale.

5.4.3. Does the nature of these markers give us any idea as to the basic pathophysiological mechanisms underlying asphyxia ?

The underlying pathophysiology of asphyxia largely remains obscure. Placental separation for what ever

cause is a clear mechanism of fetal hypoxia. Obstructed labour with prolonged repeated placental squeezing by uterine contractions leading to poor fetal perfusion is also understandable. How hypertension and toxaemia lead to fetal hypoxia is less clear but the process most probably involves decreased utero-placental blood flow. It is also clear that severe fetal hypoxia and/or hypotension may occur for no obvious reason. The occurence of "fetal distress" in this situation being no more than an indication by the fetus that it is in hypoxic difficulties and is not a diagnosis in itself.

CHAPTER 6

EPIDEMIOLOGY STUDY

6.1. INTRODUCTION :

In order to institute preventive measures for a condition it is necessary to study its epidemiological associations. Unless one has a reasonable idea as to the cause of asphyxia as it occurs locally and as to the categories of pregnant women particularly at risk, one is not in a position to institute effective preventive programmes. A number of possible associations had been suggested by local obstetricians and paediatricians. These included factors of health service use such as antenatal care and place of delivery, as well as obstetric factors such as breech delivery and vacuum extraction. The review of literature in Chapter 5 makes it clear that there are few consistent epidemiological associations with asphyxia. It was thus felt to be very important to study local factors in order to provide data relevant to a developing world situation.

The following epidemiological study was undertaken in an attempt to assemble such local data. It was hoped that the information gathered would have significance beyond the immediately local situation and be helpful at least in the Southern African context.

6.2.PATIENTS AND METHODS :

6.2.1.Patients :

The following 3 groups of mothers were investigated :

6.2.1.1.Non-Asphyxiated Controls.

All those women who delivered at Cecilia Makiwane Hospital between February and October 1984 and whose infants were 37 weeks or more of gestational age and whose 5 minute Apgar scores were 7 or more were designated as controls. These women numbered 2758.

Data was gathered routinely on all mothers delivering in the hospital and entered onto a standard form by the obstetric medical and nursing staff. It was then coded by one Obstetric Senior Medical Officer who entered it into a computer data base for analysis. The data base had been set up for the obsetric department by the author for the purpose of gathering this data.

6.2.1.2. Mothers of Infants in the therapy Trial.

A further 116 mothers were selected on the basis that their term infants had had a chorionic arterial base excess of >-11 and had had either a 5 minute Apgar score of less than 7 or had shown evidence of fetal distress.

Further details of these infants are given in section 8.2.1. of the report on the therapy trial.

6.2.1.3. Mothers of Infants with clinically evident Hypoxic Ischaemic Encephalopathy (HIE). :

Forty seven mothers whose infants were of of more than 37 weeks gestation and who exhibited clinical signs of HIE in the immediate neonatal period, were selected. Their infants had shown clinical evidence of hypoxic-ischaemic encephalopathy, the diagnosis of which was based on the following criteria :

1. Onset of encephalopathic signs such as abnormal levels of consciousness, seizures, or abnormally increased or decreased tone within 48 hours of delivery.

2. The absence of any other explanation for the encephalopathy such as meningitis, hypoglycaemia, electrolyte or other metabolic disturbance.

3. The manifestation of one of the clinical patterns typically displayed by infants with HIE.

In both of the last 2 groups of mothers, details of their antenatal course, labour and delivery were obtained by the author from the antenatal and obstetric records. In each case the specialist obstetrician in charge of the case was asked to review the case with the records and to give his opinion as to the cause of

the infant's asphyxia.

6.2.1.4. Terminology for the groups.

The mothers of infants in the therpy trial will be known as the TRIAL group and those with the encephalopathic infants as the HIE group. A combination of the above 2 groups will be referred to as the combined asphyxia group. This term is in keeping with the concept of asphyxia used throughout this thesis in which a combination of biochemical and clinical criteria reflect a failure of adequate fetal oxygenation. This has been set out in section 1.2 of the introduction. It should be noted that in terms of this concept a low Apgar score is not an absolute prerequisite for inclusion in an asphyxiated group. It must be made clear that the three groups were entirely discreet and in no way overlapped each other.

6.2.2. Data handling and statistics.

Data for the "trial" and "HIE" patients were gathered by the author on proformas and entered into a computer data base for analysis. Data relating to the controls was gathered from the obstetric data base as reported above. Statistical analyses were carried out by the author and consisted of Chi-square testing with Yates correction for small numbers where necessary (Swinscow 1977). The level of probability accepted as significant was $p=<0.01$.

6.3.RESULTS :

6.3.1. Maternal Age :

Reference to Table 6.3.1.1. will show that there was no significant difference between the maternal ages in each of the 3 groups. The mean age of the HIE group was somewhat lower than the other 2 but this difference did not reach statistical significance.

TABLE 6.3.1.1. MATERNAL AGE

YEARS	CONTROLS	TRIAL	HIE	TOTALS
-15	31	2	2	35
16-20	802	32	19	853
21-25	860	43	13	916
26-30	547	24	5	576
31-35	321	11	4	336
36-40	143	3	3	149
41-45	35	1	-	36
46+	5	-	-	5
NO DATA	14	-	1	15
TOTAL	2758	116	47	2921

TABLE 6.3.1.2. MATERNAL AGE - PERCENTAGES

YEARS	CONTROLS	TRIAL	HIE	TOTALS
-15	1.1	1.7	3.8	1.2
16-20	29.1	27.6	35.8	29.1
21-25	31.2	37.1	24.5	31.3
26-30	19.8	20.7	9.4	19.7
31-35	11.6	9.5	7.5	11.5
36-40	5.2	2.6	5.7	5.1
41-45	1.3	0.9	-	1.2
46+	0.2	-	-	0.2
NO DATA	0.5	-	1.9	0.5
TOTAL	100.0	100.0	100.0	100.0

6.3.2. Gravidity :

Reference to Table 6.3.2.1. will indicate that there was a higher proportion of primigravidae among the 2 asphyxiated groups as compared to the controls but the difference was only significant between the HIE and control groups. Chi square =16.73 DF = 3 p = < 0.001.

TABLE 6.3.2.1. GRAVIDA

GRAV	CONTROLS	TRIAL	HIE	TOTALS
1	909	54	27	990
2	784	26	3	813
3	443	17	6	466
4	243	11	5	259
5	193	3	1	197
6	96	2	1	99
7	43	1	1	45
8	21	-	-	21
9 +	19	1	1	21
NO DATA	7	1	2	10
TOTAL	2,758	116	47	2,921

TABLE 6.3.2.2. GRAVIDA - PERCENTAGES.

GRAV	CONTROLS	TRIALS	HIE	TOTALS
1	33.0	46.6	57.4	33.9
2	28.4	22.4	6.4	27.8
3	16.1	14.7	12.8	16.0
4	8.8	9.5	10.6	8.9
5	7.0	2.6	2.1	6.7
6	3.5	1.7	2.1	3.4
7	1.6	.9	2.1	1.5
8	.8	-	-	.7
9 +	.7	.9	2.1	.7
NO DATA	.3	.9	4.3	.3
TOTALS	100.0	100.0	100.0	100.0

6.3.3. Parity :

Table 6.3.3.1. shows that the pattern for parity was similar to that for gravidity. The proportion of nulliparity in the trial group was greater than for controls and even higher in the HIE group. The difference between the control and 2 asphyxiated groups taken together was significant. Chi square = 21.07 DF = 3 p = <0.001. There was no difference between the 2 asphyxiated groups.

TABLE 6.3.3.1. PARITY.

PARA	CONTROLS	TRIAL	HIE	TOTALS
0	946	56	28	1,030
1	774	25	7	806
2	426	14	5	445
3	257	11	4	272
4	181	5	1	187
5	84	2	1	87
6	47	1	1	49
7	19	-	-	19
8	7	-	-	7
9 +	9	-	-	9
NO DATA	8	2	-	10
TOTALS	2,758	116	47	2,921

TABLE 6.3.3.2. PARITY - PERCENTAGES

	CONTROLS	TRIALS	HIE	TOTALS
0	34.3	48.3	59.6	35.3
1	28.1	21.6	14.9	27.6
2	15.4	12.1	10.6	15.2
3	9.3	9.5	8.5	9.3
4	6.6	4.3	2.1	6.4
5	3.0	1.7	2.1	3.0
6	1.7	.9	2.1	1.7
7	.7	-	-	.7
8	.3	-	-	.2
9+	.3	-	-	.3
NO DATA	.3	1.7	-	.3
TOTALS	100.0	100.0	100.0	100.0

6.3.4. Antenatal Care :

A number of aspects of antenatal care were examined.

6.3.4.1. Stage of pregnancy at booking -

Table 6.3.4.1.1. shows that the asphyxiated groups together had a significantly higher proportion of unbooked mothers than the controls (Chi square = 17.96 DF = 1 p=<0.001). There was no significant difference in this respect between the 2 asphyxiated groups.

Considering only those that had booked, the asphyxiated groups tended to have booked earlier as compared to the controls. (Chi square = 12.36 DF =1 p=<0.001). There was no significant difference in this respect between the 2 asphyxiated groups.

TABLE 6.3.4.1.1. WEEKS AT BOOKING

	CONTROLS	TRIAL	HIE	TOTALS
UNBOOKED	307	28	8	343
1-12	24	-	1	25
13-16	53	3	2	58
17-20	151	10	1	162
21-24	307	9	6	322
25-28	635	35	8	678
29-32	586	16	7	609
33-36	376	13	9	398
37-40	224	-	1	225
41+		1	-	1
NO DATA	95	1	4	100
TOTALS	2,758	116	47	2,921

TABLE 6.3.4.1.1. WEEKS AT BOOKING - PERCENTAGES

	CONTROLS	TRIALS	HIE	TOTALS
UNBOOKED	11.1	24.1	17.0	11.7
1-12	.9	-	2.1	.9
13-16	1.9	2.6	4.3	2.0
17-20	5.5	8.6	2.1	5.5
21-24	11.1	7.8	12.8	11.0
25-28	23.0	30.2	17.0	23.2
29-32	21.2	13.8	14.9	20.8
33-36	13.6	11.2	19.1	13.6
37-40	8.1	-	2.1	7.7
41+	-	.9	-	
NO DATA	3.4	.9	8.5	3.4
TOTALS	100.0	100.0	100.0	100.0

6.3.4.2. Number of Antenatal visits :

Reference to Table 6.3.4.2.1. will show that the modal category of Antenatal visits was 5-8 with about 40% of all patients attending that many times. There were no significant differences between the groups in the pattern of number of visits.

TABLE 6.3.4.2.1. NUMBER ANTENATAL VISITS :

	CONTROLS	TRIAL	HIE	TOTALS
NIL	307	28	8	343
1&2	276	5	1	282
3&4	517	18	6	541
5&6	624	17	11	652
7&8	431	24	7	462
9&10	294	14	6	314
11&12	133	4	3	140
13&14	59	5	-	64
15+	36	1	1	38
NO DATA	81	-	4	85
TOTALS	2,758	116	47	2,921

TABLE 6.3.4.2.2. NUMBER OF ANTENATAL VISITS - PERCENTAGES :

	CONTROLS	TRIALS	HIE	TOTALS
NIL	11.1	24.1	17.0	11.7
1&2	10.0	4.3	2.1	9.7
3&4	18.7	15.5	12.8	18.5
5&6	22.6	14.7	23.4	22.3
7&8	15.6	20.7	14.9	15.8
9&10	10.7	12.1	12.8	10.7
11&12	4.8	3.4	6.4	4.8
13&14	2.1	4.3	-	2.2
15+	1.3	.9	2.1	1.3
NO DATA	2.9	-	8.5	2.9
TOTALS	100.0	100.0	100.	100.0

6.3.5. Antenatal Disorders :

Table 6.3.5.2. shows that the proportion in each group with any type of antenatal disorder, rose from 30% in controls to 46% in the trial and 63% in the HIE group.

For analysis the disorders were grouped into the "UTERO-PLACENTAL PATHOLOGY" group -(pregnancy induced hypertension, eclampsia, abruptio, reduced fetal movements, intrauterine growth retardation and post term), "OTHER DISORDERS", "NO DISORDERS" and "MISSING". The asphyxiated groups had a much higher proportion of disorders especially of the utero-placental pathology group. The difference between the controls and the combined asphyxia groups was highly significant (Chi square =170.04 DF=3 p=<0.001) while there was no significant difference between the trial and HIE groups. The proportion of mothers whose antenatal disorders were unknown or for which data was missing was similar in all 3 groups.

It is of interest that in no case was cephalopelvic disproportion (CPD) identified as an antenatal disorder.

TABLE 6.3.5.1. ANTENATAL DISORDERS :

	CONTROLS	TRIAL	HIE	TOTALS
NONE	1,929	57	17	2,003
PIH	258	16	8	282
ECLAMPSIA	7	1	-	8
ABRUPTIO	5	-	-	5
DIABETES	4	1	1	6
MULTIPLE PREG	6	6	2	14
PLACENTA PREVIA	3	-	-	3
OTHER APH	17	1	-	18
CARDIAC	5	-	-	5
RED FET MVT	-	1	-	1
IUGR	-	3	1	4
POST TERM	-	-	2	2
OTHER	4	3	7	14
UNKNOWN	63	27	5	95
NO DATA	457	-	4	461
TOTALS	2,758	116	47	2,921

KEY :

PIH = Pregnancy induced hypertension
OTHER APH = Other antepartum haemorrage
RED FET MVT = Reduced fetal movements
IUGR = Intrauterine growth retardation

TABLE 6.3.5.2. ANTENATAL DISORDERS - PECENTAGES.

	CONTROLS	TRIALS	HIE	TOTALS
NONE	69.9	49.1	36.2	68.6
PIH	9.4	13.8	17.0	9.7
ECLAMPSIA	.3	.9	-	.3
ABRUPTIO	.2	-	-	.2
DIABETES	.1	.9	2.1	.2
MULTIPLE PREG	.2	5.2	4.3	.5
PLAC PRAEVIA	.1	-	-	.1
OTHER APH	.6	.9	-	.6
CARDIAC	.2	-	-	.2
RED FET MVT	-	.9	-	
IUGR	-	2.6	2.1	.1
POST TERM	-	-	4.3	.1
OTHER	.1	2.6	14.9	.5
UNKNOWN	2.3	23.3	10.6	3.3
NO DATA	16.6	-	8.5	15.8
TOTALS	100.0	100.0	100.0	100.0

6.3.6. Evidence of Fetal Distress :

Evidence of fetal heart abnormalities plus meconium stained liquor was one of the major criteria for selecting the trial group so this group will be left out of the comparisons in this section.

Table 6.3.6.2. shows that 25.5% of the HIE group had had type 2 dips on fetal heart monitoring and 34.0% had meconium stained liquor only. The HIE group had significantly more fetal distress of any type than did controls. (Chi square =78.7 DF=1 p=<0.001). Reduced fetal movements as a sign of fetal distress was found in 5 controls and 4 trial patients.

TABLE 6.3.6.1. EVIDENCE OF FETAL DISTRESS

	CONTROLS	TRIAL	HIE	TOTALS
FH T2D	82	15	4	101
FH + MSL	-	25	8	33
MSL	270	57	16	343
RED FET MVT	5	4	-	9
OTHER	2	-	-	2
NONE	2,209	15	18	2,242
UNKNOWN	190	-	1	191
TOTALS	2,758	116	47	2,921

See following page for key.

TABLE 6.3.6.2. EVIDENCE OF FETAL DISTRESS - PERCENTAGES

	CONTROLS	TRIALS	HIE	TOTALS
FH T2D	3.0	12.9	8.5	3.5
FH + MSL	-	21.6	17.0	1.1
MSL	9.8	49.1	34.0	11.7
RED FET MVT	.2	3.4	-	.3
OTHER	.1	-	-	.1
NONE	80.1	12.9	38.3	76.8
UNKNOWN	6.9	-	2.1	6.5
TOTALS	100.0	100.0	100.0	100.0

KEY :

FH T2D = Fetal Heart type 2 dips or worse.
FH + MSL = As above plus meconium stained liquor.
RED FET MVT = Reduced fetal movements.

6.3.7. Method of Delivery.

As can be seen from Table 6.3.7.2. the frequency of caesarian section was 13.1, 62.1, and 48.9% in the control, trial and HIE groups respectively. For analysis the methods of delivery were grouped as normal vertex delivery (NVD), caesarian section and other. Thus grouped, the difference between the asphyxiated groups and controls was highly significant (Chi square =280.5 DF=2 p=<0.001). There were no breech deliveries among the 2 asphyxiated groups and only 1 forceps delivery. Vacuum extraction was used significantly more often in the trial and HIE groups than in the controls (Chi square = 33.4 DF=2 p=<0.001).

TABLE 6.3.7.1. METHOD OF DELIVERY

	CONTROLS	TRIAL	HIE	TOTAL
NORMAL VERTEX	2,318	35	16	2,369
CAESARIAN	360	72	23	455
BREECH	18	-	-	18
FORCEPS	2	-	1	3
VACUUM	50	9	5	64
UNKNOWN	10	-	2	12
TOTALS	2,758	116	47	2,921

TABLE 6.3.7.2. METHOD OF DELIVERY - PERCENTAGES.

	CONTROLS	TRIALS	HIE	TOTALS
NORMAL VERTEX	84.0	30.2	34.0	81.1
CAESARIAN	13.1	62.1	48.9	15.6
BREECH	.7	-	-	.6
FORCEPS	.1	-	2.1	.1
VACUUM	1.8	7.8	10.6	2.2
UNKNOWN	.4	-	4.3	.4
TOTALS	100.0	100.0	100.0	100.0

6.3.8. Duration of the first stage of labour :

As can be seen in Table 6.3.8. this stage was significantly longer in the combined asphyxiated groups than in controls (Chi square =26.57 DF=3 p=<0.001), while there was no difference between the two asphyxiated groups.

TABLE 6.3.8.1. DURATION OF STAGE 1

HOURS	CONTROLS	TRIAL	HIE	TOTALS
C/S BEFORE LABOUR	251	9	4	264
1-6	788	20	5	813
7-9	578	25	9	612
10-12	424	16	10	450
13-15	251	14	6	271
16-18	156	12	4	172
19-21	71	5	4	80
22-24	31	7	2	40
25-36	22	5	1	28
37+	4	3	-	7
NO DATA	182	-	2	184
TOTALS	2,758	116	47	2,921

TABLE 6.3.8.2. DURATION OF STAGE 1 - PERCENTAGES.

HOURS	CONTROLS	TRIALS	HIE	TOTALS
C/S BEFORE LABOUR	9.1	7.8	8.5	9.0
1-6	28.6	17.2	10.6	27.8
7-9	21.0	21.6	19.1	21.0
10-12	15.4	13.8	21.3	15.4
13-15	9.1	12.1	12.8	9.3
16-18	5.7	10.3	8.5	5.9
19-21	2.6	4.3	8.5	2.7
22-24	1.1	6.0	4.3	1.4
25-36	.8	4.3	2.1	1.0
37+	.1	2.6	-	.2
NO DATA	6.6	-	4.3	6.3
TOTALS	100.0	100.0	100.0	100.0

6.3.9. Resuscitation :

Table 6.3.9.2. shows that the two asphyxiated groups together had much higher percentages of mask and endotracheal tube (ET) ventilation than the controls (Chi square =901.2 DF=1 p=<0.001). The HIE group had the highest percentage (46.8%) of endotracheal tube ventilation and was significantly different in this to the trial group (Chi square = 5.55 DF=1 p=<0.02).

TABLE 6.3.9.1. METHOD OF RESUSCITATION

	CONTROLS	TRIAL	HIE	TOTAL
NONE	2,147	31	9	2,187
OXYGEN ONLY	380	29	5	414
MASK VENTILATION	22	19	9	50
ET TUBE VENTILATION	23	37	22	82
UNKNOWN	186	-	2	188
TOTALS	2,758	116	47	2,921

TABLE 6.3.9.2. METHOD OF RESUSCITATION - PERCENTAGES.

	CONTROLS	TRIALS	HIE	TOTALS
NONE	77.8	26.7	19.1	74.9
OXYGEN ONLY	13.8	25.0	10.6	14.2
MASK VENTILATION	.8	16.4	19.1	1.7
ET TUBE VENTILATION	.8	31.9	46.8	2.8
UNKNOWN	6.7	-	4.3	6.4
TOTALS	100.0	100.0	100.0	100.0

6.3.10. Birth Weight.

The birth weights of the 3 groups are set out in Table 6.3.10. There was no significant difference between the 3 groups in mean birth weights. Equally there was no difference in the proportions of birth weights above and below 2500 grams between the controls and the combined asphyxial groups (Chi squared = 0.18 DF = 2).

TABLE 6.3.10. BIRTH WEIGHTS IN STUDY GROUPS (Grams).

BIRTH WEIGHTS	CONTROLS	HIE	TRIAL
1500-1750	12	-	-
1751-2000	8	-	1
2001-2250	35	1	-
2251-2500	110	1	5
2501-2750	237	6	8
2751-3000	473	4	21
3001-3500	1122	16	46
3501-4000	609	16	28
4000 +	109	2	7
MISSING	43	1	-
TOTALS	2758	47	116
MEAN (Gms.)	3220	3309	3270
SD	470.6	489.2	473.1

CONTROLS vs HIE	: t = 1.276	DF = 2759	NS
CONTROLS vs TRIAL	: t = 1.122	DF = 2829	NS
HIE vs TRIAL	: t = 0.472	DF = 160	NS

6.3.11. Apgar scores of HIE group :

Finally it is of interest to look at the Apgar scores of the 47 infants who subsequently developed clinical hypoxic ischaemic encephalopathy (HIE). The control group and the trial group are biased in that they were both selected partly on the basis of the Apgar score so they will not be further considered here. The scores of the HIE group are set out in Table 6.3.10.

TABLE 6.3.11. APGAR SCORES OF HIE GROUP

APGAR SCORE	1 Minute	5 Minutes
0-3	23 (49%)	5 (11%)
4-6	14 (30%)	14 (30%)
7 +	8 (17%)	25 (53%)
MISSING	2 (4%)	3 (6%)
TOTAL	47 (100%)	47 (100%)

It is of note that 47% of these encephalopathic infants had 1 minute Apgar scores 4 or more and 83% had 5 minute scores of 4 or more.

6.3.12. Cause of Asphyxia designated by obsetrician :

The causes of asphyxia designated after review by the specialist obstetrician in charge of the case are shown in Table 6.3.12. There is no significant difference between the patterns of the trial and HIE groups. Taken together the largest group is cephalopelvic disproportion (CPD). The next largest is that in which after thorough review no cause could be assigned. Pregnancy induced hypertension (PIH), abruptio and intrauterine growth retardation (IUGR) respectively were the next most important causes. Maternal sedation, difficulties with the cord and overt maternal infection were seen to be less common.

Due to the way routine data was collected it was unfortunately not possible to discuss control cases with the obstetricians in the same way as for the HIE and TRIAL groups.

TABLE 6.3.12.1. OBSTETRICIAN'S CAUSE OF ASPHYXIA

	TRIAL	HIE	TOTALS
UNKNOWN	29	15	44
CEPHALOPELVIC DISPROPORTION	47	16	63
PREGNANCY INDUCED HYPERTENSION	10	5	15
ECLAMPSIA	2	–	2
CPD + PIH	1	1	2
PROLAPSED CORD	1	1	2
CORD AROUND NECK	2	–	2
MATERNAL SEDATION	2	–	2
ABRUPTIO	5	3	8
UTERINE INERTIA	1	–	1
PLACENTAL PREVIA	1	–	1
MATERNAL INFECTION	2	–	2
INTRUTERINE GROWTH RETARDATION	5	2	7
POST TERM	3	–	3
PROLONGED RUPTURE OF MEMBRANES	–	1	1
DIABETES	–	1	1
MISSING	5	2	7
TOTALS	116	47	163

TABLE 6.3.12.2. OBSTETRICIAN'S CAUSE OF ASPHYXIA - PERCENTAGE.

	TRIALS	HIE	TOTALS
UNKNOWN	25.0	31.9	27.0
CEPHALOPELVIC DISPROPORTION	40.5	34.0	38.7
PREGNANCY INDUCED HYPERTENSION	8.6	10.6	9.2
ECLAMPSIA	1.7	–	1.2
CPD & PIH	.9	2.1	1.2
PROLAPSED CORD	.9	2.1	1.2
CORD AROUND NECK	1.7	–	1.2
MATERNAL SEDATION	1.7	–	1.2
ABRUPTIO	4.3	6.4	4.9
UTERINE INERTIA	.9	–	.6
PLACENTA PREVIA	.9	–	.6
MATERNAL INFECTION	1.7	–	1.2
INTRA UTERINE GROWTH RETARDATION	4.3	4.3	4.3
POST TERM	2.6	–	1.8
PROLONGED RUPTURE OF MEMBRANES	–	2.1	.6
DIABETES	–	2.1	.6
MISSING	4.3	4.3	4.3
TOTALS	100.0	100.0	100.0

6.4. DISCUSSION

6.4.1. Selection bias of controls :

The selection of controls was subject to selection bias in that only selected patients delivered at the hospital. The means of selection was that those attending booking clinics at one of the peripheral clinics were assesed and referred for hospital delivery only if one or more risk factors was present. A schedule of these is provided in Appendix III.

6.4.2. Limited Number of variables :

The number of variables that could be examined was limited to the items of data routinely gathered by the obstetric department on the patients used here for controls.

6.4.2.1. Socioeconomic status :

Socioeconomic status is one item that it would have been desirable to examine. As discussed in Chapter 5 (Table 5.1.2.) asphyxia is a much more important cause of neonatal death in underdeveloped as compared to developed regions. This suggests that socioeconomic status is an important variable.

In the studies of the epidemiological associations of asphyxia summarised in Table 5.2.1. only that of MacDonald et al (1980) looked at socioeconomic status. They found that asphyxia was associated with a lower

socioeconomic status. The other studies did not investigate this factor either because the numbers were too small or because the studies were carried out in a rather uniform social environment which did not allow analysis of this factor (Bolton 1985).

6.4.3. Parity :

There was an excess of primiparous patients amongst the groups with asphyxiated infants. It is surprising that in a number of studies of the epidemiology of asphyxia the effect of gravidty and/or parity is not mentioned.

The study of Bolton (1985) from Baragwanath Hospital in Soweto is of particular interest in that it is from a community and a service with many similarities to our own. He also found an association between low parity and asphyxia. A similar association was found by Cyr et al (1984) from Montreal. On the other hand Dweck (1974) et al from Birmingham Alabama found that parity was not associated with asphyxia. Unfortunately their numbers were very small (15).

The association between asphyxia and primiparity found in the present study is strong and in view of Boltons similar finding it seems that in a developing world situation this association is real.

6.4.4. Antenatal clinic attendance :

The extent to which mothers did not book at all for antenatal care was relatively low at 11.5%. Hamilton et al (1987) are more stringent in regarding "booking" as attendance at antenatal clinic on at least 3 occasions. Even by this strict criterion only 21.4% of all deliveries in hospital were not "booked". There were significantly more unbooked mothers in the combined asphyxia groups as compared to controls.

The stage of pregnancy at booking is overall rather late with 42% booking after 28 weeks.

The number of antenatal clinic visits in the three groups was not significantly different. The number of visits was relatively high with 64% of attenders appearing 5 or more times.

The pattern of antenatal clinic use seems to be that most pregnant women delivering in the health service do book but do so relatively late and then attend frequently thereafter.

Bolton (1985) from Baragwaneth Hospital in Soweto found a mean number of visits of 4.27 and no difference between asphyxiated and control groups in this respect.

6.4.5. Antenatal disorders :

Reference to the studies detailed in Table 5.2.1. indicates that there is a group of antenatal disorders that have been regularly associated with asphyxia. This group includes hypertension, "toxaemia", pre-eclamptic toxaemia, intrauterine growth retardation, antepartum haemorrhage, prolapsed cord, prolonged rupture of membranes, features of cephalopelvic disproportion and malpresentations.

These associations are in agreement with the findings of the present study. There was a much greater incidence of antenatal disorders in the 2 asphyxiated groups as compared to controls and this was particularly so for the "utero-placental" group of disorders. On the other hand it is of note that CPD was not diagnosed as an antenatal disorder in a single case. Nevertheless even though CPD tended to be diagnosed in retrospect it was a major antenatal association with asphyxia in this study. It is striking that with the exception of the "mechanical" problems the rest of these disorders all would seem to have utero-placental pathology of one sort or another in common.

6.4.6. Fetal Distress :

Here discussion of the Trial group will be left out as it was heavily biased for signs of fetal distress by the selection criteria.

The HIE group had shown abnormalities in the rate and or pattern of the fetal heart 8.7 times more often than the controls and meconium staining of the liquor 5.2 times more often. In the HIE group 60% had shown one or more signs of fetal distress as compared to 13% in the control group. These figures indicate that the classical signs of fetal distress were neither very sensitve nor very specific for asphyxia in this study.

Reference to Table 5.2.1. reveals that every study in which the relationship between fetal distress and neonatal asphyxia was evaluated, the association was significant.

6.4.7. Mode of Delivery :

The caesarian section rate ranged from 13% in controls to 62% in the Trial group. The differences beween the controls and the two asphyxiated groups were highly significant.

Rothberg et al (1986) did not find caesarian section to be more common amongst asphyxiated infants than controls but the numbers in their study were small (13 cases). On the other hand the studies of Thomson (1977), MacDonald (1980) and Cyr et al (1984) all found that caesarian section was associated with asphyxia. MacDonald and Cyr further found that the association was only present when it had been performed for some acutely occuring

complication of pregnancy or labour and not when performed electively. It is likely that the reason for performing a caesarian section may be more important than the procedure itself.

Vacuum extraction was used infrequently but significantly more so in the trial and HIE groups (8% & 11%) than in controls (2%). It is difficult to comment on the significance of forceps delivery as only 1 HIE and 2 controls were born in this manner. Breech delivery cannot be implicated in asphyxia in this study as no asphyxiated infant was born in this way.

The mode of delivery is more likely to be a secondary phenomenon to the underlying cause of asphyxia than to be a primary cause itself. Thus CPD will cause asphyxia by prolonging labour and will for the same reason tend to lead to delivery by caesarian section. The use of the vacuum is similarly a secondary phenomenon although this instrument does have the ability to cause cerebral trauma in its own right.

6.4.8. Duration of first stage :

A long first stage of labour seems to be a significant association of asphyxia. This is not surprising considering the placental compression that occurs with each uterine contraction.

6.4.9. Resuscitation of the Infant :

This study confirms that infants who become encephalopathic in the neonatal period are not necessarily depressed at birth. It was not unexpected that 66% of subsequently encephalopathic infants needed active ventilation at birth as compared to only 1.6% of controls. On the other hand it is surprising that as many as 30% of the infants who later deveoloped encephalopathy did not need active resuscitation.

6.4.10. Birth Weight :

It is interesting to note that in the term infants studied, growth retardation was not significantly associated with asphyxia as it is here defined. There were no more growth retarded infants among the two asphyxiated groups than among the normal controls.

6.4.11. Apgar scores :

It is furthermore remarkable that half of later encephalopathic infants had Apgar scores at 1 minute of 4 or more. This is so despite the presumption that these infants had suffered significant hypoxic insults in utero. The lack of sensitivity of Apgar score in predicting encephalopathy or subsequent handicap has been discussed in section 5.4. in connection with the role of asphyxia in the aetiology of cerebral palsy.

6.4.12. Obstetric cause :

The leading cause of asphyxia assigned in retrospect by the attending obstetric specialist was cephalopelvic disproportion (39%). This is particularly significant in the light of the fact that it was not diaganosed at all as an antenatal problem.

If one creates a category broadly taking in utero-placental pathology it would include : pregnancy induced hypertension, eclampsia, abruptio, intrauterine growth retardation, post term and diabetes. This category accounts for about 22% of the cases of asphyxia.

In another 27% of all cases of asphyxia the obstetrician could assign no cause. In the absence of cephalopelvic disproportion or one of the utero-placental pathologies referred to above, it is tempting to speculate that there is a reservoir of placento-fetal pathology that is neither evident clinically nor visible on inspection of the placenta or membranes. This would include subclinical amnionitis or unrecognised disease of utero-placental vessels.

The study and elucidation of this large group of "occult" causes would seem to be of great importance as until the various at present unknown specific causes are unravelled therapeutic and preventive measures cannot be developed to combat the problem.

The problem of asphyxia seems to decline as the socioeconomic status of a community rises. While the reason for this may be partly nutritional in reducing intrauterine growth retardation, and partly to do with improvement in obstetric care, it may well be that the "occult" group of disorders disappears with rising affluence, without our ever defining the cause. The reduction in the problem in affluent societies has the effect of reducing the necessity for obstetricians in those areas who have the resources to do the necessary research to elucidate the problem further. The underdeveloped parts of the world suffering from the problem are the least able to afford research into the problem.

The knowledge and technology to avoid the adverse consequences of cephalopelvic disproportion are already available. Also the utero-placental group of causes is to a large extent already amenable to meticulous obstetric care during the antenatal period and labour. Unfortunately these conditions remain prevalent in the developing world. It must be possible to reduce the problem of asphyxia in the third world by making effective use of existing knowledge. The challenge to those working in developing world obstetrics is to organise services and to train staff in such a way as to bring that knowledge to bear on the problem.

Failure to do so will result in a continuation of the existing high incidence of major neurodevelopmental handicap in communities that do not have the resources to alleviate the social and economic burden that this places upon them.

6.5. CONCLUSIONS :

6.5.1. The positive epidemiological associations of this group of 163 asphyxiated infants were :

* Low gravidity and parity.
* Not booking for antenatal care.
* The occurence of antenatal disorders.
* The occurence of classical fetal distress.
* A prolonged first stage of labour.
* Delivery by caesarian section.
* Delivery by vacuum extraction.

6.5.2. The factors found not to be associated with asphyxia were :

* Maternal age.
* The number of antenatal visits.

6.5.3. The causes of asphyxia assigned by the obstetrician in charge of the cases were in order of importance :

* Cephalopelvic disproportion. 39%
* No cause detected. 27%
* Utero-placental pathologies. 22%
* Other 8%

6.5.4. The leading components of the utero-placental pathologies were :

* Pregnancy induced hypertension 10.4%
* Abruptio placentae 4.9%
* Intrauterine growth retardation 3.7%
* Post term 1.8%

6.5.5. The incidence of causes such as cord disorders and maternal sedation is very small.

6.5.6. Less than a half of subsequently encephalopathic infants had Apgar scores of 3 or less at one minute.

6.5.7. The obstetric challenges with repect to asphyxia in the developing world are :

* To organize health sevices and train staff of all types to bring existing knowlege to bear on the problem of this severely handicapping disorder.
* To ensure that the primiparous patient receives particular attention both antenatally and during labour and especially to ensure adequate screening of pelvic adequacy.
* To regard the "placental pathology" group of disorders as placing the pregnant woman in a very high risk group needing extra supervision during pregnancy and labour.

* To unravel the large group of apparently occult causes of asphyxia and by elucidating the causes hopefully contribute to its prevention.

CHAPTER 7

TREATMENT OF ASPHYXIA NEONATORUM

7.1. INTRODUCTION.

This chapter deals with the literature relating to the treatment of perinatal asphyxia paying special attention to the use of barbiturates and corticosteroids. It begins with a very brief review of well established general principles of treatment and goes on to deal with the evidence for a protective role for barbiturates following hypoxic-ischaemic cerebral insults. Next the literature on the theoretical and practical value of corticosteroids in this situation is examined. Finally the literature relating to the clinical use of barbiturates and corticosteroids in the clinical situation of the asphyxiated term human neonate is considered.

7.2. GENERAL MANAGEMENT OF THE ASPHYXIATED INFANT.

The general management of the asphyxiated infant has been reviewed by a number of authors including Volpe (1976), Voorhies and Vannucci (1984), and Hill (1985) and is well established. The main points will be briefly mentioned here only to place what follows in context. After adequate resuscitation the patient is transferred to a high care area for subsequent management. Throughout, adequate ventilation is essential to avoid both further hypoxia and the cerebral vasodilatation associated with hypercapnia. It

may be necessary to use assisted ventilation to achieve this. Metabolic acidosis and electrolyte disturbances need to be checked for and treated actively. An adequate circulation is required to limit further ischaemic damage to the brain and other organs. Hypotension associated with hypovolaemia may occur and blood volume restoration become necessary. Hypoxic-ischaemic myocardial damage may occur resulting in further cerebral under-perfusion. This needs to be detected and treated vigorously. Ischaemic gut damage may lead to a transient paralytic ileus needing a period of bowel rest, nasogastric drainage and on occasion, intravenous alimentation. In severe cases renal damage of sufficient severity to cause anuria occurs which needs active management of acute renal failure.

Review of some of the more contentious issues in management will follow.

7.2.1. Glucose :

An active debate has continued as to whether supra-normal blood glucose levels are helpful in limiting cerebral damage after hypoxic-ischaemic insults.

Britton (1945) and Vannucci (1978) have pointed out the dangers of hypoglycaemia superimposed on hypoxic ischaemic brain damage and most authors have advocated

active maintainance of at least a normal blood glucose.

Holowach-Thurston et al (1973, 1974) found that glucose administered to rats before a hypoxial insult had a protective effect in that the survival rate was increased 15 fold and brain energy resources were relatively spared. They also found that the glucose content of brain tissue in asphyxiated rats was low depite normal or even elevated blood levels. These findings raised the possibility that the provision of super-normal blood glucose in asphyxiated infants might be beneficial. The elevated blood glucose level might help by allowing more glucose to enter the hypoxic brain to be used as substrate in anaerobic glycolysis. On the other hand Myers and Yamaguchi (1977), using a juvenile monkey model showed that artificially induced hyperglycaemia during asphyxia contributed to subsequent cerebral oedema and aggravated the neurological condition by increasing lactic acidosis. Voorhies et al (1982) cast further doubt on the value of hyperglycaemia when they found that pretreatment of asphyxiated rats with glucose may accentuate the extent of brain damage.

The current consensus as expressed by Hill (1985) seems to be that euglycaemia is the most suitable environment for the asphyxiated human infant.

7.2.2. Management of cerebral oedema :

It has been held for some time that application of effective measures to reduce cerebral oedema would improve the outcome in asphyxiated infants. These measures have included head position, fluid restriction, and the administration of steroids and/or hyperosmolar fluids such as mannitol.

Lou Marsh et al (1977) comment that in non-newborn neurosurgical intensive care, the head-up position reduces intracranial pressure by improving venous return from the head. They also note that in patients in whom the intracranial pressure is being monitored, wide swings of pressure are seen when the patient's head is turned. Little attention seems to have been paid thus far to head position in the aphyxiated neonate with raised intracranial pressure.

Avoiding the administration of excessive quantities of hypotonic fluids to patients with cerebral oedema is normal practice. The reasons given by Fenichel (1983) are that hypotonic fluids leak easily across the damaged vascular epithelium and accumulate as tissue fluid in the brain. Furthermore inappropriate secretion of antidiuretic hormone after asphyxial brain injury leads to water intoxication with aggravation of cerebral oedema. For both of these reasons authors such as Fenichel (1983), Lou Marsh (1977) and Volpe (1976)

recommend restriction of the total fluids to 50-70% of normal.

The other agents frequently used in an attempt to reduce cerebral oedema in asphyxiated infants are steroids, particularly dexamethasone and hypertonic solutions such as mannitol. The use of dexamethasone is the subject of a separate section of this review and will not be discussed here.

The effectiveness of mannitol in severely asphyxiated term infants has been reported by Levene and Evans (1985). They monitored the intracranial pressure by means of a subarachnoid catheter and infused .20% mannitol (1gm /Kg) over 20 minutes on 9 occasions in 4 patients. They found that there was a fall of intracranial pressure within 20 minutes of starting the infusion and by 40 minutes there was a 35% drop in intracranial pressure that was sustained for a further 4 hours. In some cases they were able to monitor systemic blood pressure and so estimate cerebral perfusion pressure. In all such cases there was a significant rise in cerebral perfusion pressure which was sustained for at least a further 4 hours. No adverse alterations in serum electrolyes or urinary specific gravity were found in any case. They conclude that mannitol is a useful adjunct to the management of raised intracranial pressure in severely asphyxiated infants.

Marchal et al (1974) also reported on the use of mannitol but did not use controls and the outcome was thus uncertain. Fenichel (1983) and Voorhies and Vannucci (1984) recommend the use of Mannitol in cases of severely raised intracranial pressure in asphyxiated infants in doses of 0.25-1.00 gm/kg. given 4-6 hourly. Hahn (1980) notes that the effectiveness of hyperosmolar solutions in reducing intracranial pressure depends on the integrity of the blood brain barrier, and that in a severely asphyxiated infant this integrity is to a greater or lesser degree disturbed so that the substance tends to migrate into the tissue fluid and equilibriate with the oedematous area. At this point it loses its effectiveness. Volpe (1976) avoids the use of hypertonic solutions because of a fear of inducing intracranial haemorrhage presumably from rapid brain shrinkage inducing shearing forces on blood vessels.

In summary, the available evidence suggests that the use of mannitol in the severely asphyxiated infant with CT or ultra-sound evidence of cerebral oedema is likely to limit cerebral infarction. Further prospective trials in this area are necessary.

7.2.3. Seizure control

Seizures occur frequently in the asphyxiated infant and immediate investigations are necessary to exclude metabolic or infective causes for the seizures. These include cerebrospinal fluid examination, blood glucose, serum sodium, calcium, magnesium and urea. Such metabolic disturbances need active management.

The avoidance or early treatment of seizures is of great importance in the management of the asphyxiated infant. Meldrum and Nilsson (1976) have demonstrated a many fold increase in cerebral oxygen consumption during seizures. Furthermore King et al (1967) and Howse et al (1974) have shown that in experimental animals the energy reserves of the brain are depleted in status epilepticus. The inference is that the known increase in cerebral blood flow during seizures cannot keep pace with the increased metabolic demand and hence the possibility of further ischaemic damage to the brain is real. Another factor compounding the problem is cerebral vasodilation produced by the hypercapnia following hypoventilation during the seizure. This will contribute to an already raised intracranial pressure.

As will be reviewed below, barbiturates may possibly have a beneficial effect on the long term outcome of asphyxiated infants. For this reason it seems logical

at present to use phenobarbitone as the first line prophylactic anticonvulsant agent in these infants. The variable metabolism of phenobarbitone even in the same patient from day to day makes regular blood level measurements desirable. Fenichel (1983) prefers to use phenytoin as it is less sedating.

7.2.4. Naloxone :

Naloxone has been widely used in the resuscitation of the asphyxiated infant especially when opiate depression is thought to be the cause. Recent reports by Goodlin (1981) and Young (1984) provide evidence that naloxone may be deleterious in asphyxiated infants. Young et al used the Levine model of asphyxia in young rats who were given various doses of naloxone at various times after the asphyxial insult. As compared to controls the naloxone treated rats had greater rates of cerebral infarction and reduced survival. The reason for this is not clear but may operate through the known cardiotoxic effect of naloxone in reducing cardiac output and thus cerebral perfusion.

7.3. POSSIBLE MECHANISMS OF BARBITURATE PROTECTION .

This section will review literature relating to the theoretical mechanisms which may underly the protective effect of barbiturates against hypoxic-ischaemic cerebral injury.

7.3.1 Reduction in cerebral metabolism. :

Since the work in 1946 of Himwich et al. (1947) it has been known that barbiturates reduce cerebral oxygen consumption by up to 55%. This is clearly advantageous in a hypoxic situation.

Gardiner (1980) found that in the calf anaesthetised with sodium pentobarbitone, the cerebral metabolism was reduced by 28% as compared to controls. In lambs the reduction was 22%. Astrup et al (1981) found that pentobarbitone administered to dogs under halothane anaesthesia reduced cerebral utilisation of both oxygen and glucose by about 30%. In a similar dog model using thiopentone, Michenfelder (1974), found that despite a marked fall in oxygen uptake in the presence of the barbiturate, cerebral metabolism was not rendered anaerobic, as reflected by normal levels of adenosine triphosphate, phosphocreatine and lactate. He also found that cerebral metabolism was progressively reduced by increasing doses up to the point of electrical silence on electroencephalogram (EEG). Larger doses did not reduce cerebral metabolism further. He concludes that thiopental does provide cerebral protection up to the point of electrical silence on EEG, but not beyond that point.

Ten day old mice pre-treated with large intraperitoneal doses of phenobarbitone (150mg/Kg) before decapitation,

showed a slower rise in cerebral adenosine monophosphate and inorganic phosphate than did controls (Lowry et al 1964). The authors interpret this as being due to the effect of phenobarbitone in reducing cerebral metabolism. Wechsler et al (1951) in the study of human adults undergoing thiopentone anaesthesia also found a significant reduction in cerebral metabolic rate as measured by rate of cerebral oxygen consumption. These results were confirmed by Pierce et al (1962) in a similar study.

7.3.2. Effect on cerebral blood flow :

Gardiner in the study referred to above found a 35% decrease in cerebral blood flow in the calf under sodium pentobarbitone anaesthesia. Similar findings were reported by Astrup et al (1981) in their dog model.

Contradictory findings come from Wechsler et al (1951) who studied 12 human adults anaesthetised with thiopentone. They used the nitrous oxide method to estimate the cerebral blood flow which they found to be slightly increased. They attribute this to the vasodilating effect of the raised pCO2 which they documented. On the other hand Pierce et al (1962) in a similar human study found a reduction in cerebral blood flow under thiopentone anaesthsia which was greatly exagerated by hyperventilation. The level of pCO2 is

clearly very important factor to control for in any study of cerebral blood flow. This is because the sedative action of the barbiturate will produce hypoventilation, leading in turn to CO2 retention and hence to cerebral vasodilation. This effect may then overwhelm the vasoconstrictive effect of the barbiturate.

The cerebral vasoconstrictive effect of barbiturates is potentially protective when part of the brain is rendered hypoxic by an arterial infarct. The damaged vessels in the ischaemic area do not respond to the vasoconstrictive effect of the barbiturate which does however affect the rest of the brain. Blood would be diverted from the normal to the ischaemic area, alleviating the ischaemia to a degree. This phenomenon is known as the "reverse steal" effect (Steen (1980). This mechanism is however unlikely to protect in the case of whole brain hypoxia such as occurs in perinatal asphyxia.

7.3.3. Effect on reduction of intracranial pressure :

That barbiturates reduce raised intracranial pressure has been documented by Rockoff et al. (1979) in a group of young children and adolescents with Reye's Syndrome in an intensive care situation. They found that the dose of mannitol required to maintain a normal intracranial pressure was very much reduced by the

institution of pentobarbital therapy.

7.3.4. Effect on brain glucose :

Mayman et al 1964 report that during pentobarbital anaesthesia the concentration of glucose in mouse brain more than doubles. In the light of the discussion above on the role of glucose in the asphyxiated brain such a rise in brain glucose is probably protective to the immature individual with cerebral hypoxia.

7.3.5. Effect on catecholamine release inhibition :

Cheek et al. (1963) found that in the human fetus and newborn infant anoxia causes an increase in circulating catecholamines. Maynert (1964) has found that the release of catecholamines from the adrenal gland and brainstem can be prevented by barbiturates. This may well be important as Emerson (1942) found that pretreating anoxic animals with adrenaline shortens survival time.

7.3.6. Effect on free radical quenching :

A controversial issue is that concerning the role of the barbiturates in "quenching" free radicals (Flamm et al 1977). A review of free radicals in cellular metabolism is provided by Demopoulos (1973). Steen and Michenfelder (1980) state "a free radical is a molecule with an unpaired electron in its outer orbital and hence is in a high energy state and is extremely reactive". Superoxide is a free radical present in

normal cells. Minute amounts are generated in normal metabolism. The enzyme superoxide dismutase is present in all aerobic cells to quench this free radical and hence prevent its disruptive effects. The cellular membranes including those of the mitochondria are also capable of quenching small ammounts of free radicals formed as intermediate metabolites. In hypoxia there is a deficiency in the electron acceptor at the end of the electron transport chain. Free radicals build up beyond the membrane's capacity to buffer them and reactions are initiated which disrupt the mitochondrial membranes.

Flamm et al. (1978) found that the barbiturate methohexital could block free radical production in the brains of cats after occlusion of a middle cerebral artery. They also showed that it could scavenge certain free radicals in vitro. They concluded that methohexital's protective effect was due in part at least to its free radical quenching ability.

Smith el al. (1974) studied the in vitro free radical quenching properties of 4 different barbiturates and found that while thiopental was very active, methohexital was slightly active and pento- and pheno-barbitone not active at all. Differences in vivo free radical quenching have also been found. Flam et al. (1977, 1978) found active free radical production

after middle cerebral artery ligation despite pentobarbital anaesthesia.

Experimental studies of barbiturate protection in animals experiencing hypoxia suggest that all the above barbiturates afford protection despite these differences in their in vitro and in vivo free radical quenching properties. The role that the free radical quenching properties of some barbiturates play in the protection against hypoxia remains uncertain.

7.4. PROTECTIVE EFFECT OF BARBITURATES IN ANIMAL MODELS OF HYPOXIC-ISCHAEMIC CEREBRAL INJURY.

There have been a number of animal studies investigating the protective effect of barbiturates in cerebral hypoxia. Many of these have been concerned with the effects of barbiturates on cerebral ischaemia/hypoxia in adult animals.

7.4.1. Adult animal studies :

7.4.1.1. Treatment before insult :

The earliest work in this field came from Emerson et al (1942) who found that pretreatment with ethanol and to a lesser extent with pentobarbitone, prolonged the survival time of adult mice subjected to hypoxia by barometric decompression. Arnfred and Secher (1962) found that pretreatment with intravenous thiopentone improved mortality and survival time of adult mice subjected to hypoxia by inhalation of oxygen mixtures of 5% or less.

Later studies by Wells et al (1963), Withjelm et al (1965) and Goldstein et al (1966) all found that barbiturates given before an hypoxic/ischaemic insult minimized the subsequent neurological deficit.

7.4.1.2. Treatment during insult :

Yatsu et al (1972) using a rabbit model showed that

methohexital given during the insult was beneficial to the neurological outcome.

7.4.1.3. Treatment after the insult :

These studies are of particular interest as treatment after the insult is the only possible use of barbiturates in human asphyxia. The studies will be divided into those concerned with ischaemia of a part of the brain as opposed to those involved with whole brain insults.

7.4.1.4. Focal brain ischaemia :

Smith et al (1974) using dogs and Hoff et al (1975), Mosley et al (1975) and Michenfelder 1978 all using adult primate models of acute cerebral ischaemia in which a single cerebral artery was ligated have shown that barbiturates given after the insult are beneficial.

7.4.1.5. Whole brain ischaemia :

A interesting monkey model was that of Bleyaert et al (1978) in which whole brain ischaemia was produced by rapid neck vessel compression. The protective effect of thiopental given at various doses and various intervals after the ischaemic insult was studied. They took particular pains to standardise the life support conditions for experimental and control animals. They found a very significant protective effect which was greater the earlier the therapy was given after the

insult. These benefits were demonstrated both in the clinical neurological state at 7 days of age as well as histologically.

Todd et al (1982) examined the protective effect of high dose thiopental given to adult cats shortly after global cerebral ischaemia. They found a significant reduction in the immediate mortality from neurological causes but no protection against long term neurological deficit in survivors.

7.4.2. Neonatal animal studies :

There is a body of work concerned specifically with the protective effect of barbiturates on asphyxiated animal neonates. These are set out in Table 7.4.1.

All these studies on the effects of barbiturates in neonatal animals experiencing asphyxia show a clear protective effect except that of Fisher et al (1975) who found that phenobarbitone administered to neonatal monkeys before asphyxiation by occlusion of their endotracheal tubes had no protective effect. Their percentage of survivors and time to last gasp was no different in a group of 8 treated as compared to 6 untreated controls.

Campbell et al (1968) used 48 hour old monkey neonates who were pretreated with intraperitoneal pentobarbitone prior to subjecting them to anoxia by

TABLE 7.4.1. STUDIES ON THE PROTECTIVE EFFECT OF BARBITURATES IN NEONATAL ASPHYXIA

AUTHOR AND YEAR	Year	N	Species	Maturity	Hypoxic insult	Drug Used	Dose	Effect of protective drug.
Campbell et al (1968)	1967	62 x2	Rabbit	Newborn	100% N2 inhaled	Pentobarbitone	20mg/Kg	Duration of primary apnoea inceased. Time to last gasp significantly prolonged. Total no.gasps =
Cockburn et al (1969)	1969	21	Rhesus monkeys	Newborn	Bag over head before first breath.	Pentobarbitone	Maternal anaesthes.	Duration of primary apnoea increased. Time to last gasp significantly prolonged. Total No. gasps increased.
Goodlin (1965)	1965	138	Rabbit	Newborn	Maternal death before delivery.	Pentobarbitone	Maternal anaesthes.	Increased number of fetuses could be resuscitated.
Fisher et al (1975)	1975	14	Monkeys	Newborn	Occluded ETT.	Phenobarbitone	18mg/Kg	No protection in time to last gasp or survival.

inhalation of 100% nitrogen. They found that the pretreated group had a very significant prolongation of primary apnoea as well as of the time to the last gasp as compared to controls.

Cockburn et al (1969) produced asphyxia in neonatal monkeys by placing a fluid filled bag over their heads before the first gasp at caesarian section. In the experimental group the mothers were anaesthetized with pentobarbitone and in controls local anaesthesia was used. The duration of primary apnoea and the time to the last gasp were both significantly prolonged in the experimental group.

Both Cockburn and Campbell also looked for differences in the response to resuscitation at various times after the last gasp. Campbell's group using rabbits found that a significantly higher percentage of treated animals could be resuscitated to survival and that the treated group had a shorter time to spontaneous gasping after the initiation of resuscitation. Cockburn had very similar findings in Rhesus monkeys with a shorter time to the first spontaneous gasp as well as to the onset of rhythmic breathing. Goodlin (1965) also found that rabbit fetuses which were asphyxiated in utero by maternal death, but pretreated with pentobarbitone via the maternal anaesthetic, had a higher rate of resuscitatibility than untreated controls.

Goodlin and Lloyd (1970) in a similar study investigated the relative protective efficacy of a number of different barbiturates and found that phenobarbitone produced a higher rate of survival than pentobarbitone which is the drug used in most animal trials.

The studies of both Campbell et al (1968) and Cockburn et al (1969) included data on the acid-base status of the animals during terminal asphyxia. Campbell's group found that in the rabbits the pH one minute after the last gasp was the same in treated and untreated groups when the time of anoxia was controlled for. The pCO2 on the other hand was 30mm higher in the treated group.

On the other hand Cockburn et al (1969) with Rhesus monkeys found that the pH fell and the pCO2 rose less rapidly in the barbiturate pretreated animals. They concede that the unanaesthetised animals struggled much more than those under barbiturate anaesthesia and that this alone could account for the differences observed.

Myers (1972) found in his model of total asphyxia in newborn rhesus monkeys that pretreatment with pentobarbitone resulted in less neuropathological brain damage if the agent was given as an anaesthetic prior to asphyxia. If it was given as an injection immediately prior to the insult the protection was minimal. The difference was thought to be due to the

longer time available in the case of the anaesthetized animals for the barbiturate to penetrate brain tissue. When given to animals who were already acidotic at birth and presumably having already experienced intrauterine asphyxia it provided little protection regardless of when the barbiturate had been given.

Cockburn et al (1969) also examined the neuropathological appearances of the brains at post mortem and found that treated survivors had less severe neuropathological lesions than untreated animals. However the location of the injury was mainly in the brainstem and this is not at all similar to the pattern seen in the human asphyxiated neonate. The nature of the insults cannot thus be strictly comparable.

Brann (1970) however has described a pattern of injury similar to that in human infants in newborn monkeys. The mothers were subjected to periods of hypotension before delivery. The degree of asphyxia of the fetus was varied by altering the severity of the maternal hypotension. He showed a decrease in the severity of neurological damage for a given degree of asphyxia when the mother had received pentobarbitone as an anaesthetic agent. While this work needs to be extended and the methodology refined a protective effect of barbiturate seems likely in an animal model which seems to be quite similar to that in humans.

The other major difficulty in interpreting the significance of this experimental neonatal work is that in all cases the barbiturate was administered before the insult. This is clearly not normally possible in the human clinical situation where therapeutic agents are given after the event.

It would thus appear that in experimental models barbiturates have useful protective effects on neonatal hypoxia when administered before the insult.

7.5. THE DOSAGE OF PHENOBARBITONE IN NEONATES.

The use of phenobarbitone by intravenous and oral routes of administration in the therapy trial reported in Chapter 8 necessitates a review of dosage regimens and related serum levels in term newborns.

7.5.1. Dosage and serum levels :

Studies on the relationship between phenobarbitone dosage and serum levels were carried out by Jalling (1975) and Lockman et al (1979). Jalling studied 18 term infants with seizures. In some cases she used the oral and in others the intramuscular route of administration. Lockman et al studied 39 neonates of all birth weights and gestational ages. In both studies frequent serial phenobarbitone levels were taken after the initial loading dose or repeated oral doses.

In both studies there was a linear relationship between dosage and subsequent peak phenobarbitone level. Jalling found that the peak serum level was 1.3 x dose (in mg/kg) as micrograms (ug) per millilitre, for the intramuscular and rather lower for the oral route. For example a single intramuscular dose of 15mg/Kg produced a peak phenobarbitone level of 19.5ug/ml. Lockman et al found that to achieve a serum level of 20ug/ml it was necessary to give 18.2+-6.5 mg/Kg intramuscularly of phenobarbitone. Donn et al (1985) in a later publication used a much larger dose (intravenous loading dose of 30mg/Kg) in a group of 10 asphyxiated term newborns at risk of seizures. Phenobarbitone levels were 30.0 +- 3.2 ug/ml. at an interval of 2 hours after the dose.

Lockman et al (1979) found that the peak phenobarbitone level was not different in patients who had received the substance via the IM route, as compared to those who had received it via the IV route. Nevertheless the time after the dose at which the peak level is achieved clearly depends on the route of administration. Jalling found that 90% of the peak level was achieved within 4 hours of an IM dose and within 8-12 hours of an oral dose. Donn et al found that the peak after an IV dose occurs within minutes.

The half life of phenobarbitone after administration

was studied by these authors. In a standard dosage regimen of 30mg/kg Donn et al (1985) found a 1/2 life of 148 +-55 hours. Jalling on the other hand with a wide variety of doses and routes of administration found a 1/2 life of between 59 and 182 hours. She also found that the rate of disappearance of phenobarbitone from the blood varied from day to day in individual patients and that this variability was not attributable to birth weight, gestational age, age of infant or medications taken by the mother or infant. The differences seeemed to reflect day to day changes in the infant's condition.

Lockman found that after a loading dose (intramuscular or intravenous), the serum level did not fall significantly for the first 24 hours and did so very variably thereafter. Maintainance doses would thus not need to be started until after that time.

Phenobarbitone seems to cross into the cerebrospinal fluid in such a way that a steady CSF:plasma ratio is established after a delay of some hours. Jalling measured serial simultaneous CSF and serum phenobarbitone levels in 9 patients and found that a steady ratio of between 0.48 and 0.83 was established by about 17 hours.

7.5.2. Anticonvulsant levels of phenobarbitone in the newborn :

The studies quoted above found that the serum level of

phenobarbitone at which seizures are controlled is between 12 and 30 ug/ml. Jalling notes however that neonatal seizures have a strong tendency to resolve spontaneously which makes it difficult to be certain that a given level of anticonvulsant is responsible for the cessation of seizures in an individual patient.

Gal et al (1982) found that some infants required higher serum levels to achieve control of seizures. They found that 60 out of 71 neonates with seizures responded to phenobarbitone and the levels at which they did so were as follows :

60% responded at a serum level of <20 ug/ml.
28% " " " " " " 20-30 ug/ml.
12% " " " " " " >30 ug/ml.

The concern over the dangers of respiratory and cardiovascular depression caused by serum levels of phenobarbitone of 30-40 ug/ml seem to be unfounded as Donn et al could find no effect of the loading dose on heart rate, mean blood pressure or respiratory rate in their group of infants.

These authors all concur that seizures occuring as part of hypoxic ischaemic encephalopathy in the newborn are particularly difficult to control. Of Donn's 10 asphyxiated patients 3 had seizures and only 1 of these responded to phenobarbitone even at the higher dose that he employed.

Anticonvulsant levels of phenobarbitone are not necessarily those at which protection against asphyxial insult will be produced. The dose for this may well be higher.

7.6. THE ROLE OF CORTICOSTEROIDS IN THE TREATMENT OF HYPOXIC-ISCHAEMIC BRAIN INJURY.

The role of corticosteroids in the treatment of hypoxic-ischaemic cerebral injury is mainly involved with their ability to prevent or limit cerebral oedema. Their place in the treatment of the affected neonate remains very controversial. This section will review the available literature.

7.6.1. Cerebral oedema :

Katzman et al (1977), Anderson et al.(1979) and Fishman (1982) have reviewed the subject of cerebral oedema and they make a distinction between vasogenic and cytotoxic cerebral types. This concept seems to be important in understanding the role of steroids in this situation.

"Vasogenic" cerebral oedema results from the leakage of large molecules through the structurally altered blood-brain barrier into the extracellular space of the brain. This is followed osmotically by water which moves in the tissue planes of the white matter. An increase in arterial blood pressure will promote this type of oedema. Vasogenic cerebral oedema will show

contrast enhancement on CT scanning. Furthermore due to free communication of the extracellular space with the CSF compartment, large molecules, especially protein, will appear in the CSF.

"Cytotoxic" cerebral oedema on the other hand is the result of the breakdown of active transport systems which regulate the distribution of electrolytes and water across cell membranes. Water accumulates intracellularly and at first does not expand the extracellular space. The oedema is confined to the gray matter and is not affected by arterial pressure.

A comparison between the two types of cerebral oedema is set out in Table 7.6.1.

TABLE 7.6.1. COMPARISON OF VASOGENIC AND CYTOTOXIC CEREBRAL OEDEMA.

VASOGENIC	CYTOTOXIC
Extracellular	Intracellular
White matter	Gray matter
Affected by blood pressure	Not affected by BP
Contrast enhances CT scan	No enhancement
Blood-brain barrier affected	Celluar transport systems affected
CSF protein raised	CSF protein unaffected
Corticosteroids help	Corticosteroids said not to help

Cerebral oedema following ischaemia has been studied and found to consist of both types of process ocurring more or less in sequence. The initial ischaemic/hypoxic insult causes a cytotoxic effect with its accompaning type of cerebral oedema. As cells die and release their lysosomal contents, osmotically active substances appear in the extracellular fluid and attract water. Occuring somewhat later, there is damage to the blood-brain barrier which adds the element of vasogenic oedema. The oedema itself causes compression of cerebral capillaries which further reduces cerebral blood flow further compounding the situation.

A body of literature indicates that corticosterioids are helpful in treating cerebral oedema of the vasogenic but not the cytotoxic form. For example Yamaguchi et al (1976) found that dexamethasone did not reduce brain water in rats subjected to bilateral carotid artery ligation (cytotoxic oedema) but did so in those subjected to local brain trauma (vasogenic oedema). The oedema surrounding tumors and brain abscesses responds both experimentally and clinically to steroids.

The mechanisms underlying this action are thought to involve firstly a vascular membrane stabilizing effect in which membrane dissociation and lysosomal enzyme release is reduced and injury by free radicals is

prevented. Thus vascular permeability is controlled. Secondly the clearance of extracellular oedema fluid via its communication with the CSF is enhanced. The effect of steroids is to increase the reabsorbtion of CSF as well as to reduce production.

7.6.2. The use of corticosteroids in animal trials :

Animal studies involving the use of corticosteroids in neonatal asphyxia have been contradictory.

De Souza and Dobbing (1973) from Manchester chose to study the 5 day old rat as it closely resembles the term human neonate in its stage of brain maturation in that neuronal numbers have virtually stopped increasing and glial cells and neuronal interconnections have begun to appear. They found that the rats rendered hypoxic near to the point of death in a low oxygen tension jar had significantly increased brain water, increased brain sodium and reduced brain potassium as compared to non-asphyxiated controls. Pretreatment with dexamethasone at a dose of 20 mg/Kg intraperitoneally, significantly reduced these changes whilst lower doses did not. A similar effect was seen when dexamethasone was given at a dose of 20mg/Kg immediately after the asphyxial insult. They also noted that a rise in blood glucose seen in non-dexamethasone treated asphyxiated animals was prevented by pretreatment with dexamethasone at the same dose. Apart from a

significant increase in total brain carbohydrate, dexamethasone treatment of normal rats did not alter any of the measured parameters when examined 2 hours later.

In a further publication Adlard and De Sousa (1976) using the same animal model found that asphyxiated animals had 43% less total brain adenosine triphosphate than non-asphyxiated controls. Pretreatment with dexamethasone 20mg/Kg had a significant retarding effect on adenosine triphosphate reduction.

As a result of this work Adlard and De Sousa's group feel that the action of dexamethasone may involve a preservation of the energy dependent electrolyte pump mechanism by preserving adenosine triphosphate. The increase in brain carbohydrate may act to provide energy reserves against anaerobic metabolism.

Altman et al.(1984) studied the effect of dexamethasone on asphyxiated 7 day old rats. They used the Levine procedure in which a unilateral common carotid artery ligation was performed some 3 hours before the animals were asphyxiated in a 8% oxygen environment for 3,5 hours. They found that pretreatment with dexamethasone, either 4 or 40 mg/Kg, had no effect on the differences in brain water between the cerebral hemispheres, on the fall in brain ATP, on the fall in cerebral blood glucose or on the rise in cerebral blood lactate.

Dexamethasone treatment also made no difference to the neuropathological appearances. The only significant difference was that treated cases had a higher mortality than the controls.

This experimental model with its combination of prolonged ischaemia and hypoxia would seem to be nearer the human asphyxiated neonate and the results thus more valid than those of the Manchester group whose model involved only severe hypoxia.

7.6.3. Use of corticosteroids in human neonatal patients :

So far there have been very few studies investigating the effect of steroid treatment in the asphyxiated human neonate. A few studies such as that by Svenningsen (1975) (see above) have used dexamethasone as part of a treatment package with inconclusive results.

A recent publication from Levene and Evans (1985) reports on the effect of dexamethasone in severely asphyxiated infants with documented raised intracrainial pressure (>10mm Hg). They gave these infants a single intravenous dose of dexamethasone (4 mg) and monitored intracranial pressure via a subarachnoid catheter. They simultaneously monitored systemic blood pressure and hence derived the cerebral perfusion pressure. They found that in the 7 infants studied dexamethasone produced a fall in intracranial

pressure which was sustained for at least 6 hours. However a simultaneous fall in systemic blood pressure resulted in no net change in cerebral perfusion pressure. They conclude that there is little place for dexamethasone therapy in severely asphyxiated infants.

7.6.4. Possible undesirable effects of dexamethasone :

Early work on suckling rats by Adlard and DeSouza (1973) showed that a single dose of dexamethasone either 1 or 20mg/Kg had profoundly negative effects on the growth of the whole body as well as that of brain and thymus at 3 weeks of age. Treatment with hydrocortisone produced similar but less marked effects. It will be recalled that in rats it was a dose of 20mg/Kg that produced some degree of cerebral protection following asphyxia.

A worrying feature of the use of large doses of dexamethasone in human newborns comes from a McGill group of Fitzhardinge et al (1974). They followed a group of preterm infants who had had hyaline membrane disease and received 2 doses of hydrocortisone (12.5mg/Kg) during the first 24 hours of life as well as a carefully matched control group which had not received the hydrocortisone. At 1 year of age there were no differences in growth, number of infections nor any aspect of immune competence. The treated group had a slight increase in neurological abnormalities (3/13 vs

vs 0/14), relative delay in gross motor development and an increase in the incidence of minor EEG abnormalities. In a subsequent related publication by Gunn et al. (1981), 11 out of 14 cases and 7 out of 13 controls of the original Fitzhardinge group were seen at 5 years of age. There were no differences in somatic growth or intelligence quotient. Although there were no differences in other aspects of immune competence, cases had significantly lower T-lymphocyte counts, an increased percentage of lymphocytes with C3 receptors. There was also a suggestion that cases had had a greater number of serious infections. Eight out of 11 cases had had an episode of pneumonia or otitis media over the period 1-5 years while 2 out of 7 controls had had the same.

7.6.5. Conclusion on corticosteroids :

The place of steroids in hypoxic/ischaemic brain injury remains unclear. Despite theoretical considerations suggesting that it might be helpful for at least the vasogenic phase of this type of injury the animal and human work is very equivocal and there a dearth of adequate trials in the human asphyxiated neonate. On the specifically negative side, several studies have recorded an increased mortality among treated cases. Its effect on the growth and immune competence of the newborn rat is profound and negative effects on the

immune competence of human children aged 5 years have been documented. It is especialy worrying that the doses found to be therapeutic against asphyxia in experimental animals are large enough to cause major growth and immune problems later.

It would seem to be important to investigate the possible beneficial effect or otherwise of dexamethasone in the mild to moderately asphyxiated infant because unless a clear benefit is demonstrated its routine use in such patients should be discontinued in view of the serious potential side effects of this medication in the neonate.

7.7. TRIALS ON THE PROTECTIVE EFFECT OF BARBITURATES IN THE ASPHYXIATED HUMAN INFANT.

Two studies by Finer et al (1981 and 1983) have examined the use of phenobarbitone and betamethasone in asphyxiated term infants. In neither instance was a case/control design used. Rather, infants who had been treated with a variety of agents, as decided upon in each case by the attending physician, were evaluated as to the outcome.

The first of these two studies (Finer et al 1981) looked at 95 term infants with hypoxic-ischaemic encephalopathy. Sixty two percent were given phenobarbitone after seizures had commenced and 29%

received betamethasone prophylactically soon after birth. Some received both, and others only one, form of therapy. The numbers in each category are not stated. A variety of other agents were given in each case as the clinical need arose. Patients were not assigned to any one form of treatment on a random basis and the form of treatment was not uniform. The findings were that no significant relationship could be found between any form of drug therapy and long term neurodevelopmental outcome.

In their later study Finer et al. (1983) investigated 29 term infants with HIE who had been given prophylactic betamethasone by their attending physician. This group was not different in neurodevelopmental outcome to similar patients who had not received betamethasone. The criticisms of the first trial apply to this study also.

A Swedish prospective case/control trial of the possible protective effect of certain forms of therapy comes from Svenningsen et al. (1982). Term infants were randomly assigned either to a treatment or to a control group. The criteria for inclusion were such that infants had had inadequate respiration and severe hypotonia which had persisted after 30 minutes of intensive resuscitation. Management for each group was identical with respect to I.V. fluids, anticonvulsants

and other aspects of therapy. The treatment group received in addition phenobarbitone, betamethasone and lasix very soon after birth. Doses of phenobarbitone were large (20mg/Kg in first 24 hours and then 10 mg/Kg per 24 hours thereafter) and achieved peak levels (range 150-375 ug/l) 3 days after delivery. There was a significant difference in neonatal mortality in favour of the treated group (0/14 vs 5/16). There were significantly fewer children at 1 year with neurodevelopmental abnormalities in the treated group.

The effect of treatment on the occurence of seizures is shown below and the treated group had a lower incidence of seizures at all times.

TABLE 7.7.1. OCCURENCE OF SEIZURES IN EXPERIMENTAL AND CONTROL GROUPS.

	Rx Grp N=14	No Rx N=16
Neonatal Seizures	57%	87%
Recurrent neonatal seizures.	21%	63%
Recurrent post natal seizures.	8%	25%

From : Svenningsen et al (1982).

The reduction in the incidence of seizures in later life is particularly interesting as this suggests that therapy may indeed have a useful protective effect

against cerebral injury. One confounding variable in this trial was the time of onset of artificial ventilation. The treatment group had mechanical ventilation administered for much more liberal indications than the control group. The two groups had no significant difference in the frequency with which mechanical ventilation was used but in the treatment group it was administered significantly earlier. This factor, which in itself may well have been responsible for differences observed, makes interpretation of the effects of drug therapy difficult to evaluate.

A more recent approach has been to induce thiopentone coma in severely affected infants with the intention of maximising the effect of barbiturates on reducing cerebral metabolism.

In such a study, Eyre and Wilkinson (1986) induced thiopentone coma in 6 very severely asphyxiated infants for a median duration of 127 hours. They monitored the EEG and adjusted the rate of thiopentone infusion to keep the EEG isoelectric. They had major difficulties with circulatory hypotension related to barbiturate dosage. The study did not use controls but half of the infants died in the immediate neonatal period and the survivors all had major handicap. The authors conclude that while it is possible to maintain prolonged thiopentone coma it is technically very demanding and

the benefits not evident. It is possible that the severity of the patients selected for the therapy put the patients beyond help and that such therapy might be beneficial in somewhat less severely affected infants.

Another recent case-control study looked at the protective effect of a high dose thiopental infusion. Goldberg et al (1986) in a case-control trial studied severely asphyxiated term infants with encephalopathy requiring artificial ventilation. Cases received additional therapy in the form of a thiopental infusion for the first 24 hours while controls did not. They monitored blood pressure and intracranial pressure for the first 72 hours in both groups and followed their neurodevelopmental progress for 3 years. Blood pressure was maintained at normal levels with the use of pressor agents if necessary. Although cases needed more pressor support than controls there were no significant differences in intracranial pressure, cerebral perfusion pressure or neurodevelopmental outcome. The authors conclude that the difficulties in maintaining blood pressure with this form of therapy are not balanced by neurodevelopmental gains and that this form of treatment is not beneficial. As with the study of Eyre and Wilkinson this study involved only very severely affected infants in whom cerebral damage may well have been beyond any possible protective effect.

7.7.1. Conclusions on human trials :

There is a suggestion that in a very severely asphyxiated group the combination of phenobarbitone, betamethasone and lasix offers some benefit to patients in terms of survival and quality of outcome. Nevertheless to date there is no reported case-control trial of the effect on neurodevelopmental outcome of the combination of phenobarbitone and dexamethasone that is commonly used in neonatal units in this country.

CHAPTER 8

THERAPY TRIAL

8.1. INTRODUCTION.

Previous discussion has emphasised the importance of asphyxia as a leading cause of neonatal death and severe handicap in term infants in Ciskei. The study of epidemiology has cast some light on the factors associated with asphyxia in this area which may help to direct preventive efforts as well as indicating some priorities for further research. Whilst future prevention is important, the current problem facing paediatricians looking after newborns in the Ciskei is the number of infants asphyxiated at birth and/or developing encephalopathy in the first few hours of life. The immediate problem is to decide on the most appropriate treatment regimen for such infants with a view to limiting future handicap.

The literature review on the treatment of the post asphyxial infant has indicated that whilst certain aspects are relatively non-controversial, the issue as to whether a regimen of phenobarbitone and dexamethasone given soon after birth is beneficial, is largely undecided. The resolution of this issue becomes all the more important when it is recalled that Adlard and De Sousa (1973) have demonstrated harmful effects on the later growth of suckling mice treated with dexamethasone and that Fitzhardinge et al (1974) have found late immune defects in humans treated with

hydrocortisone as preterm infants. The routine use of dexamethasone in asphyxiated infants can only be justified if its protective advantages outweigh these possible hazards.

In the literature review much evidence was brought forth to suggest that both barbiturates and corticosteroids may be beneficial in hypoxic-ischaemic experimental animals including primates, but convincing evidence of their effectiveness when used in the human aspyhxiated infant was lacking.

Despite this lack of evidence, many centres in this sub-continent have been using phenobarbitone and dexamethasone as a protective regimen in the asphyxiated term infant. This regimen was often used in our unit before this trial and it was decided to assess its efficacy. An unfortunate but practical reason as to why such a trial could be carried out in our setting was the high incidence of asphyxia. We would be able to recruit enough cases to carry out the trial in a reasonable time span.

8.2. PATIENTS AND METHODS :

8.2.1. SELECTION OF CASES AND CONTROLS.

Potential candidates for the trial were the infants of mothers delivering at term in the labour ward of Cecilia Makiwane Hospital. This delivery facility has

24 hour resident obstetric and paediatric medical staff cover. The newborn nursery is adjacent to the labour ward and routine attendance of paediatric resident staff at all high risk vaginal and caesarian deliveries is practiced.

Patients were admitted to the trial immediately after birth on the basis of the following criteria :

(a) Being of more than 37 weeks of gestation

AND

(b) Having had a 5 minute Apgar score of less than 7

AND/OR

(c) Having shown signs of fetal distress

AND

(d) Showing a placental chorionic arterial base deficit excess of > 11.

After satisfying the selection criteria they were was divided into CASES and CONTROLS by a random process of envelope selection by the resident paediatric doctor.

Gestation was assessed by using available obstetric data. If any doubt existed as to the gestation of an infant it was confirmed using the Ballard modification of the Dubowitz method of estimating gestational age in newborns. (Ballard 1977).

Both 1 and 5 minute Apgar scores were assessed in all instances by attending paediatric residents.

Fetal distress was taken to be the presence of meconium stained liquor and/or the presence of fetal heart irregularities detected either clinically or by means of the cardiotochograph. Established reduction of fetal movements, either observed by the mother or detected by means of fetal kick chart monitoring, was also taken as evidence of fetal distress.

Placental arterial blood was obtained by the resident doctor within 10 minutes of birth by puncture of an artery running over the surface of the chorion. The blood was collected into a heparinised plastic syringe and taken immediately for blood gas estimation on a Radiometer "Blood Gas Laboratory". In the event of a delay of more than a 5 minutes the blood was placed in a plastic bag which was surrounded by crushed ice. Analysis was performed within 30 minutes.

8.2.2. TREATMENT REGIMENS.

CASES were treated from the time of selection at birth with a loading dose of Sodium Gardenal 15mg/Kg intravenously and Phenobarbitone 5mg/Kg/24 hours was given orally in 2 daily doses starting at 12 hours of age and continuing for at least 72 hours. It was continued for longer if the clinical condition indicated this. They were also given dexamethasone 0.5 mg/Kg intravenously 6 hourly for 72 hours.

CONTROLS did not receive phenobarbitone and dexamethasone.

In other respects all patients received the same treatment. In anticipation of some degree of inappropriate antidiuretic hormone secretion following the cerebral insult, the total fluid intake was restricted to 50ml/Kg/24 hours for the first 48-72 hours of life. In view of the possibility of ischaemic bowel damage, patients were kept nil by mouth for the first 48 hours and longer if necessary until adequate bowel sounds were audible. The routine intravenous fluid was NEONATALYTE (SABAX) the composition of which is set out in Appendix V. Seizures were treated with a loading dose of phenytoin 8 mg/Kg intramuscularly followed by 4mg/Kg per mouth 12 hourly thereafter.

8.2.3. BIOCHEMICAL EVALUATION.

Blood was taken by resident medical staff at between 48 and 72 hours of age for estimation of serum sodium, potassium, urea and creatinine. While every effort was made to take blood within these limits practical considerations made this sometimes impossible. The blood was submitted for routine multichannel analysis at the East London and Border Pathology Laboratory.

8.2.4. PHARMACOLOGICAL EVALUATION.

Blood was taken at the same time as in 8.2.3. above for serum phenobarbitone estimation. The serum was

separated by the hospital laboratory by centrifugation immediately and stored at -20 degrees centigrade for later transmission to the Department of Pharmacology at the University of Cape Town where estimation of serum phenobarbitone was carried out by Dr.J.S.Cridland using the EMIT immunoassay method (Syba Co.).

8.2.5. CLINICAL EVALUATION.

The infants were subject to the routine clinical care in the hospital nursery and regular clinical annotations were made by the attending medical staff. Neither the author nor the nursing staff engaged in the follow-up were at any time during the trial aware as to whether an infant was allocated as a case or as a control. The trial was in this sense truly blind. The author examined the infants at between 48 and 72 hours of age and carried out both a Prechtl assessment (Prechtl 1977) and a conventional neurological examination for which a proforma is provided in Appendix VIII. Data was recorded on data sheets and included:

8.2.5.1 Method of resuscitation, Apgar scores and the time to sustained respiration.

8.2.5.2 Prechtl evaluation by the author at 48-72 hours of age.

8.2.5.3. General and neurological examination at 48-72 hours by the author.

8.2.5.4. Daily neurological assessment by nursery medical staff.

8.2.5.5. Specific details of feeding particularly the age at which nasogastric feeding was no longer needed.

8.2.5.6. The occurence and age of onset of seizures.

8.2.5.7. The occurence and severity of jaundice.

8.2.5.8. The age at discharge.

A set of the proformas used for data recorded in the nursery is provided in Appendix VIII.

8.2.6. MATERNAL DATA.

Data was extracted from the obstetrical records soon after birth by the author and entered on a proforma. If necessary data was obtained from the obstetrical staff by personal communication. The nursery is located adjacent to the labour ward thus facilitating exchange of information.

Each case was discussed by the author and paediatric collegues with the assembled obstetric staff at a weekly perinatal meeting at which an attempt was made to assign a cause to the asphyxia ("Obstetric cause"). The opinion of the attending consultant obstetrician was taken as definitive. On occasion a particular case would miss being discussed in which case the consultant obstetrician would be asked to peruse the records and to assign a cause.

Social and residential data was obtained from the

mother prior to delivery to enable follow up at home to be carried out.

8.2.7. FOLLOW-UP SHEDULES.

Patients were visited in their homes at the following ages : 6 weeks, 3, 6 and 9 months. Data was recorded on proformas relating to the following :

Weight was recorded with the infants unclothed using a hanging spring scale which was zeroed before each measurement and was calibrated with a standard weight regularly.

Occipito-frontal head circumference was measured with a fibre glass tape measure taking at least 3 readings and using the greatest figure obtained.

Feeding performance.

Scores of performance in age appropriate test items of the Denver Developmental Screening Test (DDST). (Frankenburg and Dodds 1967).

Social Data to facilitate the next follow-up visit.

Copies of the proformas used for each follow-up visit are to be found in Appendix IX.

Follow-up visits were carried out by a team of 2 registered nurses who had been orientated in the specific items of the DDST by the author. These

specific nurses have for some years been involved in assisting at the Neurodevelopmental Clinic at the hospital and also in running a Day Training Centre for mentally retarded children.

In scoring the DDST the following procedure was used. At each follow-up visit a specific number of age appropriate test items were prescribed to be applied. Details of the items used at each visit are provided in Appendix IX. A point was scored for each item of the test passed by the baby. This was divided by the number of test items applied to the child and the result expressed as a percentage. However if a specific item could not be used on a particular baby the denominator was reduced by the number of items not applied. In categorizing results a score of less than 66% was regarded as "probably abnormal". It is appreciated that this is not the orthodox method of scoring the Denver Developmental Sceening Test but it was considered expedient under the unfavourable home circumstances in which the assessments were often made. This will be considered further in the discussion.

8.2.8. FINAL EVALUATION.

For this evaluation the patients attended the hospital out-patients department within a few weeks of their first birthday. On this occasion they were examined by the author and the following data recorded on

proformas :

Weight and Occipito-frontal head circumference.

Performance in the items of the DDST appropriate for about 1 year.

The result of a conventional neurological and general physical examination. The neurological examination was carried out in accordance with the methods of Paine and Oppe (1966) and for which a proforma is included in Appendix IX. The results of the examination was recorded as a 4 point scale modified from De Sousa and Richards (1978) according to the severity of neurological abnormality and resulting handicap :

Normal - No abnormal neurological finding.

Probably normal - Neurological findings of slight or doubtful significance.

Probably abnormal - Definite disorder but producing little or no physical handicap.

Abnormal - Definite and obviously handicapping disorder.

The outcome of the Du Toit rattle hearing test using the Du Toit rattle as prescribed by Prof. Du Toit of the ENT Dept. of Tygerberg Hospital. In

any case of doubt the child was referred to the ENT dept. of the hospital for free field audiometry.

A simple test of vision using the childs attentiveness to a 6 cm diameter red pom-pom. In any case of doubt the child was referred to the Eye Dept of the hospital for more formal assessment.

A copy of the proforma used in the final evaluation is included in Appendix IX.

8.2.9. CONSENT.

Prior to the start of the trial, the phenobarbitone and dexamethasone regimen had been used erratically in the neonatal unit. Some asphyxiated infants would receive it and others would not. This was largely determined by the personal preference of the attending consultants and doctors. The trial placed on a random basis, a decision that had hitherto been one of erratic preference.

In planning it was realised that many mothers would deliver by caesarian section under general anaesthesia and would not be in a position to give informed consent for several hours after delivery. Nevertheless it was seen as important to start the therapeutic regimen immediately after delivery if any benefit was to be obtained. In the event 62% of the patients delivered by caesarian section (see TABLE 8.3.8.). Thus, where

possible, consent was obtained for participation in the trial prior to commencement. However for the reasons given above it was not possible in many cases to obtain consent for participation in the initial selection process for the use of the drug regimen. In these cases, consent was obtained as soon as the mother was in a position to discuss the matter and always on the first day after delivery. In no case was consent refused.

8.2.10. DATA ANALYSIS :

Data from all proformas were entered by the author onto a computer data base for analysis. All such analysis and tabulation were carried out by him.

8.2.11. STATISTICAL METHODS.

Student's t-test was used when comparing mean values and the Chi- squared test or Fisher's exact probability test were used when comparing proportions of infants in various categories. If the total number in the analysis was less than 100 or if any individual data cell had a value of less than 10 the Yates correction of the Chi-square test was used (Swinscow 1977). In a number of cases tables of data had to be collapsed to allow Chi-square analysis. Details are given under results.

The Chi-square and t-tests were carried out by the author but Fisher's exact test was carried out by

statisticians of the Medical Research Council.

Unless otherwise stated, statistical significance was taken to be a probability of <0.05.

8.3. RESULTS :

A total of 116 infants entered the trial. Of these 64 were allocated as cases and 52 as controls.

DATA TO CONFIRM COMPARABILITY OF TWO GROUPS.

In this section data will be presented to indicate that the case and control groups were comparable except for the use of phenobarbitone and dexamethasone.

8.3.1. OBSTETRIC DETAILS :

8.3.1.1. Maternal age.

The mean (+-S.D.) maternal ages were :

CASES 23.4 (+-5.6) years. Range 15-43.
CONTROLS 24.2 (+-6.1) years. Range 16-38.

The difference was not significant. (t = 0.793 N=116).

8.3.1.2. Gravidity and Parity.

The distribution of gravidity and parity are shown in Tables 8.3.1.1. and 8.3.2.1.

TABLE 8.3.1.1. GRAVIDITY OF CASES AND CONTROLS

GRAVIDA	CASES	CONTROLS	TOTALS
1	29	25	54
2	16	10	26
3	11	6	17
4	4	7	11
5	1	2	3
6	2	-	2
7+	-	2	2
MISSING	1	-	1
TOTALS	64	52	116

TABLE 8.3.1.2. GRAVIDITY OF CASES AND CONTROLS PERCENTAGES.

GRAVIDA	CASES	CONTROLS	TOTALS
1	45.3	48.1	46.6
2	25.0	19.2	22.4
3	17.2	11.5	14.7
4	6.3	13.5	9.5
5	1.6	3.8	2.6
6	3.1	-	1.7
7+	-	3.8	1.7
MISSING	1.6	-	.9
TOTALS	100.0	100.0	100.0

TABLE 8.3.2.1. PARITY.

PARITY	CASES	CONTROLS	TOTALS
0	32	24	56
1	14	11	25
2	8	6	14
3	5	6	11
4	2	3	5
5	2	-	2
6	-	1	1
7+	-	1	1
MISSING	1	-	1
TOTALS	64	52	116

TABLE 8.3.2.2. PARITY - PERCENTAGES.

PARITY	CASES	CONTROLS	TOTALS
0	50.0	46.2	48.3
1	21.9	21.2	21.6
2	12.5	11.5	12.1
3	7.8	11.5	9.5
4	3.1	5.8	4.3
5	3.1	-	1.7
6	-	1.9	.9
7+	-	1.9	.9
MISSING	1.6	-	.9
TOTALS	100.0	100.0	100.0

No significant differences could be shown between the two groups by Chi squared testing :

Gravidity - Chi squared = 3.015 DF = 3.

Parity - Chi squared = 0.945 DF = 3.

8.3.1.3. Antenatal Care Usage.

Eighteen cases and 10 controls were not booked and hence did not receive antenatal care. Data for 1 case was missing which leaves data for 87 patients who attended antenatal care at least once in pregnancy. The difference between cases and controls in regard to non-booking was not significant. Chi-square = 0.88 DF=1.

Information regarding the weeks at booking, number of antenatal care visits and the weeks of gestation at the last visit are set out in Table 8.3.3.

For most continuous data, full ranges are given in Appendix VI.

TABLE 8.3.3. ANTENATAL CARE USE.

	CASES		CONTROLS		t - TEST		
VISIT	MEAN	SD	MEAN	SD	t VAL.	N	SGN
BOOKING WKS	27.6	5.3	27.0	4.8	0.526	87	NS
No.VISITS	6.71	3.1	6.97	3.0	0.393	87	NS
WKS LAST VST	38.6	1.5	38.5	1.4	0.457	87	NS

SGN = Significance.
NS = Not significant.

8.3.1.4. Complications of Pregnancy.

The distribution of complications of pregnancy as detected during antenatal care is set out in Table 8.3.4.1.

TABLE 8.3.4.1. COMPLICATIONS OF PREGNANCY.

	CASES	CONTROLS	TOTALS
UNBOOKED	17	10	27
NONE	33	24	57
PREGNANCY INDUCED HYERTENSION	6	10	16
ECLAMPSIA	–	1	1
INTRAUTERINE GROWTH RETARDATION	2	1	3
MULTIPLE	3	3	6
ANTEPARTUM HAEMORRAGE ? CAUSE	–	1	1
ALBUMINURIA	1	2	3
DIABETES	1	–	1
REDUCED FETAL MOVEMENTS	1	–	1
TOTALS	64	52	116

TABLE 8.3.4.2. COMPLICATIONS OF PREGNANCY - PERCENTAGES.

PERCENTAGES :	CASES	CONTROLS	TOTALS
UNBOOKED	26.6	19.2	23.3
NONE	51.6	46.2	49.1
PREGNANCY INDUCED HYPERTENSION	9.4	19.2	13.8
ECLAMPSIA	–	1.9	.9
INTRAUTERINE GROWTH RETARD.	3.1	1.9	2.6
MULTIPLE	4.7	5.8	5.2
ANTEPATRUM HAEMORRAGE ? CAUSE	–	1.9	.9
ALBUMINURIA	1.6	3.8	2.6
DIABETES	1.6	–	.9
REDUCED FETAL MOVEMENTS	1.6	–	.9
TOTALS	100.0	100.0	100.0

No significant differences could be shown between the two groups on Chi squared testing : 2.521 DF = 2.

8.3.1.5. Presentation.

The distribution of presentation is set out in Table 8.3.5.1.

TABLE 8.3.5.1. PRESENTATION : ALL CASES

	CASES	CONTROLS	TOTALS
VERTEX	63	52	115
BREECH	1	-	1
TOTALS	64	52	116

TABLE 8.3.5.2. PRESENTATION - PERCENTAGES.

	CASES	CONTROLS	TOTALS
VERTEX	98.4	100.0	99.1
BREECH	1.6	-	.9
TOTALS	100.0	100.0	100.0

8.3.1.6. Evidence of Fetal Distress.

The distribution of the evidence for fetal distress is set out in Table 8.3.6.1.

TABLE 8.3.6.1. EVIDENCE OF FETAL DISTRESS : ALL CASES

	CASES	CONTROLS	TOTALS
NONE	5	10	15
MECONIUM STAINED LIQUOR	33	24	57
MSL+FH	16	9	25
FETAL HEART ABNORMALITY	8	7	15
REDUCED FETAL MOVEMENTS	2	2	4
TOTALS	64	52	116

TABLE 8.3.6.2. EVIDENCE FOR FETAL DISTRESS :

PERCENTAGES.

	CASES	CONTROLS	TOTALS
NONE	7.8	19.2	12.9
MECONIUM STAINED LIQUOR	51.6	46.2	49.1
MSL+FH	25.0	17.3	21.6
FETAL HEART ABNORMALITY	12.5	13.5	12.9
REDUCED FETAL MOVEMENTS	3.1	3.8	3.4
TOTALS	100.0	100.0	100.0

No significant differences could be shown between the two groups on Chi squared testing : 3.441 DF = 2.

8.3.1.7. Complications of Labour.

The distribution of the complications of labour is set out in Table 8.3.7.1.

TABLE 8.3.7.1. COMPLICATIONS OF LABOUR.

COMPLICATION :	CASES	CONTROLS	TOTALS
NONE	22	13	35
DELAYED ACTIVE PHASE	7	11	18
MECONIUM STAINED LIQUOR	11	7	18
CEPHALOPELVIC DISPROPORTION	10	7	17
OTHER FETAL DISTRESS	7	4	11
MULTIPLE	–	2	2
CORD ROUND NECK	–	2	2
ABRUPTIO	1	2	3
ECLAMPSIA	–	1	1
PROLAPSED CORD	1	1	2
MALPRESENTATION.	2	1	3
PROLONGED RUPTURE OF MEMBRANES	1	–	1
PREGNANCTY INDUCED HYPERTENSION	2	–	2
PLACENTA PREVIA		1	1
TOTALS	64	52	116

TABLE 8.3.7.2. COMPLICATIONS OF LABOUR - PERCENTAGES.

COMPLICATION :	CASES	CONTROLS	TOTALS
NONE	34.4	25.0	30.2
DELAYED ACTIVE PHASE	10.9	21.2	15.5
MECONIUM STAINED LIQUOR	17.2	13.5	15.5
CEPHALOPELVIC DISPROPORTION	15.6	13.5	14.7
OTHER FETAL DISTRESS	10.9	7.7	9.5
MULTIPLE	-	3.8	1.7
CORD ROUND NECK	-	3.8	1.7
ABRUPTIO	1.6	3.8	2.6
ECLAMPSIA	-	1.9	.9
PROLAPSED CORD	1.6	1.9	1.7
MALPRESENTATION	3.1	1.9	2.6
PROLONGED RUPTURE MEMBRANES	1.6	-	.9
PREGNANCY INDUCED HYPERTENS.	3.1	-	1.7
PLACENTA PREVIA	-	1.9	.9
TOTALS	100.0	100.0	100.0

No significant differences could be shown between the two groups on Chi squared testing : 3.23 DF = 4.

8.3.1.8. Method of Delivery.

The distribution of the method of delivery is set out in Table 8.3.8.1.

TABLE 8.3.8.1. METHOD OF DELIVERY.

	CASES	CONTROLS	TOTALS
UNASSISTED	20	15	35
CAESARIAN SECTION	40	32	72
VACUUM	4	5	9
TOTALS	64	52	116

TABLE 8.3.8.2. METHOD OF DELIVERY - PERCENTAGES.

PERCENTAGES :	CASES	CONTROLS	TOTALS
UNASSISTED	31.3	28.8	30.2
CAESARIAN SECTION	62.5	61.5	62.1
VACUUM	6.3	9.6	7.8
TOTALS	100.0	100.0	100.0

No significant differences could be shown between the two groups on Chi squared testing : 0.078 DF = 1.

8.3.1.9. Duration of the First Stage of Labour.

This data excludes 4 cases and 5 controls who had elective caesarian sections before labour. The mean (+-S.D.) duration of the 1st stage of labour for the 2 groups was :

CASES 15.03 (17.7) hours. Range 1-131.

CONTROLS 12.69 (7.0) hours. Range 3-34.

The difference was not significant. (t = 0.852 N = 107).

8.3.1.10. Placental Weight.

Data for this item was missing for 7 cases and 4 controls. The mean (+-S.D.) placental weight for the 2 groups was :

CASES 556 (85.7) grams. Range 420-800.

CONTROLS 571 (116.8) grams. Range 450-1200.

The difference was not significant. (t = 0.782 N = 105).

8.3.1.11. Indications for Operative Delivery.

The distribution of the indications for operative delivery in the 86 relevant patients is set out in Table 8.3.9.1.

TABLE 8.3.9.1. INDICATIONS FOR OPERATIVE DELIVERY.

	CASES	CONTROLS	TOTALS
CEPHALOPELVIC DISPROPORTION	12	11	23
FETAL DISTRESS	18	12	30
ECLAMPSIA	1	1	2
PROLAPSED CORD	1	1	2
DELAYED ACTIVE PHASE	9	5	14
FETAL DISTRESS + PIH	2	3	5
POOR MATERNAL EFFORT	-	1	1
INTRAUTERINE GROWTH RETARDATION	-	1	1
MALPRESENTATION	1	-	1
ABRUPTIO	-	1	1
PLACENTA PREVIA	-	1	1
TOTALS	44	37	81

TABLE 8.3.9.2. INDICATIONS FOR OPERATIVE DELIVERY - PERCENT.

PERCENTAGES :	CASES	CONTROLS	TOTALS
CEPHALOPELVIC DISPROPORTION	27.3	29.8	28.4
FETAL DISTRESS	40.9	32.4	37.1
ECLAMPSIA	2.3	2.7	2.5
PROLAPSED CORD	2.3	2.7	2.5
DELAYED ACTIVE PHASE	20.4	13.5	17.3
FETAL DISTRESS + PIH	4.5	8.1	6.2
POOR MATERNAL EFFORT	-	2.7	1.2
INTRAUTERINE GROWTH RETARDATION	-	2.7	1.2
MALPRESENTATION	2.3	-	1.2
ABRUPTIO	-	2.7	1.2
PLACENTA PREVIA	-	2.7	1.2
TOTALS	100.0	100.0	100.0

8.3.1.12. Maternal Sedation.

The distribution of maternal sedation prior to delivery is set out in Table 8.3.10.1.

TABLE 8.3.10.1. MATERNAL SEDATION.

SEDATION	CASES	CONTROLS	TOTALS
NONE	45	36	81
PETHIDINE < 2HRS BD	6	5	11
PETHIDINE > 2HRS BD	11	10	21
VALIUM > 2HRS BD	-	1	1
MAGNESIUM SULPHATE	2	-	2
TOTALS	64	52	116

TABLE 8.3.10.2. MATERNAL SEDATION - PERCENTAGES.

SEDATION	CASES	CONTROLS	TOTALS
NONE	70.3	69.2	69.8
PETHIDINE < 2HRS BD	9.4	9.6	9.5
PETHIDINE > 2HRS BD	17.2	19.2	18.1
VALIUM > 2HRS BD	-	1.9	.9
MAGNESIUM SULPHATE	3.1	-	1.7
TOTALS	100.0	100.0	100.0

BD = Before delivery.

No significant differences could be shown between the two groups on Chi squared testing : 0.163 DF = 2.

8.3.1.13. Obstetricians Assigned Cause of Asphyxia.

The causes of asphyxia, as it is defined in this work, which were assigned in each case by the obstetrician are set out in Table 8.3.11.1.

TABLE 8.3.11.1. OBSTETRICIANS CAUSE OF ASPHYXIA.

CAUSE	CASES	CONTROLS	TOTALS
UNDETERMINED	14	15	29
CEPHALOPELVIC DISPROPORTION	31	16	47
PREGNANCY INDUCED HYPERTENSION	5	5	10
ECLAMPSIA	1	1	2
CPD + PIH	-	1	1
PROLAPSED CORD	-	1	1
CORD ROUND NECK	1	1	2
MATERNAL SEDATION	-	2	2
ABRUPTIO	3	2	5
MATERNAL INFECTION	1	1	2
INTRAUTERINE GROWTH RETARDATION	5	-	5
POST TERM	1	2	3
UTERINE INERTIA	-	1	1
PLACENTA PREVIA	-	1	1
MISSING	2	3	5
TOTALS	64	52	116

TABLE 8.3.11.2. OBSTETRICIANS CAUSE OF ASPHYXIA.

PERCENTAGES.

CAUSE	CASES	CONTROLS	TOTALS
UNDETERMINED	21.9	28.8	25.0
CEPHALOPELVIC DISPROPORTION	48.4	30.8	40.5
PREGNANCY INDUCED HYPERTENSION	7.8	9.6	8.6
ECLAMPSIA	1.5	1.9	1.7
CPD + PIH	-	1.9	.9
PROLAPSED CORD	-	1.9	.9
CORD ROUND NECK	1.5	1.9	1.7
MATERNAL SEDATION	-	3.8	1.7
ABRUPTIO	4.7	3.8	4.3
MATERNAL INFECTION	1.5	1.9	1.7
INTRAUTERINE GROWTH RETARD	7.8	-	4.3
POST TERM	1.5	3.8	2.6
UTERINE INERTIA	-	1.9	.9
PLACENTA PREVIA	-	1.9	.9
MISSING	3.1	5.8	4.3
TOTALS	100.0	100.0	100.0

No significant differences could be shown between the two groups on Chi squared testing : 6.270 DF = 5.

8.3.2. INFANTS' DATA.

8.3.2.1. Resuscitation of the Infant.

The distribution of the method of resuscitation required for each infant is set out in Table 8.3.12.1.

TABLE 8.3.12.1.RESUSCITATION.

METHOD	CASES	CONTROLS	TOTALS
NONE	19	12	31
OXYGEN	20	9	29
VENTILATION (MASK)	9	10	19
VENTILATION (ETT)	16	21	37
TOTALS	64	52	116

TABLE 8.3.12.2. RESUSCITATION - PERCENTAGES.

METHOD	CASES	CONTROLS	TOTALS
NONE	29.7	23.1	26.7
OXYGEN	31.3	17.3	25.0
VENTILATION (MASK)	14.1	19.2	16.4
VENTILATION (ETT)	25.0	40.4	31.9
TOTALS	100.0	100.0	100.0

Key : ETT = Endotracheal tube.

No significant differences could be shown between the two groups on Chi squared testing : 5.296 DF = 3.

8.3.2.2. Apgar Score at 5 minutes.

The mean (+- S.D.) 5 minute Apgar scores of the cases and controls were 7.75 (2.33) and 6.88 (2.59) respectively. This difference is not significant. (t=1.89 DF=114).

8.3.2.3. Sex of Infants.

The sex of the infants is set out in Table 8.3.13.

TABLE 8.3.13. SEX OF INFANTS

	CASES	CONTROLS	TOTALS
MALE	35	22	57
FEMALE	29	30	59
TOTALS	64	52	116

There was no significant difference in the distribution of sexes between cases and controls. (Chi square = 1.75 DF=1).

8.3.2.4. Birth Weight and Gestational age.

The data for these two parameters are set out in Table 8.3.14.

TABLE 8.3.14. BIRTH WEIGHT AND GESTATIONAL AGE.

	CASES		CONTROLS		t - TEST		
	MEAN	SD	MEAN	SD	t	N	SIG
BIRTH WEIGHT	3279	524	3251	477	0.296	116	NS
GESTATIONAL AGE	39.6	0.92	39.7	0.88	0.901	116	NS

SIG = Significance

8.3.2.5. Placental Chorionic Arterial Blood gas Determinations.

The values obtained for pH, pCO2 and base excess are set out in Table 8.3.15.

TABLE 8.3.15. PLACENTAL CHORIONIC ARTERIAL BLOOD GAS DETERMINATIONS.

	CASES		CONTROLS		t - TEST		
	MEAN	SD	MEAN	SD	t VAL	N	SIG
pH	7.072	.097	7.062	.116	0.463	116	NS
pCO2	7.98	3.17	7.18	1.94	1.577	115	NS
BASE EXCESS	-14.9	3.17	-15.8	4.39	1.148	116	NS

8.3.3. PHENOBARBITONE LEVELS.

It was intended to obtain phenobarbitone levels on all cases at 48-72 hours of age to confirm the therapeutic regimen. Unfortunately due to a power failure a number of deep frozen specimens were lost. 39 specimens were finally analysed out of a possible 64 cases.

The mean phenobarbitone level was 130.1 mmol/l (+-69.4) median 121 and range 21 to 378 mmol/l.

The mean age at sampling was 73.1 hours (+-32.8), median 71 and range 18 to 184 hours.

In order to see if the age at sampling was a important factor in the level of phenobarbitone a test of correlation was performed which showed found no association. R = -0.110.

8.3.4. OUTCOMES DURING THE INFANT'S STAY IN THE NURSERY.

8.3.4.1. Mortality.

Four infants, all in the control group, died in the early neonatal period. The difference between the 2 groups is significant. (Fisher's exact probability = 0.038). The details are set out below.

TABLE 8.3.16. DETAILS OF DEATHS IN EARLY NEONATAL PERIOD :

CASE No.	AGE AT DEATH	DETAILS OF ENCEPH.	FITS	TRAUMA	OTHER FEATURES
003	28 hrs	Hypotonia No PR Irregular respiration.	Onset 10 hrs	-	2nd twin
009	72 hrs	Hypotonia No PR	None	Caput L.Erb's Palsy.	Meconium aspir. CSF uniformly bloodstained
071	16 hrs	Hypotonia No PR	None	-	Meconium aspir.
121	5 hrs	Hypotonia No PR Irregular repiration.	None	-	-

Key: PR = Primitive reflexes.

8.3.4.2. Scores in the Prechtl Test at 48-72 hours.

The results of the Prechtl assessment were in two parts. Due to the nature of the test and its requirement that babies are in the correct state of arousal for each of the test items, it was impossible to carry out all the

items on any one baby. A "completeness score" indicates the number of items sucessfully carried out divided by the full number of items in the test expressed as a percentage. The "Prechtl score " is the number of points scored divided by the maximum possible number of points obtainable for the items tested.

Due to the author being on occasion unavailable to carry out the test, data is missing for 15 cases and 9 controls. The difference in missing data is not significant. Chi-squared (Yates) = 0.33 DF=1. The following data refers to the remaining 92 patients.

The data relating to the age in hours at performing the assessment, the completeness score and the actual scores are set out in Table 8.3.17. below.

TABLE 8.3.17. PRECHTL TEST SCORES.

	CASES		CONTROLS		t - TEST		
	MEAN	SD	MEAN	SD	t VAL.	N	SIG
AGE @ TEST	62.7	15.8	68.6	16.3	1.771	92	NS
% COMPLETE	62.1	13.5	63.6	10.9	0.611	92	NS
SCORES	50.8	12.9	65.2	15.9	4.780	92	<0.001

The cases scores significantly lower on the Prechtl assessment than did the untreated controls.

8.3.4.3. Neurological Examination at +- 48 hours.

This was carried out in 97 patients. The others being missing for reasons given in 8.3.4.2. above.

The mean (+-S.D.) age at carrying out the examination for the 2 groups was as follows :

CASES : 65.2 (21.2).

CONTROLS : 68.6 (15.9).

This difference is not significant. t = 0.903 N = 97.

The distribution of the result of the examination for each infant is set out in Table 8.3.18.1.

TABLE 8.3.18.1. NEUROLOGICAL STATE AT 48-72 HOURS.

	CASES	CONTROLS	TOTALS
NORMAL	4	21	25
PROBABLY NORMAL	5	13	18
PROBABLY ABNORMAL	7	2	9
ABNORMAL	36	9	45
MISSING	12	7	19
TOTALS	64	52	116

TABLE 8.3.18.2. NEUROLOGICAL STATE AT 48-72 HOURS

PERCENTAGES.

	CASES	CONTROLS	TOTALS
NORMAL	6.3	40.4	21.6
PROBABLY NORMAL	7.8	25.0	15.5
PROBABLY ABNORMAL	10.9	3.8	7.8
ABNORMAL	56.3	17.3	38.8
MISSING	18.8	13.5	16.4
TOTALS	100.0	100.0	100.0

It can be seen from Table 8.3.18.2. that more cases fell into the abnormal categories than did controls. This difference was highly significant on Chi squared testing : 33.935 DF = 2. p = < 0.001.

8.3.4.4. Biochemical Values.

The age in hours at sampling as well as the values for the biochemical parameters are set out below in Table 8.3.19. Data for 17 cases and 17 controls were not available. However the difference in the proportions of patients without data was not significantly different between cases and controls. (Chi square = 0.520 DF = 1).

TABLE 8.3.19. BIOCHEMICAL RESULTS.

	CASES		CONTROLS				
	MEAN	SD	MEAN	SD	t-VAL	N	SIG
Hours :							
AGE @ SAMPLING	68.3	30.7	70.4	27.7	0.313	80	NS
Mol/litre :							
SODIUM	136.7	5.9	141.0	4.1	3.624	81	<0.001
POTASSIUM	4.9	1.2	4.6	1.0	0.965	81	NS
UREA	6.8	3.3	4.1	3.5	3.643	82	<0.001
CREATININE	81.7	22.9	83.9	22.9	0.374	70	NS

8.3.4.5. Other Illness during Perinatal Period.

The occurence of other illness during the perinatal period is set out in Table 8.3.20.1.

TABLE 8.3.20.1. CONCURRENT ILLNESS IN THE NEONATAL PERIOD.

ILLNESS	CASES	CONTROLS	TOTALS
NONE	54	41	95
MECONIUM ASPIRATION	10	6	16
TRANSIENT TACHYPNOEA	-	3	3
SUBAPONEUROTIC HAEMORRAGE	-	1	1
APNOEA ? CAUSE	-	1	1
TOTALS	64	52	116

TABLE 8.3.20.2. CONCURRENT ILLNESS IN THE NEONATAL PERIOD. PERCENTAGES.

ILLNESS	CASES	CONTROLS	TOTALS
NONE	84.4	78.8	81.9
MECONIUM ASPIRATION	15.6	11.5	13.8
TRANSIENT TACHYPNOEA	-	5.8	2.6
SUBAPONEUROTIC HAEM.	-	1.9	.9
APNOEA ? CAUSE	-	1.9	.9
TOTALS	100.0	100.0	100.0

There were no significant differences in the occurence of other illness in the 2 groups . Chi square = 0.591 DF = 1.

8.3.4.6. Seizures.

The occurrence and timing of seizures in the nursery are set out in TABLE 8.3.21.1.

TABLE 8.3.21.1. SEIZURES IN THE NURSERY

	CASES	CONTROLS	TOTALS
NONE	63	44	107
@ 25-48 HRS	-	2	2
@ 13-24 HRS	1	1	2
@ 6-12 HRS	-	1	1
MISSING	-	4	4
TOTALS	64	52	116

TABLE 8.3.21.2. SEIZURES IN THE NURSERY - PERCENTAGES

	CASES	CONTROLS	TOTALS
NONE	98.4	84.6	92.2
@ 25-48 HRS	-	3.8	1.7
@ 13-24 HRS	1.6	1.9	1.7
@ 6-12 HRS	-	1.9	.9
MISSING	-	7.7	3.4
TOTALS	100.0	100.0	100.0

No significant difference could be demonstrated between cases and controls in regard to seizures.

Fisher's exact probability = 0.211

8.3.4.7. Jaundice.

The peak levels of total serum bilirubin in the nursery are set out in Table 8.3.22.1.

TABLE 8.3.22.1. NEONATAL JAUNDICE.

MMOL/L	CASES	CONTROLS	TOTALS
NIL-<150	64	41	105
150-199	-	4	4
200-249	-	1	1
250-299	-	2	2
MISSING	-	4	4
TOTALS	64	52	116

TABLE 8.3.22.2. NEONATAL JAUNDICE - PERCENTAGES.

MMOL/L	CASES	CONTROLS	TOTALS
NIL-<150	100.0	78.8	90.5
150-199	-	7.7	3.4
200-249	-	1.9	.9
250-299	-	3.8	1.7
MISSING	-	7.7	3.4
TOTALS	100.0	100.0	100.0

Seven controls developed a total serum bilirubin > 150 mmol/l while none of the cases did so. This difference was significant using Fisher's exact probability test p=0.002.

8.3.4.8. Age at Independent Feeding.

The ages at which babies were able to feed without nasogastric tube assistance are set out in Table 8.3.23.1.

TABLE 8.3.23.1. AGE AT INDEPENDENT FEEDING.

DAYS	CASES	CONTROLS	TOTALS
2	39	32	71
3	4	7	11
4	5	1	6
5	6	1	7
6	2	1	3
7-9	2	1	3
10	-	1	1
10+	2	1	3
MISSING	4	7	11
TOTALS	64	52	116

TABLE 8.3.23.2. AGE AT INDEPENDENT FEEDING - PERCENTAGES.

DAYS	CASES	CONTROLS	TOTALS
2	60.9	61.5	61.2
3	6.3	13.5	9.5
4	7.8	1.9	5.2
5	9.4	1.9	6.0
6	3.1	1.9	2.6
7-9	3.1	1.9	2.6
10	-	1.9	.9
10+	3.1	1.9	2.6
MISSING	6.3	13.5	9.5
TOTALS	100.0	100.0	100.0

There was no significant difference between cases and controls in this respect. Chi square = 2.190 DF = 3.

8.3.4.9. Age at Discharge from Nursery.

For the 112 infants who survived the mean (+-S.D) age in days on discharge from the nursery was as follows :

CASES : 7.92 (3.92) days. Range 3-21.

CONTROLS : 6.47 (4.21) days. Range 3-29.

This difference was not significant. t = 1.865 N = 112.

8.3.5. FOLLOW-UP :

Details of the deaths and losses from the trial are set out in Tables 8.3.24.1. and 8.3.24.2.

TABLE 8.3.24.1. FATE OF PATIENTS ENTERING TRIAL.

	CASES	CONTROLS	TOTAL
DIED IN NURSEY	0	4	4
DIED DURING YEAR	1*	1**	2
LOST TO FOLLOW UP	12	10	22
When last seen :			
Nursery	10	9	
6 week visit	2	1	
TOTAL DIED/LOST	13	15	28
FOLLOWED TO 1 YEAR	51	37	88
TOTALS	64	52	116

* Died at 25 weeks. ** Died at 34 weeks.

TABLE 8.3.24.2. FOLLOW UP RATE :

	CASES	CONTROLS	TOTALS
ORIGINAL No.	64	52	116
SEEN AT 1 YEAR	51	37	88
FOLLOW UP RATE	79.7%	71.2%	75.9%

There was no significant difference in the proportions of cases and controls that were lost to the trial. Chi square = 1.14 DF=1.

All the data that follows relates to the 88 patients who were sucessfully followed to 1 year of age.

8.3.5.1. Age at Follow up Visits.

The numbers of infants seen, and the mean ages in weeks at the various follow-up visits are set out in Table 8.3.25.

TABLE 8.3.25. AGE AT FOLLOW UP VISITS.

	CASES			CONTROLS			t - TEST		
VISIT	MEAN	SD	N	MEAN	SD	N	t VAL.	Tot	SIGN.
6 WEEKS	6.8	1.4	46	7.1	1.5	38	1.136	84	NS
3 MONTHS	13.3	1.7	49	13.3	1.5	35	0.113	84	NS
6 MONTHS	26.8	1.9	48	25.9	1.5	33	2.08	81	<0.05
9 MONTHS	39.7	2.3	42	39.3	2.8	31	0.662	73	NS
12 MONTHS	54.6	7.1	51	52.9	3.2	37	1.380	88	NS

8.3.5.2. Developmental Scores.

The mean percentage scores in the Denver Developmental Screening Test at the various follow-up visits are set out in Table 8.3.26.

TABLE 8.3.26. DEVELOPMENTAL SCORES AT FOLLOW-UP.

	CASES			CONTROLS			t - TEST		
VISIT	MEAN	SD	N	MEAN	SD	N	t VAL.	Tot	SGN
6 WEEKS	80.7	14.3	46	82.3	12.9	38	0.515	84	NS
3 MONTHS	88.3	10.5	49	86.9	13.3	34	0.540	83	NS
6 MONTHS	69.5	16.1	47	72.7	13.1	32	0.845	79	NS
9 MONTHS	80.7	15.3	42	81.6	13.1	30	0.256	72	NS
12 MONTHS	77.8	21.3	49	76.8	22.6	37	0.211	86*	NS

* = 2 cases were too old for the test items at 12 months.

No significant differences are demonstrated.

At the 12 month visit the number of items scheduled for testing in the Denver Developmental Screening Test was 12. The mean number tested (+-S.D.) was as follows :

Cases : 11.79 (+-0.49)

Controls : 11.59 (+-0.68)

t = 1.576 No significant difference.

Analysis of the numbers of completed items of the test at all the follow-up ages are given in Appendix VII.

8.3.5.3. Weight.

The mean weights in grams of the babies at the various follow-up visits are set out in Table 8.3.27.

TABLE 8.3.27. WEIGHT AT FOLLOW UP VISITS

	CASES			CONTROLS			t - TEST		
VISIT	MEAN	SD	N	MEAN	SD	N	t VAL.	Tot	SGN
6 WEEKS	4762	890	44	5027	817	37	1.370	81	NS
3 MONTH	6072	1158	48	6171	950	34	0.407	82	NS
6 MONTH	7929	1251	47	7930	1464	33	0.0006	80	NS
9 MONTH	9135	1667	41	9008	1316	29	0.343	70	NS
12 MONTH	10176	1647	49	9763	1567	36	1.165	85*	NS

* = 2 cases were too old to include their weights in the comparison. In one control the data were missing.

No significant differences were demonstrated.

8.3.5.4. Head Circumference.

The mean head circumferences in centimetres of the babies at the various follow-up visits are set out in Table 8.3.28.

TABLE 8.3.28. HEAD CIRCUMFERENCE AT FOLLOW UP.

	CASES			CONTROLS			t - TEST		
VISIT	MEAN	SD	N	MEAN	SD	N	t VAL.	Tot	SGN
6 WEEKS	38.7	2.2	45	39.5	1.6	38	1.711	83	NS
3 MONTH	41.3	1.6	47	41.6	1.6	34	0.852	81	NS
6 MONTH	44.1	1.8	46	44.3	1.9	33	0.289	79	NS
9 MONTH	45.7	1.9	39	46.1	1.8	29	0.343	68	NS
12 MONTH	46.9	1.7	49	46.8	1.9	37	0.101	86*	NS

* = 2 cases were too old as explained in Table 8.3.27.

No significant differences were demonstrated.

8.3.6. FINAL OUTCOMES AT 12 MONTHS.

The outcomes at 12 months for developmental score, weight and head circumference have been given above. No significant differences were demonstrated in any of these parameters. Other aspects of final outcome will be given below.

8.3.6.1. Neurolological and developmental Outcome.

Outcome is considered in terms of both neurology and development. In some cases both were abnormal, while in others only one was abnormal. These results are set out in Table 8.3.29. for cases, Table 8.3.30. for controls and in Table 8.3.31. for both combined.

TABLE 8.3.29. CASES : NEUROLOGICAL AND DEVELOPMENTAL OUTCOME.

		NEUROLOGICAL STATUS :		
		ABNORMAL	NORMAL	TOTALS
DEVELOPMENTAL STATUS :	PROBABLY ABNORMAL	4	3	7
	NORMAL	4	40	44
	TOTALS	8	43	51

TABLE 8.3.30. CONTROLS : NEUROLOGICAL AND DEVELOPMENTAL OUTCOME.

		NEUROLOGICAL STATUS :		
		ABNORMAL	NORMAL	TOTALS
DEVELOPMENTAL STATUS :	PROBABLY ABNORMAL	2	6	8
	NORMAL	2	27	29
	TOTALS	4	33	37

TABLE 8.3.31. ALL PATIENTS : NEUROLOGICAL AND DEVELOPMENTAL OUTCOME.

		NEUROLOGICAL STATUS :		
		ABNORMAL	NORMAL	TOTALS
DEVELOPMENTAL STATUS :	PROBABLY ABNORMAL	6	9	15
	NORMAL	6	67	73
	TOTALS	12	76	88

The identity of the patients in these tables is given in Appendix IV Tables. AX.IV.1 and 2.

8.3.6.2. Comparison of neurological and developmental outcomes.

Table 8.3.32. compares the neurological outcome of cases and controls.

TABLE 8.3.32. NEUROLOGICAL OUTCOMES.

	CASES	CONTROLS	TOTALS (%)
ABNORMAL	8	4	12 (13.6)
NORMAL	43	33	76 (86.4)
TOTALS	51	37	88 (100)

There was no significant difference between cases and controls in regard to neurological outcome. (Chi - squared with Yates' correction = 0.117 DF = 1).

Table 8.3.33. compares the developmental outcomes of cases and controls.

TABLE 8.3.33. DEVELOPMENTAL OUTCOMES.

	CASES	CONTROLS	TOTALS (%)
ABNORMAL	7	8	15 (17.4)
NORMAL	42*	29	71 (82.6)
TOTALS	49	37	86 (100)

Key : * = 2 cases were too old for the test items at 12 months.

There was no significant difference between cases and controls in regard to developmental outcome. (Chi - squared with Yates' correction = 0.360 DF = 1).

Table 8.3.34. compares the neurodevelopmental outcome of cases and controls.

TABLE 8.3.34. ALL NEURODEVELOPMENTAL OUTCOMES.

	CASES	CONTROLS	TOTALS	(%)
ABNORMAL	11	10	21	(23.8)
NORMAL	40	27	67	(76.2)
TOTALS	51	37	88	(100)

There was no significant difference between cases and controls in regard to any abnormal neurodevelopmental outcome. (Chi square = 0.351 DF=1).

8.3.6.3. Types of neurological abnormality.

The types of abnormal neurological outcome are set out in Table 8.3.35.

TABLE 8.3.35. DETAILS OF PATIENTS WITH ABNORMAL NEUROLOGICAL OUTCOME AT 12 MONTHS.

TRIAL No.	NEUROLOGICAL ABNORMALITY	ITEMS OF DDST PASSED
CASES :		
026	Moderately severe spastic quadri-paresis. Deaf.	0/12
036	Moderately severe quadriparesis.	4/12
054	Mild spastic quadriparesis.	1/12
079	Very mild hemiparesis	6/11
068	Squint	10/12
097	Mild spatic quadriparesis	9/12
116	Abnormally brisk arm and leg tendon reflexes.	8/11
123	Abnormally brisk arm and leg tendon reflexes.	11/12
CONTROLS :		
030	Microcephalic, severe spastic quadriparesis	0/12
088	Moderately severe spastic quadriparesis	0/12
008	Abnormally brisk arm tendon reflexes.	8/10
059	Mild spastic quadriparesis.	10/11

8.3.6.4. Hearing.

The details of hearing at the final examination is shown in Table 8.3.36.1.

TABLE 8.3.36.1. HEARING AT 1 YEAR.

HEARING	CASES	CONTROLS	TOTALS
NORMAL	45	34	79
PROBABLY NORMAL	1	-	1
PROBABLY ABNORMAL	-	1	1
ABNORMAL	4	2	6
MISSING	1	-	1
TOTALS	51	37	88

TABLE 8.3.36.2. HEARING AT 1 YEAR - PERCENTAGES.

HEARING	CASES	CONTROLS	TOTALS
NORMAL	88.0	91.9	89.9
PROBABLY NORMAL	2.0	-	1.1
PROBABLY ABNORMAL	-	2.7	1.1
ABNORMAL	8.0	5.4	6.8
MISSING	2.0	-	1.1
TOTALS	100.0	100.0	100.0

No significant differences could be demonstrated. Fisher's exact probability = 1.33.

8.3.6.5. Seizures over Follow-up Period.

The details of the occurence of seizures over the whole 12 month follow-up period are shown in Table 8.3.37.1.

TABLE 8.3.37.1. SEIZURES AT 1 YEAR.

	CASES	CONTROLS	TOTALS
NONE	50	35	85
ONCE ONLY	–	1	1
TWICE	–	–	–
> TWICE	1	1	2
TOTALS	51	37	88

TABLE 8.3.37.2. SEIZURES AT 1 YEAR - PERCENTAGES.

	CASES	CONTROLS	TOTALS
NONE	98.0	94.6	96.6
ONCE ONLY	–	2.7	1.1
TWICE	–	–	–
> TWICE	2.0	2.7	2.3
TOTALS	100.0	100.0	100.0

No significant differences could be demonstrated. Fisher's exact probability = 0.760.

8.4. DISCUSSION.

8.4.1. PATIENTS AND METHODS :

8.4.1.1. Criteria for entry into the trial :

The literature review on criteria of asphyxia revealed a wide lack of uniformity. Apgar scores, placental acid-base, time to spontaneous respiration as well as the occurence and severity of encephalopathy have all been used. It is clear that no one criterion will be adequate and the newer combination schemes of Low et al (1983) and Rothberg et al (1986) take this into account. The use in this trial of a combination of biochemical and clinical criteria was in response to this newer and more rational view of asphyxia which goes beyond a low Apgar score at the time of birth and tries to detect infants who have experienced significant intrauterine hypoxia. The choice of the placental arterial base excess as the biochemical criterion was because it has been used in a number of previous studies as described in Chapter 3, and it was easily available in the working environment. The 5 minute Apgar and evidence of fetal distress are similarly well documented criteria.

De Sousa et al (1983) reported that the combination of a low umbilical venous pH and low Apgar Score was able to predict infants who would be abnormal neurologically in the neonatal period very much better than either

criterion taken alone. A similar combination of criteria was used here in order to select infants with a significant metabolic acidosis plus either depression at birth or evidence of fetal distress. The fact that only 20 - 30 % of the controls were neurologically abnormal at 48-72 hours indicates that a group of relatively mildly affected infants were selected. In a sense one would have liked to have chosen only those who were going to develop overt encephalopathy but to wait until the infant shows signs of encephalopathy before giving the protective agent is to negate its possible protective role. Equally in the routine situation one has to start treatment for asphyxia immediately after birth on the basis of some objective criteria rather than wait for the onset of seizures or other indication of encephalopathy.

8.4.1.2. Dosage regimens.

The literature review of dosage of phenobarbitone indicated that authors such as Jalling (1975), Lockman et al (1979) and Donn et al (1985) have found that a loading dose of 15mg/kg given intravenously will produce a peak level of about 195 mmol/l within a few minutes of administration and be well sustained for 24 hours at least. The finding in this study of a mean phenobarbitone level of 130 mmol/l at a mean sampling time of 73.1 hours fits in well with these previous findings. It is of note that no previous study has

related a barbiturate blood level to its protective effect after asphyxia either in human or experimental animal work. The blood levels achieved here are in the range found to be anticonvulsant but what relationship that level has to brain protective levels is not known.

The literature review also showed that the dose of dexamethasone used in this study (2 mg/Kg/24hrs) is relatively small when compared to the doses that have been used in this situation in experimental animals. The Manchester group of DeSousa and Dobbing (1973) used 20-40mg/Kg in rats. The human infant has however been shown to respond to a dose of 4 mg with reduction in measured intracranial pressure by Levene and Evans (1985).

8.4.1.3. Use of Placental chorionic arterial sampling for fetal acid-base status :

The use of placental arterial sampling to assess fetal acid base status has been reported by Rothberg et al (1986) and Bolton (1985). Sykes et al (1982) in their very large study on neonatal acid- base status used the arterial side of umbilical cord segments. Furthermore it appears to be in order to sample from the placental vessels for a period after delivery. Woods et al (1986) have shown that the acid base values in placental arterial samples are well preserved for up to 10 minutes after normal delivery of the placenta.

8.4.1.4. Neurodevelopmental Evaluation.

The method chosen to evaluate the neurological status of the infants at 48-72 hours of age was that of Prechtl (Prechtl 1977). This is a detailed neurological assessment taking about 30 minutes to carry out, but is useful for two main reasons. Firstly it has a large number of test items and secondly it takes into account the state of arousal of the infant in that he/she must be in the correct state for each item. Test schemes without these 2 features can easily provide a false picture of a newborn infant's neurological state. This requirement inevitably means that not every item can be carried out on every infant. Nevertheless the large number of related test items provides enough testable items to obtain a reliable assessment. The main purpose of the test in this trial was to compare the neurological state of the 2 groups rather than to document the absolute condition of each infant. The scoring system devised for use in this trial was intended to provide a means of expressing the neurological state numerically and is not part of Prechtl's original scheme. It showed that there was no difference in the number of test items completed in the two groups but that there was a significant difference in the neurological state as measured by the test items.

For the follow-up visits and the final assessment at 12

months of age the Denver Developmental Screening Test (Frankenburg and Dodds 1967) was used. It was chosen because it is a relatively simple scheme which could easily be taught to the nursing staff who made the home visits. Furthermore the author, who is a general, rather than a neurodevelopmental, paediatrician felt that it was more appropriate to his level of skill than more specialised schemes. The method of expressing the scores for this test needs some comment. The orthodox method would have been to use the whole test at each follow up visit and express the result as a developmental quotient. This was difficult for practical reasons. The often crowded and noisy home situation, both in township and rural areas usually did not lend itself to the performance of an "all item" test. Therefore a form containing all the items relevant to the age of the visit was used. The score for each visit was taken as the number of items passed, divided by the number of items tested, expressed as a percentage. This was an adaptation of the test to the local practical situation.

The decision to follow up for only 1 year was taken mainly for practical reasons. Amiel-Tison and Ellison (1986) reviewing the age of appearance of handicap after perinatal asphyxia, conclude that very few new cases of major neurological deficit will be found after the first year of life, although lesser degrees of

handicap will continue to be found with increasing age. This is relevant to the decision to follow up for 1 year which period was chosen as a compromise between practicality and sensitivity.

8.4.2. RESULTS :

8.4.2.1. Comparability.

This set of comparisons of cases and controls serves to show that in all respects, other than the use of phenobarbitone and dexamethasone, the cases and controls were highly comparable. These included :

* Maternal age
* Gravidity and Parity
* Antenatal care useage
* Complications of pregnancy
* Presentation
* Occurence of fetal distress
* Complications of labour
* Duration of the first stage of labour
* Method of delivery
* Indications for operative delivery
* Placental weight
* Maternal sedation
* Obstetricians designated cause of asphyxia
* Birth weight
* Resuscitation
* Placental arterial acid base values.

8.4.2.2. Phenobarbitone levels :

These refer to cases only. As explained in the results section, 25 specimens were lost in a power failure.

Nevertheless but it is felt reasonable to assume that this was a random event and that the surviving specimens are as representative as those that were lost.

There was quite a wide range of phenobarbitone levels obtained with a range of 21 to 378 mmol/l resulting from the same dosage. This is in agreement with Jalling (1975) who found marked patient to patient variability in the half life of phenobarbitone and furthermore that this varied from day to day in the same patient. It may be that in further studies more frequent phenobarbitone levels would need to be done to document therapeutic levels in each patient. Nevertheless levels thought to be anticonvulsant were achieved in most cases.

8.4.3. NEONATAL OUTCOMES :

In the period of stay in the nursery a number of significant differences were found between the cases and controls. These were:

* Mortality - Untreated higher.
* Prechtl test at 48-72 hours
  - Treated more depressed.
* Neurological evaluation at 48-72 hours
  - Treated more abnormal
* Occurence of neonatal jaundice - Treated less

* Biochemical values - Sodium - Treated lower
  Urea - Treated higher

In the nursery other outcomes were no different. These were :

* Occurence of other illnesses in the nursery period.
* Occurence of seizures.
* The age at independent feeding.
* The age at discharge from the nursery.
* Biochemical values - Potassium
  - Creatinine

A similar reduction in neonatal mortality was seen in the study of Svenningsen et al (1982) which was a prospective trial of an intensive care package which included vigourous ventilation, phenobarbitone, dexamethasone and lasix given to cases as compared to the routine supportive care given to controls. The infants were very much more severely asphyxiated than those in the present study in that they were chosen by their failure to establish regular respiration at 30 minutes. They found a neonatal mortality reduction in that 0/14 of the treated cases died as compared to 5/16 in controls. This is a similar effect to that seen in this trial but there were additional items of treatment in their regimen and so direct comparisons are

difficult. These differences have been discussed in Chapter 7.

The reduction in immediate mortality with no difference in the long term neurological deficits in survivors found in the trial was interestingly similar to the experimental work in adult cats by Todd et al (1982) discussed in section 7.4.1.5.

The difference both in the Prechtl and in the conventional neurological state at 48-72 hours is not surprising in view of the presence of therapeutic blood levels of phenobarbitone. Some degree of depression is to be expected.

Similarly to be expected was the fact that there were fewer cases of significant jaundice among the treated infants considering the well known effect of phenobarbitone in inducing the liver enzyme glucuronyl transferase (Conney 1967 & Trolle 1968).

The effect of treatment upon the serum sodium and urea is less easy to explain. One might speculate that the steroid effects of dexamethasone may have increased the intravascular volume leading to a minor reduction in serum sodium as was seen. Also that by increasing body catabolism the blood urea may have been raised.

There were proprtionately fewer cases of seizures among the treated infants but the difference was small and

did not reach statistical significance. This effect may well have been real as even though the number of patients having seizures was small the trend was visible. The low incidence of fits in such a group of infants is surprising. A possible explanation for this is that the selection criteria defined a very mildly affected group. However the 23.8% incidence of neurodevelopmental abnormality found at 1 year for the group as a whole would not support this. A real possibility also exists that in an often crowded and busy neonatal unit such as ours, subtle neonatal seizures might be missed by mothers and staff and that the true incidence is higher than recorded here.

8.4.4. LATER FOLLOW UP.

At the final 12 month visit 88 (75.9%) out of the original 116 patients were examined . As stated in the results section there was no difference in the numbers lost between the two groups. It is a possibility that at least some of the infants who were lost to follow up, died. It must be emphasised that in that case, they must have first moved away from their last address without our knowlege as deaths at known addresses were all accounted for.

At 12 months there were no significant differences between the two groups in respect of :

* Death
* Developmental scores at all follow-up stages
* Growth parameters - Weight
  - Head circumference
* Neurological status
* Hearing status
* Occurence of seizures

The lack of difference in the long term outcome between these two groups is perhaps suprising in view of the differences seen in the neonatal period. The possibility exists that an effect of the regimen was present but could not be demonstrated for methodological reasons. There are three obvious variables which might have made a difference :

(a) Dose of agents. The dose of phenobarbitone chosen in this study was that conventionally used for stopping seizures in the human neonate. It is possible that one might need to use much higher doses of the agent to achieve protection. In animal exerimental work pentobarbitone rather than phenobarbitone has been used in doses of 20mg/Kg. Unfortunately no animal study has included blood levels of barbiturate but protective benefits have been demonstrated at these doses. Guidance from human studies is also very scanty. The

only other prospective study of the use of phenobarbitone in the asphyxiated human term infant is that of Svenningsen et al 1982 who used a loading dose of 10mg/Kg IV of phenobarbitone and 10mg/Kg daily thereafter. This regimen produced peak levels of 150-350mmol/l at 48-72 hours after delivery and the authors demonstrated a protective effect for phenobarbitone in combination with a number of other agents and treatments.

The dose of dexamethasone used by Svenningsen et al 1982 was 2mg IV 6 hourly. This is very similar to the 0.5 mg/kg IV 6 hourly in the present study.

(b) Severity of asphyxia : The protective effect of an agent in a mild insult will clearly be more difficult to document than in a more severe one. The patients selected into this trial were much less severely affected than were those of Svenningsen et al (1982) who chose patients who had failed to establish spontaneous respiration by 30 minutes. The severity in that trial was reflected by a mortality of 30% at 1 year as compared to 5% in this trial. It is possible that if the selection criteria had been more severe an effect may have been shown.

(c) Length of follow-up. Patients were only followed for 1 year and it is likely that a longer follow up

period would allow more subtle developmental defects to become detectable. Measurable differences between the groups might then appear.

8.4.5. OUTCOME OF GROUP AS A WHOLE :

Although it was not one of the original aims of this study, it is of interest to summarise the outcome of a group of 116 infants selected as being asphyxiated by these criteria in terms of mortality and neurological outcome at 1 year.

The neonatal mortality was 4 out of 116 infants (3.4%). It is interesting to compare this mortality to figures from other follow-up studies of asphyxia as reviewed in Chapter 4 Table 4.3.1. The report of Nelson and Ellenberg (1981) is from the large and authoritative "Collaborative Study of Cerebral Palsy, Mental Retardation and other Neurological and Sensory Disorders of Infancy and Childhood " from the US National Institute Of Neurological and Communicative Disorders and Stroke. The collaborative study looked at the outcome of a complete grid of possible Apgar scores. Scores of 0-3 at 1 minute were associated with a 1 st year mortality of 5.6% which was very similar to that in this study. Most of the other studies included in Table 4.3.1. show very much higher mortalities. Typical of this pattern is the study from Cape Town of Molteno (1976) who used a selection criterion of Apgar

score at 1 minute of 3 or less and found a mortality of 13%.

In the present study, at 1 year the neurological abnormality picture was that 3 (3.4%) infants had severe neurological disorders and 9 (10.2%) had milder neurological deficits. A further 9 (10.2%) had abnormal developmental scores but no hard neurological findings. Overall therefore 23.8% had some degree of neurodevelopmental abnormality.

Again it is interesting to compare the outcome in terms of the rate of severe neurological deficit. Reference to Table 4.3.1. will show that Nelson and Ellenberg (1981) from the collaborative study give a figure of 1.5% associated with the Apgar 0-3 at 1 minute. Molteno (1976) gives a figure of 5.5% with similar selection criteria to Nelson and Ellenberg. The present study found a rate of 3.4%. Many other studies have given figures of that order.

It seems that in comparison to many of the reported follow up studies of asphyxia neonatorum, this study gives a very similar rate of severe neurological deficit but a much lower mortality. The main but important exception to these other studies is part of the collaborative study from the US. The reasons for this discrepancy are not clear but it must be restated that until more uniformity of selection criteria is

obtained it will remain very difficult to compare studies meaningfully.

That asphyxia in the term infant leads mainly to spastic quadriparesis is supported by the findings in this study. Of the 12 infants with hard neurological deficits 9 had various degrees of spastic quadriparesis. Only 3 did not have this type of lesion. All 3 of the severly affected children had spastic quadriplegia, one of whom had associated microcephaly. A review of studies giving the types of cerebral palsy resulting from perinatal asphyxia is set out in Table 2.4.2. The table shows that the commonest outcome was spastic quadriparesis varying from 20 to 70 % of the total. The present study yielded 9/12 or 75% spastic quadriparesis.

8.5. CONCLUSIONS :

8.5.1. A treatment regimen consisting of phenobarbitone and dexamethasone given to asphyxiated term neonates was shown to have the following effect :

* A significant reduction in neonatal mortality.
* Neurological depression at 48-72 hours.
* A significant reduction in neonatal jaundice.
* Alteration in some biochemical values
  - Serum sodium was reduced slightly.
  - Blood urea was slightly raised.

8.5.2. There were no differences between treated and control groups in respect of growth or development.

8.5.3. At final evaluation at one year there was no significant difference between treated and control groups with respect to the occurence of objective neurological abnormality or developmental criteria.

8.5.4. The outcome of a group of term infants selected as being asphyxiated on the basis of a placental arterial base excess of >11 AND either an 5 minute Apgar score of <7 or objective signs of fetal distress was as follows :

Neonatal mortality - 4/116 (3.4%)

1 year outcome :

Severe neurological deficits	- 3/88	(3.4%)
Minor neurological deficits	- 9/88	(10.2%)
Delayed development only	- 9/88	(10.2%)
All neurodevelopmental deficits	- 21/88	(23.8%)

8.5.5. The pattern of resulting abnormal neurological outcome was such that 9/12 (75%) had spastic quadriparesis.

This final chapter reviews the extent to which the hypotheses advanced at the outset of this study can be accepted. It also makes some general conclusions and points out where the findings may lead in the future.

9.1. FIRST HYPOTHESIS.

"ASPHYXIA NEONATORUM IS THE LEADING ASCERTAINABLE CAUSE OF CEREBRAL PALSY AMONG HANDICAPPED CHILDREN IN DEVELOPING COMMUNITIES IN SOUTHERN AFRICA."

For the area of the Ciskei studied, the leading ascertainable cause of cerebral palsy was asphyxia and so this hypothesis is accepted. How far it is true for similar communities is less certain but the scanty literature from similar areas suggests that a similar situation exists there too.

The severity of the difficulties faced by the parents of a handicapped child in the urban areas of the developing world cannot be overemphasised. Community faciliies for managing the problems of the handicapped are very inadequate. The much vaunted "extended family network" which is said to look after these children, is largely a myth in the urban situation.

The literature shows that spastic quadriparesis is the leading form of cerebral palsy following hypoxic ischaemic encephalopathy. This is bourne out in the

present study. It seems reasonable to assume that in a community in which spastic quadriparesis is the dominant form of cerebral palsy, one may be reasonably confident that asphyxia is unduely prevalent and that active steps to prevent it should be taken.

9.2. SECOND HYPOTHESIS .

"DATA ON THE EPIDEMIOLOGY OF ASPHYXIA NEONATORUM WILL BE HELPFUL IN LIMITING THE UNDUELY HARMFUL EFFECTS WHICH THIS CONDITION IS HAVING IN DEVELOPING COMMUNITIES AT PRESENT."

A number of factors in the antenatal and intrapartum periods have been shown to be significantly associated with asphyxia. In that a number of these are amenable to intervention, this hypothesis is accepted.

The importance of antenatal care was highlighted as was the particularly vulnerable position of the primiparous woman. The antenatal detection of cephalopelvic disproportion and of disorders associated with utero-placental dysfunction is particularly important. During labour the early detection and active management of fetal distress is crucial. It is likely that the association of prolonged first stage of labour and operative delivery with asphyxia was due to the consequences of cephalopelvic disproportion and placental disorders.

All of the above factors are amenable to good obstetric care presently available in theory if not in practice. The challenge is to make such care easily available to as many women as possible and to get them to make use of such services. This involves the planning and creation of appropriate obstetric services, particularly at primary care level and the training of medical and midwifery staff. During this training particular emphasis needs to be laid on the disorders associated with asphyxia.

The occurence of a sizable group of cases of asphyxia in which no clear cause could be found by the attending obstetrician, leads to speculation as to the existence of a group of disorders, presumably utero-placental, that are as yet unrecognized. This surely represents a great investigational challenge for the disipline of obstetrics.

The fact that the quality of obstetric care is traditionally measured only in terms of mortality has resulted in a relative insensitvity of obstetricians and midwives to outcomes of pregnancy that may be more disastrous than perinatal death, namely the survival of severely physically and mentally handicapped children. It is suggested that the routine use of an index involving the incidence of perinatal asphyxia would provide an ongoing assessment of this problem. Such

monitoring might lead to a more active approach to this disastrous disorder.

9.3. THIRD HYPOTHESIS.

"DATA ON THE EFFICACY OF TREATMENT REGIMENS FOR ASPHYXIA NEONATORUM WILL BE HELPFUL IN LIMITING THE UNDUELY HARMFUL EFFECTS THAT THIS CONDITION IS HAVING IN DEVELOPING COMMUNITIES AT PRESENT".

The treatment regimen used in the therapy trial did not make a significant difference to the long term neurodevelopmental outcome of survivors. In view of this the hypothesis cannot be accepted. However it is possible that with higher dosages of phenobarbitone a protective effect may be demonstrated in future trials. Work that has been published since this study was undertaken has indeed proceeded along these lines. Other protective agents may emerge in future and that some form of therapeutic intervention may be found to be beneficial remains a strong and desirable possibility.

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APPENDICES

APPENDIX I : SCHEMES FOR GRADING HYPOXIC-ISCHAEMIC ENCEPHALOPATHY.

TABLE AX.I.1. SARNAT SCHEME FOR GRADING ENCEPHALOPATHY.

ITEM	STAGE 1	STAGE 2	STAGE 3
Level of consciousness	Hyperalert	Lethargic	Stuporose
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermit. decerebr.
Stretch reflexes	++++	++++	- or absent
Suck	Weak	Weak or abs	Absent
Moro	Strong	Weak	Absent
Oculovestibular	Normal	++++	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized Parasymp.	Both depressed
Pupils	Mydriasis	Miosis	Variable
Heart rate	++	--	+-
Bronchial & salivary secretions	--	++	+-
GIT motility	N or -	++++	+-
Seizures	None	Common focal or multifocal	Uncommon excl. decer.
EEG	Normal	delta/theta later - periodic	periodic later - isopot-ential
Duration	< 24 hr	2-14 days	Hrs -wks

From Sarnat and Sarnat (1976).

Amiel-Tison and Ellison (1986) propose a scheme with 3 stages of severity each with a subdivision.

Stage I : Characterized by hyperexcitability and mild abnormalities of tone. Subdivision is by duration of symptoms for more or less than 7 days.

Stage II : Deepening CNS depression defined as lethargy or light coma. Subdivision is on the occurrence of seizures.

Stage III : Deep coma. Subdivision is by presence of brain stem signs especially the occulovestibular response.

The authors also classify the special investigations usually asociated with the vaious degrees of encephalopathy :

TABLE AX.I.2. SPECIAL INVESTIGATIONS ASSOCIATED WITH GRADES OF ENCEPHALOPATHY.

	Stage I		Stage II		Stage III	
	a	b	a	b	a	b
NMR	N	? Abn	? Abn	Abn	Mod to sev Abn.	
CT scan	N		Abn		Mod to sev Abn.	
Ultrasound	N		Abn		Mod to sev Abn.	
EEG	N		Mild Abn		Severe Abn.	
BAER	N		N		N	Abn

Key : NMR Nuclear magnetic resonance.
BAER Brainstem auditory evoked response.
Abn Abnormal.

TABLE AX.I.3. FENICHIEL SCHEME FOR GRADING ENCEPHALOPTHY.

MILD	:	Minor disturbances of tone, hyperalertness, and slight feeding difficulties recovering by 48 hours after birth.
MODERATE	:	Lethargy, more pronounced abnormalities of tone, poor feeding and convulsions with signs of recovery by 7 days.
SEVERE	:	Coma, failure to maintain adequate ventilation, profound hypotonia and seizures.

From Fenichiel (1983).

TABLE AX.I.4. BROWN SCHEME FOR GRADING ENCEPHALOPATHY.

Brown used a large number of neurological and other parameters to characterise degrees of encephalopathy. In relating outcome to severity of encephalopathy he used patterns of muscle tone as follows :

Flexor - extensor - extensor/hypotonia - hypotonia.

From Brown et al (1974).

APPENDIX II : COMBINATION SCHEMES FOR DEFINITION OF ASPHYXIA.

TABLE AX.II.1. LOW'S COMBINATION SCHEME FOR DEFINING ASPHYXIA.

Stage 1A : Fetal metabloic acidosis.

Children with evidence of fetal metabolic acidosis of a significant degree (umbilical artery buffer base of <34 mEq/L) and duration as defined by intrapartum acid-base measures. The diagnosis of fetal metabolic acidosis may be supported by evidence of hypoxemia, hypercarbia, and hyperlactemia with an increased lactate-pyruvate ratio.

Stage 1B : Fetal metabolic acidosis plus newborn depression.

Children with evidence of significant fetal metabolic acidosis with evidence of fetal depression as expressed by an Apgar score at 1 minute <3 and at 5 minutes <7 and/or respiratory delay >5 minutes requiring assisted ventilation.

Stage 2 : Fetal metabolic acidosis plus neonatal encephalopathy.

Children with evidence of significant fetal metabolic acidosis and neonatal encephalopathy as expressed by abnormal neurological signs in respect to consciousness, tone, seizures, primitive reflexes and autonomic nervous system function.

From Low et al (1983).

TABLE AX.II.2. ROTHBERG'S COMBINATION SCHEME FOR DEFINING ASPHYXIA.

	Clinical Features	Apgar Scores.
Grade 1 :	TSR<5 min +- brief IPPR	1 min <4 and/or 5 min <7
Grade 2 :	TSR>5 min requiring IPPR +- cardiac support and resusc. medications.	1 min <4 and/or 5 min <7 rapid recovery - 7-10 @ > 15 min.
Grade 3 :	TSR> 5 min, continued IPPR +- cardiac support and resusc medications.	1 min <4 and/or 5 min <7 and/or persistently low scores - <7 @ >15 min.
Grade 4 :	Above plus neonatal encephalopathy (continued IPPR, seizures, altered consciousness, autonomic dysfunction).	As for Grade 3.

* This scheme takes note of the fact that Acid-base measurements are not always or even often available.

Key :

TSR Time to sustained respiration
IPPV Intermittent positive pressure ventilation.

From Rothberg et al (1986).

APPENDIX III - CRITERIA FOR REFERRAL OF OBSTETRIC PATIENTS FOR HOSPITAL DELIVERY.

REFERRAL CRITERIA :

1. AT BOOKING

1.1. MEDICAL INDICATIONS

Diabetes
Cardiac disease
Known hypertension
Renal disease
Active Tuberculosis

1.2. OBSTETRIC INDICATIONS

Previous caesarian section
Previous stillbirth
Previous neonatal death
Previous instrumental delivery
Previous congenital abnormality
Previous premature delivery
Previous pre-eclampsia/eclampsia
Previous baby >4 Kg
Family history of diabetes
Palpation/dates discrepancy

2. FROM ANTENATAL CLINIC

If any of above conditions present
Glycosuria on 2 occasions
Hypertension with or without proteinuria
Proteinuria (2+) with or without hypertension
A.P.H.
Abnormal lie at 36 weeks
Rhesus or ABO antibodies
Anaemia - Hb =< 8 G%
Hb =< 9 G% if no response to iron
Rupture of membranes
Multiple pregnancy at 28 weeks

3. IN LABOUR

Primigravida
Multigravida (G4 and above)
Previous post partum haemorrhage
Delay
Bleeding
Hypertension
Preterm labour
Meconium stained liquor
Fetal distress
Intrauterine death
Abnormal lie
All patients seen in hospital during antenatal clinic and assessed for hospital delivery.

Note : The above are referred only if the clinic is sure that the patient will not deliver before arrival in hospital.

From Dr.R.Jones Department of Obstetrics - Cecilia Makiwane Hospital.

APPENDIX IV - IDENTITY OF PATIENTS WITH ABNORMAL NEURODEVELOPMENTAL OUTCOMES AT 12 MONTHS.

TABLE AX IV.1. CASES : ABNORMAL NEUROLOGICAL AND/OR DEVELOPMENTAL OUTCOME. TRIAL IDENTITY NUMBERS.

		NEUROLOGICAL STATUS		
		ABNORMAL	NORMAL	TOTALS
DEVELOPMENTAL STATUS :	PROBABLY ABNORMAL	026 036 054 079	084 070 136	7
	NORMAL	068 097 116 123		4
	TOTALS	8	3	11

TABLE AX IV.2. CONTROLS : ABNORMAL NEUROLOGICAL AND/OR DEVELOPMENTAL OUTCOME. TRIAL IDENTITY NUMBERS.

		NEUROLOGICAL STATUS		
		ABNORMAL	NORMAL	TOTALS
DEVELOPMENTAL STATUS :	PROBABLY ABNORMAL	030 088	007 017 031 082 092 103	8
	NORMAL	008 059		2
	TOTALS	4	6	10

APPENDIX V COMPOSITION OF "NEONATALYTE - SABAX"

Neonatalyte is an intravenous fluid preparation intended for use in the neonatal period. Its composition is as follows in millimoles per 1000 ml. :

Sodium	20
Potassium	15
Calcium	2.5
Magnesium	0.5
Chloride	21
Lactate	20
Phosphate	3.75

In addition it contains dextrose, 100gm per litre (10%).

Manufactured by SABAX Johannesburg.

APPENDIX VI RANGES OF DATA IN THERAPY TRIAL

TABLE AX.VI.1. RANGES FOR ANTENATAL CARE USE

	CASES	CONTROLS
BOOKING WEEKS	16-42	16-36
NUMBER OF VISITS	1-14	2-15
WEEKS AT LAST VISIT	35-43	36-41

(see TABLE 8.3.3.)

TABLE AX.VI.2. RANGES FOR BIRTH WEIGHT AND GESTATIONAL AGE.

	CASES	CONTROLS
BIRTH WEIGHT - Gms.	1970-4430	2400-4600
GESTATIONAL AGE - Wks.	38-43	38-42

(see TABLE 8.3.14.)

TABLE AX.VI.3. RANGES FOR PLACENTAL CHORIONIC ARTERIAL BLOOD GAS DETERMINATIONS.

	CASES	CONTROLS
pH	6.69 - 7.225	6.827 - 7.24
BASE EXCESS	11.10 - 25.9	11.3 - 29.3
pCO2	4.06 - 19.67	3.82 - 13.11

(see TABLE 8.3.15.)

TABLE AX.VI.4. RANGES FOR PRECHTL TEST SCORES.

	CASES	CONTROLS
Hours : AGE AT TESTING	43 - 120	40 - 120
% COMPLETE	23.7 - 99.0	26.3 - 84.0
SCORE	22.0 - 99.0	22.2 - 90.0

(see TABLE 8.3.17.)

TABLE AX.VI.5. RANGES FOR BIOCHEMICAL RESULTS

	CASES	CONTROLS
Hours : AGE AT SAMPLING	35 - 184	43 - 168
MMol/litre :		
SODIUM	124 - 145	131 - 148
POTASSIUM	3.3 - 9.4	3.1 - 7.9
UREA	1.3 - 14.7	1.2 - 20.8
CREATININE	38 - 130	55 - 161

(see TABLE 8.3.19.)

TABLE AX.VI.6. RANGES FOR AGES AT FOLLOW UP VISITS (Weeks).

	CASES	CONTROLS
6 WEEKS	4 - 11	5 - 13
3 MONTHS	10 - 19	9 - 18
6 MONTHS	25 - 35	24 - 32
9 MONTHS	35 - 48	36 - 45
12 MONTHS	47 - 65	47 - 63

(see TABLE 8.3.25.)

TABLE AX.VI.7. RANGES FOR SCORES AT FOLLOW UP VISITS

	CASES	CONTROLS
6 WEEKS	7.0 - 100.0	40.0 - 100.0
3 MONTHS	53.8 - 100.0	61.5 - 100.0
6 MONTHS	20.0 - 93.3	43.3 - 93.3
9 MONTHS	23.0 - 100.0	0.0 - 100.0
12 MONTHS	0.0 - 100.0	0.0 - 100.0

(see TABLE 8.3.26.)

TABLE AX.VI.8. RANGES FOR WEIGHT AT FOLLOW UP VISITS (GMS).

	CASES	CONTROLS
6 WEEKS	2750 - 6500	3400 - 7000
3 MONTHS	3600 - 8600	4000 - 8120
6 MONTHS	5500 - 11000	5200 - 10900
9 MONTHS	5500 - 14400	6000 - 12000
12 MONTHS	6000 - 14500	6200 - 14000

(see TABLE 8.3.27.)

TABLE AX.VI.9. RANGES FOR HEAD CIRCUMFERENCE AT FOLLOW UP VISITS (CMS).

	CASES	CONTROLS
6 WEEKS	32.0 - 45.0	36.0 - 42.0
3 MONTHS	37.0 - 45.0	39.0 - 45.0
6 MONTHS	40.0 - 48.5	39.0 - 48.0
9 MONTHS	43.0 - 51.0	42.0 - 50.0
12 MONTHS	43.5 - 51.5	42.0 - 50.0

(see TABLE 8.3.28.)

APPENDIX VII TEST ITEMS COMPLETED AT FOLLOW-UP VISITS

The number of items tested at each visit are as follows :

6 weeks : 7

3 months : 13

6 months : 15

9 months : 13

12 months : 12

The nature of the items may be seen in Fig.1 and in the proformas included in Appendix IX.

The degree to which each patient was assesed on the full set of items at each age is set out in Tables AX.VII 1-7.

TABLE AX.VII.1 SIX WEEKS FOLLOW-UP : TEST ITEMS COMPLETED

ITEMS	4	5	6	7	TOTAL
CASES	1	-	10	35	46
CONTROLS	1	2	7	27	37
TOTALS	2	2	17	62	83

TABLE AX.VII.2 THREE MONTHS FOLLOW-UP : TEST ITEMS COMPLETED

ITEMS	10	11	12	13	TOTAL
CASES	1	3	4	40	48
CONTROLS	-	5	3	27	35
TOTALS	1	8	7	67	83

TABLE AX.VII.3 SIX MONTHS FOLLOW-UP : TEST ITEMS COMPLETED

ITEMS	11	12	13	14	15	TOTAL
CASES	1	–	2	10	34	47
CONTROLS	–	1	1	8	23	33
TOTALS	1	1	3	18	57	80

TABLE AX.VII.4 NINE MONTHS FOLLOW-UP : TEST ITEMS COMPLETED

ITEMS	10	11	12	13	TOTAL
CASES	–	1	2	39	42
CONTROLS	1	–	–	30	31
TOTALS	1	1	2	69	73

TABLE AX.VII.5 TWELVE MONTHS FOLLOW-UP : TEST ITEMS COMPLETED

ITEMS	10	11	12	TOTAL
CASES	2	5	44	51
CONTROLS	4	7	26	37
TOTALS	6	12	70	88

APPENDIX VIII PROFORMAS FOR NURSERY.

These proformas are copies of the forms used in the gathering of data in the labour ward and nursery.

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DEPARTMENT OF PAEDIATRICS

ASPHYXIA RESEARCH PROFORMA.

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RESUSCITATION OF INFANT

1. Case Number _____ 1 [ ][ ][ ]

Mother's Name _____

2. Mother's Folder No. _____ 2 [ ][ ][ ][ ][ ][ ]

Date of Delivery _____

Time of Delivery _____ [ ][ ]

3. METHOD OF RESUSCITATION (Tick)

None

Face Mask O_2 alone

Face Mask IPPV 3 [ ]

Endotracheal Intubation IPPV

Other

Give details _____

_____ 4 [ ]

6. Apgar Scores: 1 min. _____ 5 mins. _____ 5 [ ]

10 mins. _____ 15 mins. _____ 6 [ ]

INTRAVENOUS MEDICATION GIVEN (Tick)

7. Sodium Bicarbonate 8% _____ mℓ. 7 [ ][ ]

8. Dextrose 50% _____ mℓ. 8 [ ][ ]

9. Narcan _____ mg. 9 [ ][ ]

0. Time to sustained spontaneous respiration _____ 10 [ ][ ]

_____ min

. ASTRUP POST DELIVERY

1. Time taken post delivery _____ min. 11 [ ][ ]

2/.....

12. SITE FROM WHICH TAKEN (Tick)

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Placental Artery

Umbilical Cord Artery

Other

Specify _____

_____

Result : 13. PH _____ 14. PC_2 _____

15. PCO_2 _____ 16. BE _____

17. SB _____

Details Recorded By _____

Date _____

Please now take the next envelop in the Series.

Is this baby to be a case or a control? _____

If a case please prescribe the Anti Cerebral oedema measures as soon as possible and on any case before 6hrs. of age.

12 ☐

13 ☐☐☐

14 ☐☐☐

15 ☐☐☐

16 ☐☐☐

17 ☐☐☐

18 ☐☐

19 ☐

20 ☐☐

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B. LABOUR AND PREGNANCY

Case number _____

Mother's name _____

25. Mother's address _____ 25. [ ][ ][ ][ ]

_____

26. Mother's folder number _____ 26. [ ][ ][ ][ ][ ][ ]

27. Baby's folder number _____ 27. [ ][ ][ ][ ][ ][ ]

L A B O U R

28. Duration of 1st stage of labour _____ hours. 28. [ ][ ]

29. Duration of 2nd stage of labour _____ mins. 29. [ ][ ]

30. In which stage of labour did the mother arrive at Cecilia Makiwane Hospital? (Circle) 30. [ ]

Before labour
1st stage
2nd stage

Did the mother receive any of the following sedative medications in the 72 hours prior to delivery (circle and state date and time of last dose for each)

31. Valium _____ last dose at _____ 31. [ ][ ]

32. Pethidine _____ last dose at _____ 32. [ ][ ]

33. Magnesium Sulphate _____ last dose at _____ 33. [ ][ ]

34. Other (specify _____ 34. [ ]

_____ last dose at _____

35. Were any complications of labour detected? YES/NO 35. [ ][ ]
If YES, please circle:

Multiple pregnancy
Abruptio Placentae
Placenta Praevia
Prolapsed Cord
Cord around infant's neck
Other (specify) _____

_____

36. Presentation (circle) 36. [ ]

Vertex Face
Brow Breech
Other (specify) _____

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37. Method of delivery (Tick) 37. ☐

Unassisted

Breech

Forceps

Vacuum

Caesarean Section

Other (specify)_____

38. Indications for assisted delivery _____ 38. ☐☐

_____

39. Was any evidence of fetal distress detected? 39. ☐

YES / NO

40. Meconium stained liquor YES / NO 40. ☐

41. Was any fetal heart abnormality found on auscultation? YES / NO 41. ☐

42. Was cardiotachograph recording carried out during labour? YES / NO 42. ☐

43. If yes, did it show evidence of fetal distress? YES / NO 43. ☐

44. Was fetal scalp sampling carried out? 44. ☐

YES / NO

45. If yes, give result of test nearest to delivery. 45. ☐

PH ____ PO_2____ PCO_2____ BE____ SB _____

46. What is obstetrician's assessment of cause of asphyxia? _____ 46. ☐☐

_____

47. Weight of placenta. _____ 47. ☐☐☐☐

48. Condition of placenta _____ 48. ☐☐

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PREGNANCY

49. Mother's age _____ years 49. ☐☐

50. Gravida _____ 50. ☐

51. Parity _____ 51. ☐☐

52. On how many occasions did the mother attend A.N.C. in this pregnancy? _____ 52. ☐☐

53. At what stage did she first attend A.N.C.? _____ weeks. 53. ☐☐

54. How long before delivery was the last A.N.C. visit? _____ weeks. 54. ☐☐

55. Were any of the following complications of pregnancy detected? YES / NO 55. ☐

If yes, please circle.

Pregnancy induced hypertension
Eclampsia
Intrauterine growth retardation
Diabetes Mellitus
Cardiac disease
Other (specify) _____

_____

56. Were any special investigations carried out in pregnancy? YES / NO 56. ☐

If yes, please tick.

Ultra sound. Once only
Serial ultra sound
Fetal movement monitoring
Non-stress C.T. test
Stress C.T. test
Other (specify) _____

_____

Details of above tests done _____

_____

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57. How was the mother referred to hospital for delivery? (circle) 57. ☐

Self

Private doctor

Herself

Other (specify) _____

_____

58. Reason for referral _____ 58. ☐☐

_____

59. Details recorded by _____ 59. ☐

Date: _____

[illegible] MALAWANE [illegible]
[illegible] DEPARTMENT OF PAEDIATRICS.

ASPHYXIA RESEARCH PROFORMA.

C. First Assessment of Infant at 48 - 72hrs.

Case Number _____

Mother's Name _____

Babies Folder Number _____

60 Birth Weight _____ kg. 60 [ ][ ][ ][ ]

61 Sex _____ 61 [ ]

62 Head Circumference _____ Cm. at Birth 62 [ ][ ][ ]

63 Gestational Age (Scored) _____ weeks 63 [ ][ ]

64 Classification (tick) AGA 64 [ ]
SGA
LGA

65 Respiratory Distress Since Birth YES/NO 65 [ ][ ]

If yes _____ Diagnosis _____

66 Scalp Bleeding Tick YES/NO If "Yes", Circle 66 [ ]
Cephalhematoma
Sub-aponeunotic haemorrhage
Other (Specify) _____

Now Carry out Neurological Assessment_____
(Proforma D).

67 Date and Time of Drawing 67 [ ][ ]
Blood Sample _____

Results

68 Phenobarbitone _____ 68 [ ][ ][ ][ ]

69 Dexamethasone _____ 69 [ ][ ][ ][ ]

70 Na _____ 70 [ ][ ][ ]

71 K _____ 71 [ ][ ]

72 Urea _____ 72 [ ][ ]

73 Ca _____ 73 [ ][ ][ ]

74 Mg _____ 74 [ ][ ][ ]

75 Pi _____ 75 [ ][ ][ ]

76 Details Recorded By _____ 76 [ ]

Date of Recording _____

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D. NEUROLOGICAL ASSESSMENT

Mother's name _____

Baby's Folder Number _____

91. Baby's age (in hours) _____ (Give in days if 7 days or more) 91. ☐☐

92. Weight today _____ Axillary Temp. _____ °C. 92. ☐☐☐

93. Time since last feed _____ hrs. 93. ☐☐

Stool consistency _____

94. If jaundiced - TSB _____ mm 94. ☐☐☐

95. PCV _____ % 95. ☐☐

96. Method of feeding today (circle) 96. ☐

- Nil per mouth
- Nasogastric
- Fully by breast or bottle

97. If so, state age in days at which baby fed independently 97. ☐☐

Other (specify) _____

_____

98. Have there been seizures since the last neurological assessment? YES/NO 98. ☐

99. How long after birth did they begin _____ hrs. 99. ☐☐

100. How long is it since the last seizure _____ 100. ☐☐

Please give results of investigations carried out at the time of onset of seizures.

101. Dextrostix _____ 101. ☐☐☐

Na^+ _____

K+ _____

Ca _____

Mg _____

102. CSF _____ 102. ☐

_____

EXAMINATION (Circle where appropriate)

Heart rate _____

103. Head circumference cm _____ 103.

Salivation (Circle) Normal
Excessive

Note: Now carry out examination and fill in Prechtl proforma before filling in below.

104. Normal and symmetrical YES/NO 104.

Asymmetrical YES/NO

Opisthotonus: No, Slight, Marked.

Frog Position: YES/NO

105. Limb Posture - arms and legs - predominantly flexion, semi flexion, extension 105.

Motility

106. Hyperkinetic -, +, ++. 106.

Hypokinetic -, +, ++.

Pathological Movements

107. Overshooting movements: absent, slight, marked 107.

108. Tremor Incidence: -. +, ++. 108.

Frequency: absent, low, high

Amplitude: absent, low, high

Motor System

109. Hypertonia: -, +. ++ 109.

Hypotonia : -, +, ++.

Threshold Responses

110. Average threshold: low, medium, high 110.

Tendon Reflexes

111. Intensity: -, +, ++, +++, ++++ 111.

Threshold: low medium, high

Moro Response

112. Average Intensity : low, medium high 112.

Threshold: low, medium high

State

113. Initial —— 113.

114. Final _____ (highest state reached) 114.
easy to pacify, difficult to pacify

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Crying

115. Type : normal, grunt, high pitched
Intensity low, medium, high

115. ☐

116. Hemi Syndrome (asymmetry)

116. ☐

posture : Arm: -, +, ++
leg: -, +, ++

motility : Arm: -, +, ++
leg: -, +, ++

motor system: Arm: -, +, ++
leg: -. +, ++

asymmetry in responses: arm:-, +, ++
leg:-, +, ++

117. Syndromes of abnormal reactivity

117. ☐☐

absent YES/NO

hyperexcitable : -, +, ++

apathetic :

comatose : -, +.

118. Diagnosis _____

118. ☐☐

_____

_____

119. Recorded by _____

Date: _____

For Office Completion

120. Brown State
Hypotonia, Hypo-ext, Extension/Flexion

120. ☐

121. Sarnat Stage

121. ☐

122. Prechtl Optimality Score

122. ☐

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E. DISCHARGE DETAILS

Case number .

Mother's name

Baby's Folder no.

240. Age _____ days 240. [ ][ ][ ]

241. Weight: _____ kg. 241. [ ][ ][ ][ ]

242. Head circumference _____ cm. 242. [ ][ ]

243. P.C.V. _____ % 243. [ ][ ]

Address to which baby is proceeding

Other address(es) which may be useful in keeping contact with the baby

244. Outcome of mother after delivery (circle): Alive Dead 244. [ ]

245. Is the baby being discharged with its mother 245. [ ]

YES/NO. If "NO", Why not?

Name and address of person taking the baby out of hospital

Date of discharge

Note: Carry out a neurological assessment (Proforma D) unless one has been performed within the previous 4 days.

246. Details recorded by 246. [ ].

Date of record

APPENDIX IX PROFORMAS FOR FOLLOW UP.

These proformas are copies of the forms used at the various stages of follow up.

CECILIA MAKIWANE HOSPITAL

DEPARTMENT OF PAEDIATRICS

ASPHYXIA RESEARCH PROFORMA

F. FOLLOW UP HEADER SHEET : FILL IN AT FIRST VISIT AND AGAIN IF THE CARETAKER OR THE ADRESS CHANGES.

1. CASE NUMBER_____ 2. BABY'S FOLDER NO _____

3. MOTHER'S NAME _____

4. DATE OF BIRTH ____/____/____ 5. DATE OF DISCHARGE ____/____/____

6. KNOWN HOME ADRESS _____

_____

7. OTHER ADRESS A. _____

_____

8. OTHER ADRESS B. _____

_____

9. CARETAKER :WHO (OTHER THAN A NANNY) IS RESONSIBLE FOR THE DAY TO DAY CARE OF THE BABY ?

* MOTHER * FATHER'S MOTHER * MOTHER'S MOTHER
* OTHER RELATIVE * OTHER PERSON (SPECIFY)_____

10. DOES THE ABOVE PERSON HAVE A REGULAR JOB AT PRESENT ?
YES /NO

11. IF YES : WHO CARES FOR THE CHILD DURING THE DAYTIME ?
* RELATIVE * PAID NANNY * OTHER (SPECIFY) _____

12 DOES THE CARETAKER RECIEVE REGULAR FINANCIAL SUPPORT ? YES/NO

13. IF YES : WHO FROM ? _____

14. IF THE MOTHER IS NOT THE CARE TAKER ; WHY NOT ?

_____

15. DOES THE MOTHER (WHEREVER SHE IS) HAVE A REGULAR JOB YES/NO

16. WHAT IS/WAS THE MOTHER'S FATHER'S OCCUPATION ?

_____

17. WHAT IS THE CHILD'S FATHER'S OCCUPATION ?

_____

18. IS THE CHILD'S FATHER : * LIVING IN THE CHILD'S HOME ?
* LIVING ELSEWHERE BUT IN REGULAR CONTACT ?
* A MIGRANT WORKER ? * NOT IN ANY CONTACT ?

19. DOES THE CHILD'S FATHER SUPPORT ? YES / NO

20. WHAT TYPE OF HOUSE IS THE BABY LIVING IN ?
* TOWNSHIP HOUSE * SHACK * TRADITIONAL HUT
* OTHER (SPECIFY) _____

21. HOW MANY ROOMS DOES IT HAVE (EXCLUDING KITCHEN AND BATHROOM)
_____

22. HOW MANY PEOPLE (ADULTS PLUS CHILDREN) SLEEP IN THE HOUSE EACH NIGHT ? _____

23. DOES IT HAVE RUNNING WATER INSIDE THE HOUSE ? YES / NO

VISIT CONDUCTED BY _____ DATE ___/___/___

14/11/83

CECILIA MAKIWANE HOSPITAL

DEPARTMENT OF PAEDIATRICS

ASPHYXIA RESEARCH PROFORMA

6. INTERVIEW SHEET : FILL IN AT EACH VISIT.

WHICH VISIT ? (CIRCLE) : 6 WK 3M 6M 9M 12M

1. CASE NUMBER _____ 2. BABY'S FOLDER NO _____

3. MOTHER'S NAME : _____

4. ADRESS FOR VISIT : _____

_____

5. DATE OF INTERVIEW ___/___/___ 6. BABY'S AGE IN WEEKS _____

7. STATUS OF BABY : ALIVE / DEAD / LOST TO FOLLOW UP.

IF DEAD : DATE OF DEATH ___/___/___ PLEASE GIVE DETAILS.

_____

8. HAS THE BABY BEEN ADMITTED TO HOSPITAL SINCE THE LAST VISIT ?

YES / NO IF YES : DATE OF ADMISSION ___/___/___
HOSPITAL _____ WARD _____
REASON FOR ADMISSION _____

_____

9. ANY FITS SINCE DISCHARGE OR LAST VISIT ? YES / NO
IF YES GIVE AGE AT FIRST FIT _____ MONTHS
ALSO APROX. NUMBER IN SAME PREIOD _____

10. HAVE THERE BEEN ANY OTHER MAJOR PROBLEMS SINCE THE LAST VISIT OR DISCHARGE FROM WARD 17.
YES / NO
IF YES PLEASE GIVE DETAILS : _____

_____

_____

11. HAS THE CARETAKER OR HER ADRESS CHANGED SINCE THE LAST VISIT ?
YES /NO IF YES PLEASE FILL IN A NEW
FORM "F :FOLLOW UP HEADER SHEET."

12. WILL THE CARETAKER BE CHANGING HER ADRESS BEFORE THE NEXT VISIT?
YES /NO IF YES ENTER THE NEW ADRESS ON FORM F.

13. NOW PLEASE FILL IN THE FOLLOW UP SHEET FOR THE CORRECT AGE.

VISIT CONDUCTED BY _____ DATE ___/___/_____
14/11/83

CECILIA MAKIWANE HOSPITAL

DEPARTMENT OF PAEDIATRICS

ASPHYXIA RESEARCH PROFORMA

H: 6 WEEK FOLLOW UP . CASE NO. _____

A. ASK THE CARETAKER THE FOLLOWING QUESTIONS :

1. IS THE BABY FEEDING WELL ? YES /NO IFNOGIVE DETAILS
_____
_____

2. IS THE BABY CONTENT OR RESTLESS ? _____
IF RESTLESS - GIVE DETAILS _____
_____

3. HOW IS THE BABY FEEDING ? BREAST ONLY /BOTTLE ONLY /MIXED

4. DOES HE GET ANY SOLID FOOD YET ? YES /NO
IFYESDOES HE HAVE DIFFICULTY TAKING IT ? YES /NO

5. DOES THE BABY QUIETEN AND PAY ATTENTION WHEN YOU SPEAK TO HIM/HER ? YES /NO/ NOT SURE

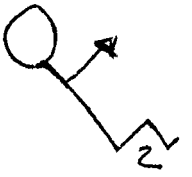
6. DOES HE/SHE WATCH YOU WITH HIS/HER EYES WHEN YOU FEED OR TALK TO HIM/HER ?
YES/ NO/ NOT SURE

7. HAS HE /SHE BEGUN TO SMILE BACK AT YOU WHEN YOU TALK TO HIM ?
YES/NO/ DON'T KNOW

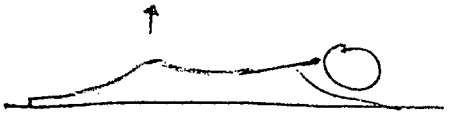
B.EXAMINATION OF THE BABY : UNDRESS THE BABY INCLUDING NAPKIN AND LIE HIM/HER ON THE BACK.

8. DOES HE SHE MOVE ALL 4 LIMBS EQUALLY ? YES/NO/NOT SURE

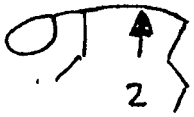
9. PULL THE BABY TO SIT : WHICH OF THESE IS MOST APPLICABLE ? (___)



10. PLACE THE BABY ON THE ABDOMEN :OBSERVE THE HIPS IN THE AWAKE CHILD : WHICH OF THESE IS MOST APPILICABLE ? (___)



11. HOLD THE BABY UNDER THE ABDOMEN AND OBSERVE THE HEAD AND LIMBS. WHICH OF THESE IS MOST APPLICABLE ?



(—)

12. WEIGHT __/_____KG.

13. HEAD CIRC. _____CM

14. LENGTH. .....CM

15. IF THERE ARE ANY OTHER PROBLEMS WITH THE BABY PLEASE RECORD THEM HERE : _____

_____

_____

_____

_____

16. CONCLUSION : * NORMAL BABY * ABNORMAL BABY FOR REFERRAL
DATE OF APPT: ../../..

VISIT CARRIED OUT BY _____ DATE ___/___/___

****

OFFICE USE ONLY :

RESULT : NORMAL _____(1)
ABNORMALITY 1 _____(____)
ABNORMALITY 2 _____(____)
ABNORMALITY 3 _____(____)

30/11/83 # FOLLUP6W

CECILIA MAKIWANE HOSPITAL

DEPARTMENT OF PAEDIATRICS

ASPHYXIA RESEARCH PROFORMA

I: 3 MONTH FOLLOW UP . CASE NO. _____

A. ASK THE CARETAKER THE FOLLOWING QUESTIONS :

1. IS THE BABY FEEDING WELL ? YES /NO IF NO GIVE DETAILS
_____
_____

2. IS THE BABY CONTENT OR RESTLESS ? _____
IF RESTLESS - GIVE DETAILS _____
_____

3. HOW IS THE BABY FEEDING ? (CIRCLE)
BREAST ONLY /BOTTLE ONLY /MIXED

4. DOES HE GET ANY SOLID FOOD YET ? YES /NO
IF YES DOES HE HAVE DIFFICULTY TAKING IT ? YES /NO

5. DOES THE BABY QUIETEN AND PAY ATTENTION WHEN YOU SPEAK TO HIM/HER ? YES /NO/ NOT SURE

	CARETAKER	:	INTERVIEWER
6. DOES THE BABY SMILE AT YOU NOW ? -----	YES/NO	:	YES/NO
7. DOES HE SOMETIMES PUT HIS HANDS TOGETHER? -----	YES/NO	:	YES/NO
8. DOES HE/SHE SOMETIMES REACH OUT TO TAKE AN OBJECT ? -----	YES/NO	:	YES/NO
9. DOES HE/SHE LAUGH ? -----	YES/NO	:	YES/NO
10. DOES HE/SHE SOMETIMES ROLL OVER?-----	YES/NO	:	YES/NO

EXAMINATION OF THE BABY : UNDRESS THE BABY INCLUDING THE NAPPY AND LIE HIM/HER ON A BED OR OTHER SURFACE.

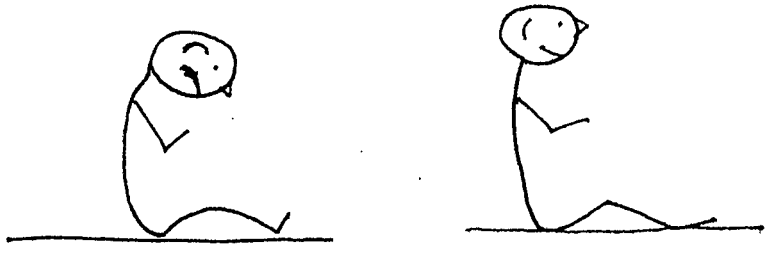
	INTERVIEWER'S OBSERVATION
11. DOES HE GRASP A RATTLE ?	YES/NO
12. DOES HE LOOK AT A SMALL OBJECT ?	YES/NO
13. THROUGH WHAT ANGLE WILL HE FOLLOW A WOOL BALL ?	0-90 DEG 90-180 DEG

14. NOW PULL THE BABY TO SIT : WHICH OF THE FOLLOWING DIAGRAMS IS MOST APPLICABLE ?

(__)

15. NOW SIT THE BABY UP HOLDING HIM/HER UNDER THE ARMS :

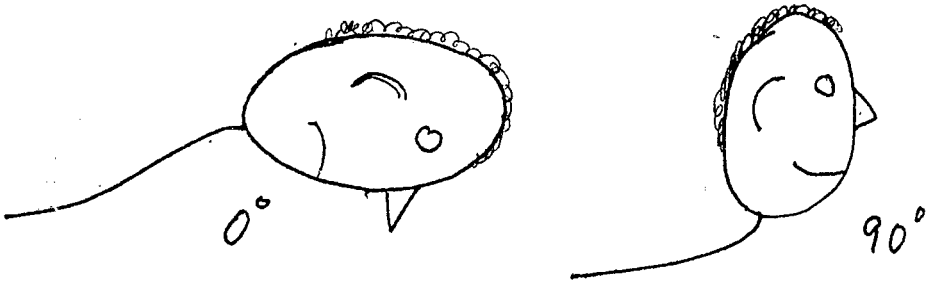
DOES HE/SHE HOLD THE HEAD STEADY ? YES/NO



16. NOW TURN THE BABY OVER TO LIE ON HIS/HER STOMACH : OBSERVE THE POSITION OF THE HEAD:

DOES HE/SHE HOLD IT UP TO AN ANGLE OF:

(A) 0-45 DEGREES
(B) 45-90 DEGREES



17. DOES HE/SHE SUPPORT HIS/HER CHEST OFF THE BED WITH THE FOREARMS ?

YES/NO

18. ARE THERE ANY OTHER MAJOR HEALTH PROBLEMS ? YES/NO

IF YES PLEASE GIVE MORE DETAILS :

_____

_____

_____

19. WEIGHT ___.___KG 20. LENGTH _____CM

21. HEAD CIRCUMFERENCE _____CM.

22. IF THERE ARE ANY OTHER PROBLEMS WITH THE BABY PLEASE RECORD THEM HERE : _____

_____

_____

_____

_____

23. CONCLUSION BY INTERVIEWER : (CIRCLE *)

* NORMAL BABY
* ABNORMAL BABY - FOR REFERRAL.

VISIT CARRIED OUT BY : _____DATE ___/___/___

****

OFFICE USE ONLY :

RESULT : NORMAL .....(1)
ABNORMALITY 1 .....(....)
ABNORMALITY 2 .....(....)
ABNORMALITY 3 .....(....)

30/11/83 FOLLUP3M

CECILIA MAKIWANE HOSPITAL

DEPARTMENT OF PAEDIATRICS

ASPHYXIA RESEARCH PROFORMA

J: 6 MONTH FOLLOW UP . CASE NO. _____

EQUIPMENT NEEDED: TOY OR POM-POM : WOODEN CUBE : SCALE: MEASURING FRAME : TAPE MEASURE

A : ASK THE CARETAKER THE FOLLOWING QUESTIONS :

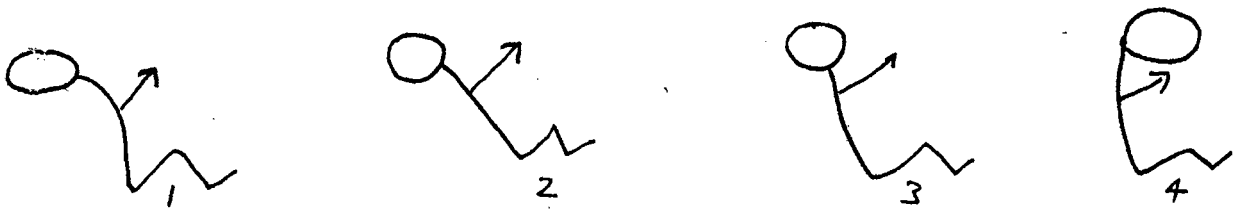
1. CAN THE BABY GET HIMSELF UP TO SITTING FROM LYING DOWN ? YES/NO/?
2. CAN (S)HE PULL HIMSELF UP TO STANDING ? YES/NO/?
3. CAN (S)HE STAND UP HOLDING ON TO THE FURNITURE ? YES/NO/?
4. CAN (S)HE FEED HIMSELF A BISCUIT OR OTHER PIECE OF FOOD ? YES/NO/?
5. IS (S)HE SHY WITH STRANGERS ? YES/NO/?
6. DOES (S)HE MAKE A QUITE A FEW DIFFERENT SOUNDS ? YES/NO/?

B : UNDRESS THE BABY COMPLETELY AND PLACE HIM IN THE SITTING POSITION IF POSSIBLE OR OTHERWISE LYING ON HIS BACK ON A BLANKET ON A BED OR ON THE FLOOR.
NOW CARRY OUT THE FOLLOWING ITEMS OF EXAMINATION :

7. GIVE HIM A TOY. WHEN HE IS PLAYING WITH IT TRY GENTLY TO REMOVE IT FROM HIM.
DOES (S)HE RESIST YOU ? YES/NO/NOT SURE
8. PUT THE TOY JUST OUT OF HIS REACH -- DOES (S)HE TRY TO GET TO THE TOY? YES/NO /NOT SURE
9. IN THE SITTING POSITION : DROP THE TOY OUT OF HIS SIGHT -- DOES (S)HE TRY TO LOOK WHERE IT WENT ? YES/NO/NOT SURE
10. PLACE A WOODEN CUBE IN ONE HAND -- DOES (S)HE PASS IT TO THE OTHER HAND ? YES/NO/NOT SURE
11. CAN (S)HE HOLD A WOODEN CUBE IN EACH HAND AT THE SAME TIME ? YES/NO/NOT SURE

12. WITH THE BABY LYING ON HIS BACK -- PULL HIM TO SITTING.
WHICH OF THE FOLLOWING DIAGRAMS IS MOST APPLICABLE ?

(_____)



13. IS THE BABY ABLE TO SIT SECURELY WITHOUT SUPPORT ? YES/NO/?

14. CAN (S)HE TAKE SOME WEIGHT ON HIS LEGS WHEN HELD IN THE STANDING POSITION ? YES/NO/NOT SURE

15. PERFORM THE HEARING TEST USING YOUR VOICE AS THE TEST NOISE.
DOES (S)HE TURN TO THE SOUND ON THE LEFT: YES/NO/NOT SURE
RIGHT: YES/NO/NOT SURE

16. WEIGHT _____.___KG 17. LENGTH ____CM

18. HEAD CIRCUMFERENCE _____ CM

19. ARE THERE ANY OTHER MAJOR HEALTH PROBLEMS PRESENT ? YES/NO
IF YES GIVE DETAILS : _____
_____
_____

20 CONCLUSION BY INTERVIEWER :

* NORMAL BABY
* ABNORMAL BABY -- FOR REFERRAL

VISIT CARRIED OUT BY : _____
DATE ____/____/_____

****

OFFICE USE ONLY :

RESULT : NORMAL ----------(_____)
ABNORMALITY 1 --------(_____)
ABNORMALITY 2 --------(_____)
ABNORMALITY 3 --------(_____)

5/2/84 FOLLUP6M

CECILIA MAKIWANE HOSPITAL

DEPARTMENT OF PAEDIATRICS

ASPHYXIA RESEARCH PROFORMA

K: 9 MONTH FOLLOW UP. CASE NO. _____

EQUIPMENT NEEDED: TOY OR POM-POM : 2 WOODEN CUBES :SCALE: MEASURING FRAME :TAPE MEASURE: DU TOIT RATTLE.

A: ASK THE CARETAKER THE FOLLOWING QUESTIONS:

1. CAN THE BABY GET HIMSELF TO SITTING FROM LYING DOWN ? YES / NO /?

2. CAN HE PULL HIMSELF TO STANDING ? YES / NO / ?

3. CAN HE STAND ALONE WELL ? YES / NO / ?

4. CAN HE STAND UP HOLDING ONTO THE FURNITURE ? YES /NO / ?

5. CAN HE WALK HOLDING ONTO THE FURNITURE ? YES ? NO ? ?

6. IS HE SHY AT FIRST WITH STRANGERS ? YES / NO / ?

7. DOES HE SAY "MAMA / TATA " (TO ANYONE)? YES / NO / ?

8. DOES HE MAKE OTHER SOUNDS THAT AT LEAST SOUND LIKE SPEECH ? YES / NO / ?

9. IF HE IS HOLDING AN OBJECT IN EACH HAND DOES HE SOMETIMES BANG THEM TOGETHER ? YES / NO / ?

B: SIT THE BABY ON A BLANKET ON A BED OR ON THE FLOOR : NOW CARRY OUT THE FOLLOWING EXAMINATION.

10. GIVE HIM A TOY. WHEN HE IS PLAYING WITH IT,GENTLY TRY TO PULL IT AWAY FROM HIM. DOES HE RESIST YOU ? YES / NO /?

10. TRY PLAYING PEEK-A-BOO WITH THE BABY. (PLACE YOURSELF OUT OF THE BABY'S VISION AND THEN SUDDENLY REAPPEAR WITH A CRY.) DOES HE PLAY THE GAME WITH YOU ? YES / NO /?

11. PLACE A SMALL ROUND OBJECT EG. A SMALL PELLET OF PAPER ABOUT THE SIZE OF A PEA, ON THE FLOOR / BED IN FRONT OF THE BABY AND BRING HIS ATTENTION TO IT. WATCH HOW HE PICKS IT UP. REPEAT THIS SEVERAL TIMES AND OBSERVE HIS PERFORMANCE WITH EITHER HAND.

WAS THE OBJECT PICKED UP :

A : BETWEEN THUMB AND SIDE OF HAND
B : BETWEEN THUMB AND SIDE OF FORE FINGER
C : BETWEEN TIP OF THUMB AND TIP OF FOREFINGER

12. PERFORM THE HEARING TEST USING THE DU TOIT RATTLE AS THE TEST SOUND. DOES HE TURN TO THE SOUND ON THE :

LEFT: YES / NO / ?
RIGHT: YES / NO / ?

WILL HE LOOK UP OR DOWN AT THE SOUND WHEN OFFERED ABOVE OR BELOW HIS EAR LEVEL ?

YES / NO / ?

13. WEIGHT : _____._____KG. 14. LENGTH : _____CM.

15. HEAD CIRCUMFERENCE : _____CM.

16. ARE THERE ANY OTHER MAJOR HEALTH PROBLEMS PRESENT? YES / NO
IF YES PLEASE GIVE DETAILS: _____
_____
_____
_____

17. CONCLUSION BY INTERVIEWER :

* NORMAL BABY.
* ABNORMAL BABY - FOR REFERRAL.

VISIT CARRIED OUT BY : _____
DATE : __/__/__

****

OFFICE USE ONLY :

RESULT : NORMAL (_____)
ABNORMALITY 1 (_____)
ABNORMALITY 2 (_____)
ABNORMALITY 3 (_____)

CECILIA MAKIWANE HOSPITAL
DEPARTMENT OF PAEDIATRICS
ASPHYXIA RESEARCH PROFORMA

L: 12 MONTH FOLLOW UP. CASE NO. _____

NAME: _____ FOLDER NO. _____

EQUIPMENT NEEDED: BALL: SMALL OBJECT : DIAGNOSTIC SET :SPATULA HAEMOGLOBINOMETER :PATELLA HAMMER :SCALE : TAPE MEASURE :DU TOIT RATTLE :

A: ASK THE CARETAKER THE FOLLOWING QUESTIONS:

1. CAN THE CHILD SHOW YOU WHAT HE WANTS, OTHER THAN BY CRYING ? YES/NO/?
   DETAILS: _____

2. CAN HE DRINK FROM A CUP ? YES/NO/?

3. DOES HE BANG AN OBJECT IN EACH HAND TOGETHER ? YES/NO/?

4. DOES HE USE THE WORDS "MAMMA" AND "TATA" WITH THE CORRECT MEANING ? YES/NO/?

5. HOW MANY WORDS DOES HE USE APART FROM "MAMMA" AND "TATA"?
   DETAILS : _____

6. CAN HE STAND ALONE FOR A SHORT TIME ? YES/NO/?

7. CAN HE STAND ALONE WELL ? YES/NO/?

8. CAN HE WALK HOLDING ONTO THE FURNITURE ? YES/NO/?

9. CAN HE BEND OVER AND STAND UP STRAIGHT AGAIN ? YES/NO/?

10. CAN HE WALK WELL ? YES/NO/?
    DETAILS : _____

B: HAVE THE BABY DRESSED SITTING COMFORTABLY ON A LEVEL SURFACE

11. PLACE A SMALL OBJECT (THE SIZE OF A RAISIN) ON THE SURFACE IN FRONT OF THE CHILD. BRING HIS ATTENTION TO IT AND OBSERVE HOW HE GRASPS THE OBJECT WITH EACH HAND SEVERAL TIMES.

    WAS THE OBJECT PICKED UP : (CIRCLE)

    A: BETWEEN THE THUMB AND SIDE OF THE HAND ?
    B: BETWEEN THE THUMB AND SIDE OF FOREFINGER ?
    C: BETWEEN THE TIP OF THUMB AND TIP OF FOREFINGER?
    D: OTHER (SPECIFY): _____

12. OBSERVE THE CHILD PLAYING WITH A BALL. DOES HE PLAY COOPERATIVELY WITH YOU ? YES/NO/?
    DETAILS: _____

C: GENERAL PHYSICAL EXAMINATION :

GENERAL :
CVS :
RS :
ABDO :
ENT :
MUSCULO-SKELETAL :

DETAILS OF ANY ABNORMALITIES:

D: CNS EXAMINATION :

HEAD :
EYES :
VISION :
HEARING : (RATTLE TEST) R: L:
(OTHER TEST) R: L:
POSTURE :

LIMBS			RIGHT	LEFT
TONE:	UPPER			
	LOWER			
POWER	UPPER			
	LOWER			
COORD.	UPPER			
	LOWER			
REFLEXES	UPPER	BICEPS		
		BRACHIOR.		
	LOWER	KNEE		
		ADDUCTOR		
		ANKLE		
CLONUS				

DIAGNOSIS :

E: WEIGHT : KG. LENGTH: CM.

HEAD CIRCUMFERENCE: CM. HAEMOGLOBIN: GM.

F: CONCLUSIONS :

1. ARE THERE ANY HEALTH PROBLEMS PRESENT OTHER THAN THOSE OF THE CNS ? YES/NO/?
IF YES SPECIFY : _____

2. ARE THRE ANY NEUROLOGICAL PROBLEMS PRESENT ? YES/NO/?
IF YES SPECIFY : _____

3. CLASSIFICATION :

* NORMAL CHILD
* GENERAL ABNORMALITY ; CNS NORMAL
* GENERAL ABNORMALITY ; CNS ABNORMAL
* GENERAL NORMAL ; CNS ABNORMAL

EXAMINATION CARRIED OUT BY : _____

DATE : ___/___/____

****

OFFICE USE ONLY :

RESULT : NORMAL (_____)
ABNORMALITY 1 (_____)
ABNORMALITY 2 (_____)
ABNORMALITY 3 (_____)

07/08/84 FOLLUP12