

**RESPIRATORY DISTRESS IN NEWBORN INFANTS**

**T H E S I S**

**SUBMITTED FOR THE DEGREE OF DOCTOR OF MEDICINE**

**by**

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TO MY PARENTS

## ABBREVIATIONS

RR	Respiratory Rate
IDM	Infant of Diabetic Mother
RDS	Respiratory Distress Syndrome
IRDS	Idiopathic Respiratory Distress Syndrome
HMD	Hyaline Membrane Disease
CHMD	Clinical Hyaline Membrane Disease
NT	Neonatal Tachypnoea
IPPR	Intermittent Positive-Pressure Respiration
BE	Base Excess
BB	Buffer Base
CS	Caesarean Section
PET	Pre-Eclampsic Toxaemia
NVD	Normal Vertex Delivery
VE	Vacuum Extraction
S	Survived
D	Death (hours)
ND/NND	Neonatal Death (days)
B	Birth
W	White
C	Cape Coloured
B	Bantu
M	Male
F	Female
GSH	Groote Schuur Hospital
RCM	Red Cross War Memorial Children's Hospital
MMH	Mowbray Maternity Home
PMH	Peninsula Maternity Home
StM	St. Monica's Maternity Home
NSH	New Somerset Hospital

## SYMBOLS

PO <sub>2</sub>	Oxygen tension
PaO <sub>2</sub>	Arterial oxygen tension
PAO <sub>2</sub>	Alveolar oxygen tension
PCO <sub>2</sub>	Carbon dioxide tension
PaCO <sub>2</sub>	Arterial carbon dioxide tension
R.Q.	Respiratory quotient
S	% saturation of haemoglobin
$\bar{v}$	Mean venous
QT	True right to left shunt

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**PART I**

**GENERAL**

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CHAPTER 1INTRODUCTION

"Perinatal deaths account for the loss of thousands of potential citizens, apart from parental grief which cannot be measured."

W.C.W. Nixon (1963)

The greatest loss of infant life occurs around the time of birth (Eliot, 1958) and the mortality rate for first day deaths has shown less improvement than for any other time during the first year (Arey and Dent, 1953).

"Once the human foetus has attained a gestational age permitting extra-uterine survival, neonatal death may be more commonly associated with failure of respiratory adaptation than with any other adaptational failure." (Smith, 1964). About two-thirds of all deaths in the newborn are associated with respiratory failure (Briggs and Hogg, 1958; Driscoll and Smith, 1962; Fearon et al., 1964). Hutchison et al. (1962) stated that the pulmonary syndrome of the newborn is probably the major problem of present day neonatal paediatrics.

Significant lowering of the mortality rate for full-term infants ( $> 2.5$  kg) has been achieved by antibiotics and general improvement in the standard of obstetrics. Despite these advances the lowest present day mortality figures for premature infants ( $< 2.5$  kg) are little better than those published by Flynn in 1919 (James, 1959). Premature infants account for 60 - 70% of neonatal

deaths in Canada (Swyer, 1960) and 77.5% of neonatal deaths in one survey in Britain (Dunn, 1965). Baird (1964) has estimated that although fewer than 10% of all babies weigh less than 2.5 kg at birth they provide more than 50% of all deaths during the first week of life. The higher mortality rate in premature infants is largely due to the respiratory distress syndrome (Weber, 1961a).

Respiratory problems, therefore, present the chief threat to survival in newborn infants and contribute inestimably to morbidity in this age group (Driscoll and Smith, 1962; Peterson and Pendleton, 1955). A certain percentage of neonates who suffer from respiratory disease die, but it must be borne in mind that a large, unrecorded number of those who do not die may suffer permanent damage. Premature birth, in particular, is known to be associated with mental and physical defect in some of the survivors (Brillien, 1964 and Heimer et al. 1964). Intensive care is essential if any reduction in these late sequelae is to be achieved.

Paediatricians, and obstetricians also, should be able to recognise the difference between the normal and the abnormal in their smallest infants. Above all, they should remember that the newborn infant is not merely a very young baby but that he presents certain problems of his own (Irving, 1963).

Although a tremendous amount of research has gone into the understanding of the respiratory physiology and pathology of the newborn in other parts of the world, no work has hitherto been done in this country. No reports on the incidence and extent of respiratory distress are available for South Africa and information is also lacking

on whether or not there are any racial differences.

Most recent investigations have been of a highly complex nature which could not be emulated without expensive equipment and technical staff. It appeared important, therefore, to examine the problem as a whole in Cape Town, concentrating mainly on the clinical aspects and on those investigations which could be carried out. The present work is based on observations on 288 affected infants and 2,515 infants without respiratory distress. The survey covered live births in 5 maternity hospitals as well as neonates admitted to two general hospitals in Cape Town over a period of 12 months. Clinical examinations and observations were carried out by the author with the assistance of the nursing staff. Blood specimens were collected and analysed for acid-base and blood gas values by the author who was also responsible for all calculations and analysis of the data. Routine biochemical determinations were done by the Pathology Department of the University of Cape Town Medical School.

The aim of the survey was to investigate and record the following:

- (a) Respiratory rates and respiratory patterns in the first 24 hours of life
- (b) Criteria for diagnosis of respiratory distress
- (c) Clinical and radiological classification of RDS
- (d) Incidence, pathology and mortality of RDS
- (e) Clinical findings in RDS
- (f) Acid-Base and blood gas disturbances in RDS
- (g) Biochemical values in RDS
- (h) General and metabolic treatment of RDS
- (i) Indications for, and value of, IPPR in RDS

The study is intended to serve as a basis for any future research in this field. If it should stimulate greater interest in the care of newborn infants and be instrumental in improving morbidity and survival rates, the time and effort will have been well spent.

CHAPTER 2MATERIAL AND METHODSInfants

The survey was mainly concerned with infants born in the 5 maternity hospitals attached to the University of Cape Town Medical School during the 12 month period from March, 1964 to February, 1965. The respective maternity hospitals were the Newbray Maternity Home; Maternity Section, Grootse Schuur Hospital; Peninsula Maternity Home; St. Monica's Maternity Home and New Somerset Hospital. Newborn infants with respiratory difficulties admitted directly to the Neonatal Respiratory Unit in Grootse Schuur Hospital or the Red Cross War Memorial Children's Hospital were included for investigation. They represent infants born in Greater Cape Town and the surrounding country districts within a radius of 140 miles.

The infants were representative of the population in Cape Town which is comprised of 3 different ethnic groups: White, Cape Coloured and Bantu. The Whites are mainly descendants of immigrants from Europe and Britain. The Cape Coloured people originate from an admixture of European, Hottentot and Malay stock, while the Bantu are descended from the people of Central Africa. Infants with birth weights below 2.5 kg were classified as premature and those over 2.5 kg as 'term' infants.

Observations

Neonatal observation charts (Appendix 1) were kept by the

nursing staff on 2,768 infants considered to be at possible risk. These included premature infants; infants born of diabetic mothers; infants delivered by Caesarean section and forceps, vacuum or breech extraction; infants born of pregnancies and labour complicated by pre-eclamptic toxæmia, antepartum haemorrhage or foetal distress; and any infant who was unwell in the first 24 hours of life. Observations were made at  $\frac{1}{2}$  - 1 hourly intervals for the first 24 hours and thereafter if indicated by the condition of the child. The pulse rate, respiratory rate and temperature were recorded and notes made on the presence or absence of cyanosis (indicating the oxygen requirement), retraction (suprasternal and costal), grunting, apnoea or any other abnormality. There was often a delay of up to 1 hour between birth and admission to the nursery. Respiratory rates were not counted during crying or feeding.

#### Investigations

Although it was possible to record observations in a large number of infants in the maternity hospitals, only a limited number were intensively studied. Infants admitted to the neonatal respiratory unit were thoroughly investigated but admission to this unit was available only for Whites. Facilities for investigation of non-White infants were available at the Maternity Section, Groote Schuur Hospital and the Red Cross War Memorial Children's Hospital. Radiology, electrocardiography and blood chemistry were therefore done at these institutions and not at Mowbray, Peninsula and St. Monica's Maternity Hospitals unless the infants were transferred. Very few infants at

New Somerset Hospital were investigated. The distances between the maternity hospitals also made it impossible for the author to examine every infant with respiratory distress.

The following routine was carried out in the neonatal respiratory unit and whenever possible in the Maternity Section, Greeto Schuur Hospital and the Red Cross War Memorial Hospital. Observations were made  $\frac{1}{2}$  hourly as outlined above (Appendix i). The nurses were also requested to keep a special intake/output chart (Appendix ii). A full clinical examination by the author was carried out every 2-6 hours and the findings at each examination recorded on a special chart (Appendix iii). A standard index for recording the severity of grunting, recession, diminished air entry and oedema was compiled and followed throughout the study (Appendix iv). From these charts it was possible to assess progress and obtain the necessary information for subsequent analysis.

A chest radiogram was obtained as soon after admission as possible and usually repeated 24 hours later. Further films were requested in sudden deterioration or if progress was not as rapid as had been expected. The undesirable aspects of removing the infant from a source of constant oxygen, heat and humidity was overcome by nursing the infants on a radio-transparent platform inside the incubator (Silver and Nyham, 1954). A sliding opening allowed cassettes to be placed directly underneath the platform. In the scrutiny of the films special attention was paid to the following aspects: quality, degree of aeration, cardio-thoracic index, lung translucency and the presence or absence of an air-bronchogram, reticulate-granular pattern, atelectasis, emphysema or extrapulmonary air.

Whenever possible an umbilical arterial catheter was passed and left in situ. Arterial blood was analysed for oxygen content or tension and acid-base values. When arterial blood was not available, arterialised capillary blood was used for acid-base determinations. These parameters were measured approximately every 6 hours and then less frequently when improvement occurred. Blood was also taken initially for serum potassium, sodium and chloride, blood urea, blood sugar, serum proteins and haematocrit. The potassium and blood sugar were usually repeated after 12 - 24 hours.

#### Treatment

General management consisted of nursing these infants in incubators with high temperature and humidity. Sufficient oxygen was given to relieve cyanosis or maintain a  $\text{PaO}_2$  level of 100 mmHg. In the more severe cases intravenous fluid was administered via a scalp vein with the addition of sodium bicarbonate to correct metabolic acidosis. IPPR was employed as a last resort in terminal cases. Cloxacillin and ampicillin were given when the umbilical catheter was left in situ, when infection was suspected from the history or radiography and always with IPPR. Autopsies were performed when possible to establish the nature of the pulmonary pathology and/or other lesions such as intracranial haemorrhage. The Malay community would not consent to autopsy studies because of religious beliefs.

CHAPTER 3REVIEW OF THE LITERATURE

Before considering the findings in this study, it is appropriate to review the published reports on the subject.

Although more than forty causes of respiratory distress in newborn infants have been described, hyaline membrane disease (HMD) remains the most common cause numerically. Most reports in the literature deal with HMD and any review will reflect this trend. This review will cover the broad outline of respiratory distress with the accent on HMD. Pertinent details will be discussed in the relative chapters.

Historical

In 1903 Hochheim described a peculiar membrane in the lungs of 2 infants who died shortly after birth. Johnson and Meyer (1925) described the histological findings in 8 cases with membrane formation. The membranes were considered to be aspirated vernix (Farber and Sweet, 1931).

In 1949 Miller and Hamilton first questioned aspiration of vernix as the cause of these hyaline membranes. In the following year, 1950, Miller and Jennison drew attention to the high incidence of hyaline membranes at autopsies on liveborn premature infants. This was confirmed by Elystad et al. (1951) who also evaluated the clinical aspects of the illness, which became known as HMD.

De and Anderson (1953) reviewed the literature up to 1953. They discussed the theories of formation of the hyaline membranes and the different names given to this condition.

The past 12 years have seen a flood of articles on the incidence, mortality, pathogenesis, histology, clinical aspects, biochemical findings and treatment of HMD. During the same period other causes of respiratory distress such as congenital pneumonia, pneumothorax, aspiration syndromes, diaphragmatic hernia, intracranial lesions and cardiac conditions have been investigated and described.

Review articles on the physiology and disorders of respiration in the newborn have been written by De and Anderson (1953), James (1959), Gregg and Bernstein (1961), Usher (1961a), Strang (1963), James and Adansons (1964), Daves (1965) and Gairdner (1965). Avery (1964) has compiled a detailed volume on the lung in the newborn infant.

### Terminology

Much confusion has arisen all over the world due to lack of agreement on terminology. At an international symposium in 1959 there was difference of opinion on the scope and terminology of respiratory distress in newborn infants (Rudolph and Smith, 1960).

Numerous names have been used to describe HMD. De and Anderson (1953) listed 9 for the same histological lesion:

Myelin formation in lungs  
 Congenital aspiration pneumonia  
 Asphyxial membrane  
 Desquamative anaerosis  
 Congenital alveolar dysplasia  
 Vernix membrane  
 Hyaline membrane  
 Hyaline-like membrane  
 Hyaline atelectasis

Since then the following have been suggested:

Pulmonary syndrome of the newborn (Bound et al., 1956)  
 Hyaline membrane syndrome (Driscoll et al., 1960)  
 Respiratory distress syndrome (Rudolph and Smith, 1960)  
 Idiopathic respiratory distress syndrome (Rudolph and Smith, 1960)  
 Idiopathic respiratory distress syndrome of prematurity (Usher, 1961)  
 Clinical hyaline membrane disease (Stahlman, 1964)  
 Pulmonary hyperperfusion syndrome (Chu et al., 1965).

The terms most commonly used are HMD and RDS. The former implies a histological diagnosis and is therefore not acceptable to all clinicians. Although IRDS was voted as the most suitable clinical name for HMD (Rudolph and Smith, 1960), it has not received universal acceptance and many authors still prefer RDS. This has resulted in a most unsatisfactory situation where readers are often in doubt whether an author is referring to any cause of respiratory distress or to HMD in particular. The question can usually be resolved provided that additional evidence of radiography and pathophysiological investigations are presented. Without such evidence there will always be some doubt about the diagnosis.

It would seem that the recommendation to use the term RDS for all causes of respiratory distress is a sound one (Rudolph and Smith, 1960; Hanley et al., 1963). HMD or IRDS should be reserved for that group where a presumptive diagnosis of hyaline membranes is made. Stahlman's preference for CHMD (1964) is the most logical one as it retains the widely used pathological name and signifies a diagnosis during life. Hyaline membrane syndrome appears to have gained favour again (Smith, 1965), probably because it has been clearly established that the hyaline membranes are not the most characteristic histological finding in these infants. The introduction of names such as pulmonary hyperperfusion syndrome (Chu et al., 1965) has no advantage. While they may describe more correctly the underlying pathology, it only adds further to the confusion.

Smith (1965) has stated that it does not matter very much what name is used as long as the condition is clearly defined. As there does not seem to be any prospect of agreement on nomenclature, this is excellent advice to all authors. In this review RDS is used to describe all causes of respiratory distress. Specific conditions are referred to by the names most often used in the literature.

### Criteria

As with terminology, there is no unanimity on criteria for the diagnosis of RDS (Miller, 1962 and 1963; Hutchison et al., 1962; Jelly et al., 1962; Davis, 1963; Gomez and Graven, 1964 and Troelstra et al., 1964) and IRDS (Usher, 1961; Driscoll and Smith, 1962; Hutchison et al., 1964 and Robertson et al., 1964).

The following clinical criteria have been observed in RDS: rapid RR (usually  $> 60/\text{min}$ ) or RR increasing after first  $\frac{1}{2}$  - 1 hour, expiratory grunting, cyanosis, recession, pulmonary crepitations, diminished air entry on auscultation, generalised oedema and prolonged pulsation of the umbilical vessels. The different criteria are discussed in Chapter 4.

#### Classification

Although the individual causes of respiratory distress in the newborn are well recognised, authors differ in their approach to the subject.

McKay and Smith (1960) divided respiratory distress and failure into 2 groups depending on whether primarily there was central nervous system failure or peripheral respiratory difficulty.

The presence or absence of obstruction to the airways was used by Schaffer (1960) as the main classification for dyspnoea. The obstruction to the airways could be at any level, those in the chest being the most important group. Intracranial haemorrhage and cardiac failure formed the non-obstructive group.

A different approach was employed by Hanley et al. (1963) for classification of symptomatic neonatal respiratory distress. They listed 4 categories:

- A. Pulmonary - Idiopathic Respiratory Distress Syndrome (IRDS)  
- Other specific causes
- B. Extra-pulmonary
- C. Cardiac
- D. Undiagnosed

### Incidence

Much information about the incidence of RDS and other statistics must necessarily be obtained from fatal cases (Driscoll and Smith, 1962).

The incidence of HMD as a cause of neonatal death has been recorded by many investigators including Arey and Dent (1953); Claireaux (1953); Latham et al. (1955); Silverman and Silverman (1958); Avery and Drolette (1958); Cohen et al. (1960); Avery and Oppenheimer (1960); Gregg and Bernstein (1961); Driscoll and Smith (1962); Barrie (1962); Rosahn and Sheanakul (1961); Webb et al. (1962); Younosai (1962) and Chuang (1962). Few have recorded the actual incidence during life: Miller (1957); Driscoll and Smith (1962); Usher (1963); Gairdner (1965) and Dunn (1965). In every series male infants predominate: Usher (1961); Hanley et al. (1963); Miller (1963); Robertson et al. (1964) and Troelstra et al. (1964). Several authors have drawn attention to the increased number associated with Caesarean section, antepartum haemorrhage and maternal diabetes (Latham et al., 1955; Rogers et al., 1956; Cohen et al., 1960 and Usher, 1961). Miller and Jennison (1950) first drew attention to the association of HMD with prematurity. All recorded cases to date have occurred in premature or immature infants. Gairdner (1965) stated that other factors are unimportant compared with the basic factor of prematurity.

The occurrence of other causes of neonatal pulmonary deaths such as pneumonia, amniotic or meconium aspiration, pulmonary haemorrhage and structural immaturity were determined by Briggs and Hogg (1958);

Claireaux (1958); Landing (1957); Ahvenainen (1959) and Sivanesan (1961). These reports agreed that HMD was the most frequent single cause of death.

Bound et al. (1956); Benirschke (1960) and Butler and Bonham (1963) also gave details of the incidence of pulmonary pathology in relation to congenital malformations, trauma and Rhesus incompatibility.

#### Clinical picture

Detailed clinical descriptions of HMD have been published by Usher (1961), Driscoll and Smith (1962) and Stahlman (1964).

Contrary to earlier belief, infants with HMD are affected from their first breath (Miller, Behrle and Skull, 1958; Stahlman, 1964 and Gairdner, 1965). They are often apnoeic at birth and may require resuscitation (Miller 1962a, 1963). The RR is usually raised (Driscoll and Smith, 1962; Schaffer, 1960; Miller, Behrle and Skull, 1958). These infants usually have cyanosis (Miller 1962 and Stahlman 1964) and oedema (Smith et al., 1949; Sutherland et al., 1959; Bauman, 1959; Usher, 1961; Hutchison et al. 1964 and Stahlman, 1964). On auscultation there may be diminished air entry (Usher, 1961) and crepitations (Schaffer, 1960; Usher, 1961 and Stahlman, 1964). Jaundice is a common finding (Usher, 1961 and Hutchison et al., 1964).

Renal function is depressed (Cort, 1962) and the severely ill infants are limp and unresponsive (Stahlman, 1964). Cardiovascular disturbances are raised pulse rate (Usher, 1961), variable systolic murmurs (Burnard, 1959; Usher, 1961 and Driscoll and Smith, 1962) and systemic hypotension (Meligan and Smith, 1960).

Complications include apnoeic attacks (Miller et al., 1959; Usher, 1961; Avery, 1964 and Stahlman, 1964), intracranial haemorrhage (Hanley et al., 1963; Stahlman, 1964 and Hutchison et al., 1964) and pneumothorax (Smith, 1964). Infection is not usually a problem (Gairdner, 1965).

The course of the illness may vary from rapid improvement to gradual worsening of the respiratory failure. The peak of the HMD occurs at 48 - 72 hours of age (Hanley et al., 1963). The survivors then gradually improve to complete recovery.

### Radiology

Chest radiography is the single most useful investigation in infants with RDS (Harris, 1963). The value of serial films has been stressed by Steiner (1954), Peterson and Pendleton (1955) and Schaffer (1960).

Donald and Steiner (1953) first described a specific radiographic appearance in HMD. They found fine military mottling throughout the lung fields associated with an air bronchogram (air-filled bronchi). These findings were confirmed by Meschan et al. (1953). Peterson and Pendleton (1955) in their description of the contrasting appearances of HMD and aspiration syndromes, referred to the patchy mottling as 'reticulogranular'. The characteristic appearance in HMD has been well documented by Feinberg and Goldberg (1957), Ellis and Madelhaft (1957), Schultze (1958) and Bauman and Madelhaft (1958). The correlation between the radiographic and autopsy diagnoses is better than 85% (Hanley et al. 1963 and Prod'homme et al. 1965).

The radiographic changes in aspiration syndromes have been

recorded by Petersen and Pendleton (1955), Schultze (1958), Gaffey (1956), Hanley et al. (1963) and Harris (1963). Steiner (1954) described the differences between pneumonia and HMD.

### Electrocardiogram

Usher (1959) noted ECG changes between 12 - 60 hours in infants with RDS. He related these changes to raised serum potassium levels. Keith et al. (1961) described the patterns seen in cases with poor prognosis. Recently, Sutin et al. (1965) drew attention to the P waves as a guide in the assessment of severity and prognosis. They found no relationship to the serum potassium levels.

### Biochemistry

The biochemical disturbances have been recorded by several investigators. Most found high serum potassium levels (Usher, 1959; Nicolescules and Smith, 1961; Stahlman, 1964 and Troelstra et al. 1964). Hutchison et al. (1964) did not observe hyperkalaemia and Payne and Acharya (1965) found high levels terminally only.

Sodium levels were not materially different from controls (Nicolescules and Smith, 1961; Troelstra et al. 1964 and Payne and Acharya, 1965). Although Shelly (1964) found the carbohydrate reserves depleted at autopsy, blood sugar levels have been very variable during life (Heardon et al., 1957; Usher, 1961; Kerpel-Fronius et al., 1964; Hutchison et al., 1964 and Payne and Acharya, 1965).

### Blood gas and Acid-base values

The RDS was usually associated with marked changes in the  $PCO_2$ ,  $PaO_2$  and pH.

The  $PCO_2$  was the most variable of all parameters measured (Boston et al., 1964). Although most had a respiratory acidosis (James, 1959; Usher, 1961 and Elystad, 1956a) some had normal levels (Strang and MacLeish, 1961). High  $PCO_2$  levels were a sign of severe respiratory failure (Hutchison et al., 1962) and might have been the cause of unresponsiveness and cerebral haemorrhage (Strang and MacLeish, 1961).

The  $PaO_2$ , on the other hand, was a very good guide to the progress of the infant (Smith, 1964). The  $PaO_2$  or arterial oxygen saturation was almost always low when compared with normal infants (Warley and Gairdner, 1962; Strang and MacLeish, 1961; Nelson et al., 1963; Prod'homme, 1964 and Stahlman, 1964).

The hypoxia and respiratory acidosis resulted in a metabolic (non-respiratory) acidosis (James, 1959; Usher, 1961; Warley and Gairdner, 1962; Stahlman, Young and Payne, 1962a; Troelstra et al., 1964 and Gairdner, 1965).

Detailed blood gas values in HMD have been published by Stahlman et al. (1963).

#### Pathophysiology of respiratory distress

Great credit is due to the various workers who have overcome the difficulties of making accurate measurements on very small and very sick newborn infants (Daves, 1965). Every aspect of pulmonary physiology has been investigated in HMD with the following results.

The minute volume was increased due to increased respiratory rate (Karlberg et al., 1954) while the tidal volume remained normal

(Karlberg et al., 1954) or was decreased (Strang, 1963 and Prod'hom, 1964). Karlberg et al. (1954) found the physiological alveolar ventilation within normal limits but Strang and MacLeish (1961) recorded decreased values. The dead space/tidal volume ratio was increased (Karlberg et al., 1954 and Cook, Barrie and Avery, 1960). The functional residual capacity was decreased (Prod'hom, 1964).

The values for the mechanics of respiration were summarized by Cook, Barrie and Avery (1960). They included raised intra-oesophageal pressure changes (Karlberg et al., 1954 and Stahlman, 1964), decreased lung compliance (Behrle et al., 1951; Cook et al., 1957; Gribrets, Frank and Avery, 1959 and Craig, Fenton and Gitlin, 1958) and a 4 - 10 times increase in the work of breathing (Karlberg et al., 1954 and Cook et al., 1957).

Nelson et al. (1961, 1962) found a moderate impairment of the distribution of gas and a severe degree of non-perfusion with both  $PO_2$  and  $PCO_2$  gradients. The ventilation/perfusion impairment was best examined by raising the ambient oxygen to 100% and measuring the  $PaO_2$  (Strang and MacLeish, 1961; Nelson et al., 1961 and Prod'hom, 1964).

Right-to-left shunts have been determined by means of oxygen studies by Strang and MacLeish (1961); Warley and Gairdner (1962); Nelson et al. (1963) and Prod'hom (1964). Stahlman (1964) found similar values on dye dilution curves. The R - L shunt could be at atrial (foramen ovale), ductus arteriosus or intrapulmonary level.

### Mortality

The variable basis for the diagnosis of RDS makes it impossible to compare mortality figures from different hospitals (Hutchison et al. 1966).

Mortality rates as high as 66% (Hutchison et al., 1964) and as low as 17% (Usher, 1963) have been recorded. Usher (1961), Hanley et al. (1963) and Troelstra et al. (1964) found a higher mortality for male infants while Miller (1963) in his series refuted this on statistical grounds.

Death occurred between 8 - 48 hours in the majority of infants (Lathan et al., 1955; Driscoll and Smith, 1962; Robertson, 1963 and Miller, 1963). Butler and Bonham (1963) found 68.4% of HMD deaths on the first day of life while pulmonary haemorrhage deaths occurred later. The causes of deaths were multiple and included exhaustion of respiratory muscles (Miller, Behrle and Skull, 1958 and Gairdner, 1965); respiratory acidosis and anoxia (Miller, Behrle and Skull, 1958); intracranial haemorrhage (Stahlman, 1964 and Hutchison et al., 1964) and infection (Hutchison et al., 1964).

Driscoll and Smith (1962) stated that it was difficult to estimate the prognosis in a disturbance of such rapid course and varied severity. Various parameters have been proposed as indices of severity. They are the pH (Usher, 1963; Troelstra et al., 1964; Kerpel-Fronius et al., 1964 and Gairdner, 1965);  $PCO_2$  (Hutchison et al., 1962 and Kerpel-Fronius et al., 1964);  $PaO_2$  (Usher, 1963; Stahlman, 1964 and Boston et al., 1964) and blood lactic acid (Stahlman, Young and Payne, 1962a). Usher (1961) reviewed the clinical signs associated with a poor prognosis.

#### Pulmonary histology

Potter (1953) described the difference between lungs that had never contained air and those with secondary atelectasis. Pulmonary immaturity was associated with infants weighing less than 1.0 kg (Potter, 1953 and Hanley et al., 1963).

The striking finding in HMD is complete collapse of the alveoli, called resorption atelectasis (Potter, 1953), associated with dilatation of the respiratory bronchioles and alveolar ducts. The respiratory bronchioles and alveolar ducts may or may not be lined by an eosinophilic membrane from which the condition takes its name. These membranes may be universal or limited to a few alveolar ducts only. The detailed histological findings of atelectasis & hyaline membranes were described by Potter (1953), Gruenwald (1955), Rogers et al. (1956), Claireaux (1958), Briggs and Hogg (1958) and many others since. There is often associated oedema and haemorrhage (Claireaux, 1958; Robertson, 1963 and Gruenwald, 1964). Hyaline membranes were not found in stillbirths (Potter, 1953) and seldom under 3 hours of age (Potter, 1953; Driscoll and Smith 1962 and Craig, 1963). Gruenwald (1955) was the first to suggest that the atelectasis and not the hyaline membranes was the underlying cause of this condition.

Driscoll and Smith (1962) and Robertson (1963) have given excellent descriptions of the stages of evolution and repair of the lesions. Stahlman (1964) recorded late changes after assisted ventilation. Histological confirmation of areas of interstitial emphysema was produced by Craig (1963). Stahlman et al. (1964) described in detail the progressive pulmonary changes in experimental HMD in newborn lambs.

In severe asphyxiation syndromes squamous cells, and in some instances meconium, were associated with focal emphysema and atelectasis (Peterson and Pendleton, 1955 and Avery, 1964).

### Pathogenesis of Hyaline Membrane Disease

The earliest theory was that aspirated vernix (Farber and Sweet, 1931) caused the hyaline membranes. This concept was challenged in 1949 by Miller and Hamilton. Gitlin and Craig (1956) found that the membranes were composed largely of fibrin together with lipid and squamous cells from the amniotic fluid. In the same year, Neustein and van Broomen (1956) demonstrated with electron microscopy that the membranes contained fibrin, cellular debris and plasma proteins. Chapple (1958) thought that the high maternal hormone levels in prematurity, Caesarean section and diabetes caused the transudation of serum through the capillary membrane. Barrie (1960) suggested that the increased transmural pressure in severe respiratory effort sucked fibrinous exudate from the pulmonary vascular bed.

In 1955 Pattle described the finding of an alveolar lining layer secreted in the depths of the lung. This was confirmed by Clements (1957) who identified the surface-active material in saline extracts of rat, cat and dog lungs. The appearance of this film (lipoprotein) coincided with the appearance of alveolar lining cells and was absent from the lungs of infants who died from profound atelectasis and HMD (Avery, 1962 and Pattle et al., 1962). The lipoprotein, called surfactant, has the remarkable properties of changing surface tension with surface area and confers stability on the terminal airspaces, preventing their collapse at end-expiration (Avery, 1964 and Gruenwald, 1964).

Stahlman et al. (1964) proposed that diminution of the nutrient blood supply to the foetal lung would cause necrosis of the

epithelium, exudation of protein-rich fluid and inactivation or destruction of surfactant. Tooley et al. (1961) found increased surface tension in dogs with unilateral pulmonary artery ligation. The association between pulmonary arterial flow and surfactant was demonstrated in an unusual patient with a vascular anomaly of the lung (Doris, 1963) and fully discussed by Daves (1965) and Chu et al. (1965). Asphyxia and acidosis did not seem to play an important role in the pathogenesis of IRDS (Levison et al., 1964 and Daves, 1965).

Ambras et al. (1963) found deficient fibrinolysis within the lungs of premature infants, especially those with respiratory distress. The relationship of this observation with other factors was reviewed by Lieberman (1963).

Graven and Misenheimer (1965) recently reported a group of mothers whose offspring had a very high incidence of RDS provided they were of low birth weight. An immune reaction was suggested by Hardie, Heese and Kench (1965). Both these reports point to some maternal or genetic predisposition.

Finally, Moss, Duffie and Fagan (1963) and Wallgren et al. (1964) suggested that hypovolaemia might be a factor in the pathogenesis of RDS. This was not found by Debbs et al. (1961) and Barrie (1962). Gairdner (1965) stated that the question whether the placental transfusion affects the issue at all remains unanswered.

### Treatment

The principles of treatment in HMD were stated by Stahlman (1964): "The disease process is frequently self-limited, and we know of no specific therapy once the pathological process is fully established. Nevertheless we are convinced of the salutary effects of correcting or

nullifying certain of the secondary effects of this process as they arise. Until specific therapy is found, we advocate an approach which is based on information related to the individual baby's pathophysiology."

General care was the same as for premature infants with particular attention to maintenance of body temperature (Usher, 1961; Jelly et al., 1962; Beard et al., 1963; Day et al., 1964; Bostow et al., 1964 and Avery, 1964) and high humidity (Silverman and Blanc, 1957 and Gairdner, 1963). Handling was reduced to a minimum (Usher, 1961). Antibiotics were not given routinely by Gairdner (1963) but used by Stahlman (1964) and Oppé et al. (1965) with indwelling catheters, and by Fearon et al. (1964) with endotracheal intubation.

Oxygen therapy has been shown to be the most important form of treatment. The aim was to restore the oxygen tension in the tissues towards normal (Blystad et al., 1956a; Warley and Gairdner, 1962). In order to raise the  $PaO_2$  to a "high normal" level, Warley and Gairdner (1962) gave 25% more oxygen than was required to abolish cyanosis. Stahlman (1964) controlled the ambient oxygen to maintain a  $PaO_2$  of between 80 - 150 mmHg. Hyperbaric oxygen has not proved to be of additional value (Hutchison et al., 1962 and Cochran et al., 1963). Usher (1962) reported no retrolental fibroplasia in 100 patients on high ambient oxygen concentrations.

The rationale of metabolic treatment is that correction of the pH and provision of carbohydrate which can be readily metabolised will enable the infant to survive while the pulmonary disorder improves (Warley and Gairdner, 1962; Beard et al., 1963 and Oppé et al., 1965).

Daves et al. (1963, 1964) showed that the provision of glucose and alkali in asphyxiated animals will prolong survival and reduce brain damage. Reardon et al. (1957) first postulated better perfusion with the intravenous use of 5% dextrose and 0.45% saline. Usher has been the main protagonist of early treatment with glucose and sodium bicarbonate. Experience with this form of therapy has now been reported from many centres (Usher, 1961; 1963; Stahlman, 1964; Hutchison et al., 1964; Troelstra et al., 1964; Boston et al., 1964; Gairdner, 1965 and Tunell et al., 1965). Usher (1963) and Hutchison et al. (1964) claimed improved survival rates within their own units. The organic buffer tris (hydroxymethyl)aminomethane (Tham) has some advantages over sodium bicarbonate but has more side effects (Kaplan, 1962 and Mahas, 1962). Its use has been reserved for infants with severe respiratory acidosis (Stahlman, 1964; Hutchison et al., 1964; Troelstra et al., 1964 and Gupta, 1965) or a pH below 7.10 (Tizard, 1964a).

Although Stahlman (1964) reported improvement in the pH and  $PCO_2$  after digitilisation alone and digoxin prolonged survival in HMD in guinea pigs (Jaco, 1963), it is usually reserved for cardiac failure. The routine use of digoxin for the prevention of RDS was not recommended by Martin (1963). Insulin was used routinely by Usher (1961) and in hyperkalaemia by Stahlman (1964). Small blood transfusions were given for haematocrit values below 38% (Deliveria-Papadopoulos et al., 1964) or 40% (Gairdner, 1965).

The administration of human albumin to premature infants did not reduce the incidence or mortality from RDS (Frailen and Kitchen, 1962; Gyvin, 1965 and Habelth, 1965). Antihistaminics had no value

in the treatment of RDS (Davis, 1963; Bower and Cross, 1964 and Mitchell, 1964). Treelstra et al. (1964) administered parathormone when the serum phosphorus was high and the serum calcium low. They also gave calcium gluconate intravenously.

Specific attempts have been made to correct the underlying pathophysiological disturbances. Robillard et al. (1964) reported encouraging preliminary results in HMD with micro-aerosol administration of a synthetic surfactant. The problem was to get it into the alveoli (Daves, 1965). Gomez and Graven (1964) used a fibrinolysin but the high mortality with this form of treatment makes the risk of further trials prohibitive. Early pulmonary vasodilatation would lead to tremendous benefit of the distressed infant (Daves, 1965). Good results following the infusion of acetyl choline have been claimed by Chu et al. (1965) on this basis. Donald and Lord (1953) first employed assisted ventilation in respiratory failure, but this form of treatment has been disappointing in HMD. The greatly decreased compliance of the lungs in infants with HMD makes artificial ventilation difficult (Avery, 1964). Recent reports (Stahman, 1964; Fearon et al., 1964 and Thomas et al., 1965) give more encouraging results.

The nursing and medical care of infants with respiratory distress is of the greatest importance. The establishment of special units for the care of these infants has been strongly urged by Stahman (1964) and Cook and Cochran (1964).

**PART II**

**OVERALL RESULTS**

<b>Chapter 4</b>	<b>Diagnosis of the Respiratory Distress Syndrome</b>
<b>Chapter 5</b>	<b>Classification of RDS</b>
<b>Chapter 6</b>	<b>Results</b>
<b>Chapter 7</b>	<b>Discussion</b>

CHAPTER 4DIAGNOSIS OF THE RESPIRATORY DISTRESS SYNDROME

The term RDS is used throughout this study to describe a clinical picture of abnormal breathing, irrespective of cause (Hanley et al., 1963). RDS should be diagnosed on the clinical criteria and radiography and appropriate tests done to elucidate the underlying pathology (Harris, 1963 and Daves, 1965). Despite the importance of RDS in newborn infants there is no general agreement on the criteria for diagnosis.

Criteria for diagnosis

For a diagnosis of RDS in this study, 2 or more of the following were required:

1. A respiratory rate of more than 60/min. maintained for more than 3 hours.
2. Expiratory grunting present after 3 hours of age.
3. Cyanosis in room air.
4. Marked costal and sternal recession.
5. Pulmonary crepitations.

These criteria were chosen on the basis of clinical experience and are deliberately very wide to include all possible cases of respiratory distress. The criteria of other authors are set out in Table 1. It is assumed that they were describing RDS without differentiation of underlying pathology. In cases where it has not been indicated it is not clear how many criteria are demanded for a positive diagnosis.

TABLE 1 CRITERIA FOR DIAGNOSIS OF RESPIRATORY DISTRESS SYNDROME

Author	Miller 1963	Hatchison et al. 1964	Davis 1963	Gomez & Graven 1964	Jolly et al 1962	Troelstra et al. 1964	Malan
Basis for diagnosis :	Any 1 1 - 30 hrs	not specified	At 4 hours	6 - 18 hours	Any 3 criteria	not specified	Any 2 criteria
Respiratory rate :	>65 15 above RR 1st hour	>60 after 1 hr	Rising	>60	Increased	Usually >60	>60 for 3 hours After 3 hours
Grunting :	After 1 hour	+	+	+	+	+	+
Cyanosis (room air) :		+	+	+	+	+	+
Recession :		+			+	+	Marked costal and sternal
Crackles :					+	+	+
Decreased Air Entry :					+		
Oedema :							

TABLE 2 CRITERIA FOR DIAGNOSIS OF IRDS

Author	Usher, 1961	Driscoll and Smith 1962	Hatchless et al. 1964	Robertson et al. 1964
Basis for Diagnosis :	All 3 during and beyond first 3 hrs	Any 2 criteria > 60 at 2 hours	All 5 criteria > 60 after 1 hr.	Not specified
Respiratory rate :				High
Grunting :	+	+	+	
Cyanosis (room air) :		(with retraction)		+
Recession :	+		Marked	Severe
Chest radiogram :	See text	Characteristic (RGP + AB)	RGP + AB x	RGP*
Decreased Air Entry :	+			
Nostril breathing :				+

\* RGP = Reticulogranular pattern

x AB = Air bronchogram

The criteria for IRDS (Table 2) include the characteristic radiographic appearance as described by Donald and Steiner (1953). Usher (1961) did not always X-ray his patients.

#### Clinical appraisal of diagnostic criteria

The RR and presence or absence of grunting, cyanosis and marked costal or sternal recession were recorded in the 2,768 newborn infants on 24-hour observation. The frequency of occurrence of these 4 criteria of respiratory distress is shown in Table 3. It will be seen that grunting was the most frequent sign. Cyanosis and a  $RR > 60/\text{min.}$  were also very commonly seen. Marked recession, however, was present in only half the cases.

TABLE 3 FREQUENCY OF CRITERIA IN NEWBORN INFANTS

	<u>2,768 infants observed</u>	<u>218 infants with RDS</u>
$RR > 60$ for 3 hrs	483	152 (70%)
Grunting after 3 hrs	201	178 (82%)
Cyanosis in Room Air	157	157 (72%)
Marked recession	115	115 (53%)

#### Discussion

A comparison of diagnostic criteria is only possible when RDS is clearly defined. Too often one is left in doubt whether other conditions are included or only HMD is referred to. Similarly the reader should always be told the number of criteria which must be fulfilled before a diagnosis can be made. It is also of value to stipulate time limits where these are applicable.

### Respiratory rate

There seems to be universal agreement that a RR > 60/min. is significant of disturbed respiration. Miller (1963) and Phillips et al. (1959) have also shown that a rise of 10 - 15/min. after the first hour is frequently associated with respiratory distress. Why a rate of 60 has been adopted as the critical figure is not clear. Phillips et al. (1959) regarded normal rates as between 31 - 59. Not all infants with RDS have RR > 60 and indeed, the ones with slow rates have the worse prognosis (Phillips et al., 1959 and James, 1959).

On the other hand, a rate of more than 60 alone does not signify RDS. This is clearly shown by 331 infants in this survey. James (1959), Usher (1961), Jelly et al. (1962) and Prod'homme et al. (1964) have all stated that a raised RR alone does not establish a clinical diagnosis of RDS. A respiratory rate of more than 60 alone is called Neonatal Tachypnea in this study.

### Grunting

Grunting has been said to be the most characteristic sign of RDS (Usher, 1961) and is, in fact, quoted by all authors. In the present survey, audible grunting was the most constant finding. To be significant, it must persist beyond the third hour of life. Grunting was not infrequently heard in both premature and full-term infants in the first 1 - 2 hours after birth.

Whether grunting after 3 hours of age as a single sign constitutes a very mild form of respiratory distress is debatable. Miller (1963) regarded grunting alone as mild RDS. In many of the

23 infants in this series, the grunting cleared dramatically when the ambient oxygen concentration was increased. Stahlman (1964) also records this experience in her RDS group with moderate illness. None of the 'grunters' showed any other abnormality.

### Cyanosis

Clinical cyanosis in room air signifies quite a marked degree of arterial desaturation. This was present in 70% of infants with RDS including 3 cases of congenital heart disease. The mild degrees of RDS had no clinical detectable cyanosis. Occasionally a moribund infant with RDS was seen to have gross cyanosis and slow RR but no grunting or recession. In these cases associated crepitations or radiographic abnormalities were invariably present.

### Recession

Because of the many degrees of severity, recession is difficult to define and evaluate. Silverman and Anderson (1956) devised a method of scoring the severity of retraction. Many normal premature infants have a mild degree of retraction (Usher, 1961 and Miller, 1962). The retraction in RDS normally involves the costal margins and sternum and is more severe than in small prematures. For this reason only marked recession was considered significant and this was present in 57% of the RDS infants. One does not need to rely on retraction to make the diagnosis of RDS as it never occurs without other supporting signs. Bauman (1959) stated that most HMD deaths will have retraction scores (Silverman and Anderson, 1956) of more than 2. If authors stipulate marked recession, no one would question the validity of their observations.

### Crepitations

The presence of crepitations on auscultation of the chest may be present in several conditions such as HMD, pneumonia and meconium aspiration (Avery, 1964).

### Oedema and decreased air entry

These are constant findings in infants with HMD but not necessarily so in other manifestations of respiratory distress.

### Conclusions

The criteria for the diagnosis of RDS in this survey work very well in practice and compare favourably with those in the literature. At least 2 of the criteria should be present before a positive diagnosis is justified. Only a limited number of infants will fulfil all the criteria. The diagnosis of RDS seldom depends on the additional radiological evidence of chest pathology.

The clinical observations in 2,768 newborn infants confirm that a respiratory rate over 60/min. alone does not signify respiratory distress and that expiratory grunting is the most constant sign of the RDS. To be significant, grunting should be present 3 hours after birth. Cyanosis is a very common finding while marked recession was present in only half the cases.

CHAPTER 5CLASSIFICATION OF THE RESPIRATORY DISTRESS SYNDROME

Once the diagnosis of RDS has been made the clinician must seek to recognise the causative pathology. This differentiation is based on a detailed history of the pregnancy, labour, delivery and post-natal events and a full clinical examination paying particular attention to the respiratory, circulatory and central nervous systems. Investigations include chest radiogram, electrocardiogram, blood gas analysis, blood culture, histological examination of the placenta and membranes and a lumbar puncture when in doubt; and the passage of an oesophageal catheter and contrast media studies when local anatomical lesions are suspected.

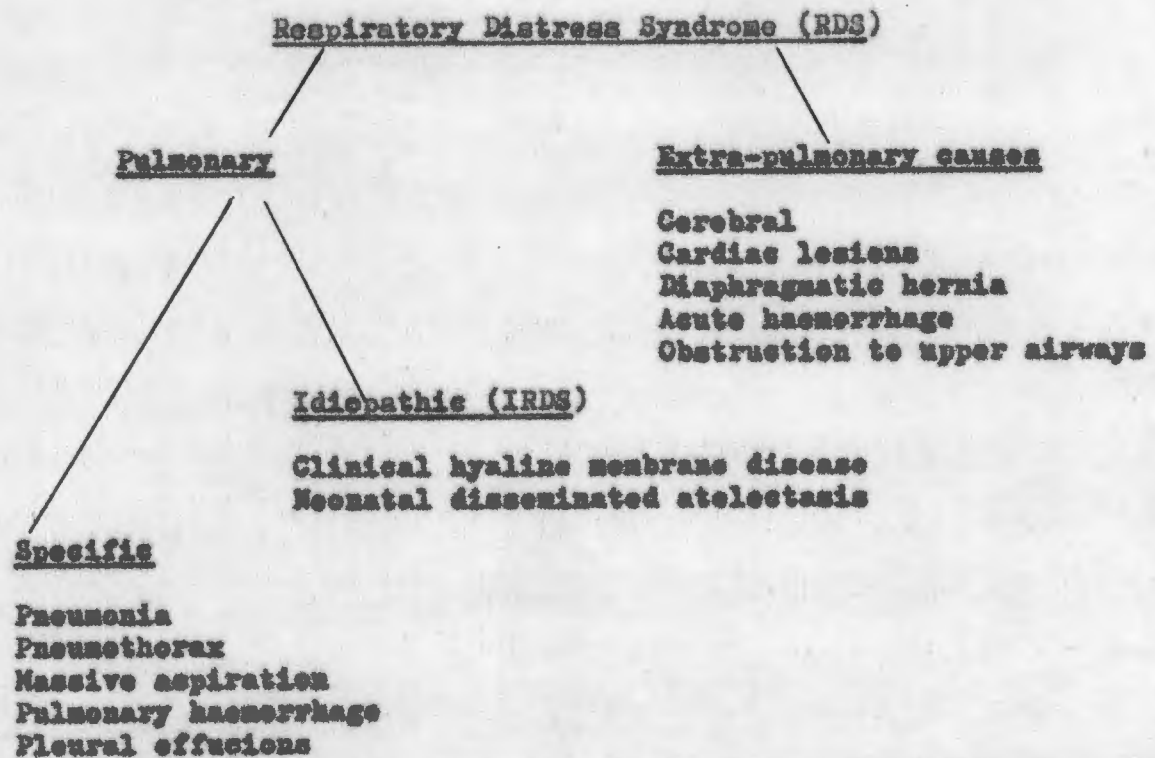
The identification of the primary cause of the RDS in newborn infants may be very difficult. The successful adaptation to extra-uterine life depends on the inter-relationship of the respiratory, circulatory and central nervous systems (Kariberg and Gelander, 1965). Rapid respirations and retraction usually point to lung pathology but none of the signs are pathognomonic of any one condition. The value of frequent observations and examinations and serial X-ray films cannot be too greatly stressed.

Radiology is the single most useful investigation in identifying the primary pathology in RDS. "Roentgenologic examination of the newborn with respiratory distress often provides pertinent data allowing a

specific diagnosis to be made or, equally important, the exclusion of diagnoses which might otherwise have been considered." (Harris, 1963).

The classification of RDS in this survey is given in Table 4.

**TABLE 4    SCHEMATIC OUTLINE OF CAUSES OF THE RESPIRATORY DISTRESS SYNDROME**



It will be seen that RDS is divided into 2 main groups, pulmonary and extra-pulmonary. Pulmonary causes are further sub-divided into specific conditions and idiopathic types. The term massive aspiration is used to embrace the more severe aspiration of meconium, squames and blood. Pneumothorax and pleural effusion are, strictly speaking, extra-pulmonary lesions but are included in this category because they are usually secondary to underlying pulmonary pathology.

IRDS refers to the group of patients in whom other specific causes of respiratory distress have been ruled out by the appropriate clinical and special investigations. CHMD (the term used for HMD) belongs to this sub-division. It has recently been suggested that the IRDS is not a homogeneous group but consists of classical HMD and an aspiration syndrome, here called Neonatal Disseminated Atelectasis (Kettler, Malan and Heese, 1964; Prod'ham, 1964 and Prod'ham et al., 1965). These two conditions may be indistinguishable on initial clinical examination and in this survey differentiation was made on the radiographic appearance.

The extra-pulmonary group consists largely of cerebral or, more correctly, intracranial causes. In a large number of RDS infants in this survey the cause of the respiratory distress remained undetermined because of lack of facilities for special investigations.

CHAPTER 6RESULTSInfants

The total number of live births in the 5 maternity hospitals in the period under review was 10,412 of whom 1,306 (12.5%) were under 2.5 kg in birth weight. The racial distribution and details of maternal complications, delivery and neonatal deaths are given in Table 5.

TABLE 5 TOTAL BIRTHS IN MATERNITY HOSPITALS

	<u>White</u>	<u>Cape Coloured</u>	<u>Bantu</u>	<u>Total</u>
Live births	2,115	6,744	1,553	10,412
Premature	161 (7.6%)	1,000 (14.9%)	145 (9.4%)	1,306 (12.5%)
Infants of diabetic mothers	5	42	3	49 (0.47%)
Caesarean section	110 (5.2%)	627 (7.6%)		737 (7.1%)
Vacuum extraction	32 (1.5%)	251 (3.0%)		283 (2.7%)
Forceps delivery	179 (8.5%)	435 (5.2%)		614 (5.9%)
Antepartum haemorrhage	116 (5.5%)	402 (4.8%)		518 (5.0%)
Pre-eclamptic toxemia	194 (9.2%)	889 (10.1%)		1,083 (10.4%)
Breech delivery	45 (2.1%)	301 (3.6%)		346 (3.3%)
Neonatal deaths (0 - 28 days)	47 (2.2%)	237 (2.9%)		284 (2.71%)

Figures in brackets represent percentage of totals

Observations were completed on 2,768 neonates, representing 88% of infants at possible risk. These were premature infants; infants born of diabetic

mothers; infants delivered by Caesarean section and forceps, vacuum or breech extraction; infants born of pregnancies and labour complicated by pre-eclamptic toxæmia, antepartum hæmorrhage or foetal distress; and any infant who was unwell in the first 24 hours of life. The observations probably included all infants with noticeable illness in the first 24 hours of life. Infants developing respiratory distress for the first time after 24 hours were not included in this survey. There were several cases of pneumonia, septicaemia and hæmorrhagic disease which fell into this category.

#### Incidence of RDS

The incidence of RDS and prematurity together with the mortality in the various maternity hospitals is shown in Table 6. The total of 255 infants with RDS includes the 23 infants with grunting alone and 14 cerebral infants who presented mainly with rapid respiratory rates.

**TABLE 6** DISTRIBUTION OF RDS IN MATERNITY HOSPITALS

<u>Maternity hospital</u>	<u>Number with RDS</u>	<u>Incidence RDS</u>	<u>Mortality RDS</u>	<u>Incidence Prematurity</u>
MMH (W)	16	1.74%	50%	6.2%
GSH (NW)	52	7.15%	48%	29.1%
GSH (W)	40	3.34%	40%	9.5%
PMH (NW)	96	2.46%	41%	13.9%
StM (NW)	16	1.27%	56%	10.8%
NSH (NW)	35	1.45%	74%	10.6%
<b>Total</b>	<b>255</b>	<b>2.44%</b>	<b>50%</b>	<b>12.5%</b>

W = White  
NW = non-White

The incidence of RDS in all hospitals was 2.44% and the mortality rate

50%. The incidence of RDS varies greatly and usually follows the percentage of premature births. The very high incidence of prematurity in non-white infants at Grootse Schuur Hospital is due to the preferential admission of mothers with complicated pregnancies to the hospital. Only deaths in the first 5 days were considered to be attributable to the respiratory disorder.

The racial incidence of RDS is given in Table 7.

TABLE 7 RESPIRATORY DISTRESS SYNDROME - RACIAL INCIDENCE

	<u>White</u>	<u>Cape Coloured</u>	<u>Bantu</u>
Premature infants < 2.5 kg	39/161 = 24.2%	116/1,000 = 11.6%	21/145 = 14.5%
'Term' infants	17/1954 = 0.9%	48/5744 = 0.8%	14/1408 = 1.0%
Total	56/2115 = 2.6%	164/6744 = 2.2%	35/1553 = 2.7%

While the incidence in 'term' infants is very similar there appears to be a considerable variation in prematures. Closer examination reveals an association of RDS with the varying racial incidence of prematurity as judged by birth weight. Table 5 shows prematurity figures of 7.6% in Whites, 14.9% in Cape Coloured and 9.4% in Bantu.

#### Disturbed respiration

A summary of infants with disturbed respiration is given in Table 8 which includes 331 with NT and 255 with RDS. All figures, except percentages, are average values. The RDS infants are subdivided according to their clinical presentation or pathology. Clinical details of the individual infants are set out in Appendix v - xvii. In 13

TABLE 8 SUMMARY OF 586 INFANTS WITH DISTURBED RESPIRATION

DIAGNOSIS	No.	% Total Births		% Infants at Risk		M : F Prem. Term		Wt. (kg)	Apgar at 1 min	Onset signs (hrs)	Resp. rate	R to 60 (hrs)	Grunting %	Grunting (hrs)	Recession %	Cyanosis %	Mortality	Average Death (hrs)	
		Prem. Term	Term	M	F	Prem. Term %	Term %												
<u>Neonatal Tachypnoea</u>	<u>331</u>	12.1	1.8	11.9	59	41	48	52	2.63	5.9	2.1	67	17	-	-	-	1.5	61	
<u>Respiratory Distress Syndrome</u>																			
Grunting	23	1.1	0.1	0.8	64	36	57	43	2.21	4.6	1.0	45	-	100	6	-	8.7	60	
Grunting + NT	13	0.7	0.04	0.5	54	46	69	31	2.24	6.2	1.0	70	8-23	100	6	15	0	-	
Clinical HMD	43	2.9	0.06	1.5	58	42	86	14	1.94	5.7	1.2	70	67	86	18	88	93	38	
NDA	10	0.3	0.06	0.4	60	40	40	60	2.67	4.9	3.0	69	29	70	11	70	70	38	
HMD-Autopsy Diag.	11	0.6	0.04	0.4	91	9	64	36	2.08	2.7	0.5	50	25	73	9	45	91	29	
RDS - Undetermined	96	6.9	0.1	3.5	55	45	91	9	1.66	4.4	1.2	54	41	89	12	48	75	19	
Pneumonia	13	0.5	0.08	0.5	69	31	54	46	2.53	4.6	1.2	60	37	85	17	38	69	34	
Pneumothorax	5	0	0.05	0.2	80	20	0	100	3.19	5.8	2.0	72	70	60	3	80	80	-	
Massive Aspiration	5	0.3	0.03	0.2	60	40	40	60	2.42	3.5	1.8	47	14	100	20	100	100	32	
Cong. Heart Disease	4	0.1	0.03	0.1	50	50	25	75	2.62	4.0	1.0	73	74	-	-	25	75	200	
Cerebral	21	0.3	0.2	0.8	71	29	19	81	3.04	3.4	2.3	68	34	33	7	14	28	72	
Miscellaneous	11	0.4	0.06	0.4	36	64	45	55	2.67	4.6	0.8	69	56	55	7	38	69	26	
<u>Total RDS</u>	<u>255</u>	<u>14.0</u>	<u>1.85</u>	<u>9.3</u>	<u>60</u>	<u>40</u>	<u>69</u>	<u>31</u>	<u>2.10</u>	<u>4.7</u>	<u>1.8</u>	<u>58</u>	<u>37</u>	<u>69</u>	<u>14</u>	<u>50</u>	<u>68</u>	<u>50</u>	<u>35</u>

instances, grunting with minimal recession and no cyanosis preceded a later rise in RR. Although the grunting and tachypnea were not present at the same time there can be little doubt that these infants had mild RDS. HMD was diagnosed at autopsy in 11 infants not investigated during life. The largest group of all is the undetermined group.

Both NT and RDS had a higher incidence in premature infants, 12.1% and 14.0% as opposed to 1.8% and 1.8% in 'term' infants respectively. NT was found in 11.9% and RDS in 9.3% of observed newborns. Male preponderance is a constant finding in NT and RDS with the exception of the congenital heart disease and miscellaneous groups. The actual numbers within the two weight groups influence the average birth weights. The Apgar scores (Apgar et al., 1958) are on the whole low but the range in 'normal' infants was not determined. The onset of signs varied from birth to several hours. The average recorded onset may well be somewhat later than was actually the case because of delay in commencing observations. The RR was calculated from the onset of signs until death or the disappearance of the signs. The average was over 60/min. in most groups but 58/min. for RDS as a whole. Grunting, recession, cyanosis and mortality are expressed as percentages while the duration of signs and age of death are given in hours. These figures are often heavily biased by autopsy diagnoses and are not necessarily a true reflection of the various conditions. The mortality in NT was only 1.5% as opposed to 50% in RDS.

### Acid-Base values

The average acid-base values in RDS are shown in Table 9. These figures represent determinations on the initial examination. Serial acid-base determinations are given in Appendix xviii - xxv. In some groups only one or two determinations were done, which detracts from their possible value. Normal values in premature and full term infants are included for comparison (Appendix xxvi). The infants with grunting alone had values comparable with normal prematures. Grunting followed by NT was associated with a combined metabolic and respiratory acidosis. The undetermined group had values very similar to CHMD and NDA.

### Infants of diabetic mothers

The association of disturbed respiration and IDM is summarised in Table 10. Both NT (18%) and RDS (20%) had a higher incidence in these infants. The conditions causing RDS are similar to those in Table 8 except that the sex ratio was reversed. The much greater weights of IDM are evident.

### Referred infants

Thirty-five newborn infants were referred from Greater Cape Town for investigation and treatment (Table 11). The individual case details are given in Appendix xvii. The infants were most often referred for the signs of grunting, recession and cyanosis. The majority suffered from IRDS while NT was found in 2 cases. The sex incidence, weights and clinical signs are similar to those in Table 8.

### Radiological diagnoses

The radiological diagnoses in 112 newborn infants with

TABLE 9 DISTURBED RESPIRATION - AVERAGE INITIAL ACID-BASE VALUES

DIAGNOSIS	No. of cases	pH	PCO <sub>2</sub> mmHg	Base Excess mEq/L	Buffer Base mEq/L	Standard HCO <sub>3</sub> <sup>-</sup> mEq/L	Actual HCO <sub>3</sub> <sup>-</sup> mEq/L
Grunting	1	7.395	39.2	-4.0	43.5	20.8	20.5
Grunting + NT	1	7.230	47.4	-8.8	40.8	17.6	19.1
Clinical RMD	30	7.184	55.2	-8.5	38.5	17.5	19.9
RDA	7	7.245	55.2	-6.2	41.7	19.3	21.9
RMD - Antepay diagnosis	1	7.220	66.5	-3.4	45.0	21.3	25.8
RDS - Undetermined	7	7.210	53.5	-7.7	40.6	18.2	20.2
Pneumonia	1	7.435	31.5	-2.0	47.0	22.5	21.2
Pneumothorax	5	7.368	32.5	-5.3	43.1	19.9	18.1
Massive Aspiration	2	7.160	61.3	-9.3	38.8	16.9	21.2
Congenital Heart Disease	1	7.385	30.0	-5.3	44.0	20.0	17.3
Cerebral	2	7.379	35.0	-3.7	48.0	21.1	20.2
Miscellaneous	5	7.189	52.4	-9.5	39.0	17.0	19.6

TABLE 10 SUMMARY OF DISTURBED RESPIRATION IN IDM\*

DIAGNOSIS	No.	Ratio		Onset signs (hrs)	Resp. rate	RR > 60 hrs.	AVERAGE		Weighting (hrs)	Resuscitation	Cyanosis	Med	Age Death (hrs)
		M : F	Prem:Term				Wt. (kg)	RR > 60 hrs.					
Neonatal Tachypnea	9	7 : 2	2 : 7	0.8	71	24	3.71	0.8	71	-	-	-	-
Clinical RHD	4	1 : 3	2 : 2	3.0	61	55	2.58	3.0	61	2	3	1	57
NDA	2	2 : 1	0 : 2	1.5	68	27	3.06	1.5	68	1	2	-	-
RDS - Undetermined	1	0 : 1	0 : 1	-	60	81	3.17	-	60	-	1	1	81
Pneumonia	1	1 : 0	0 : 1	B	96	48	5.11	B	96	-	1	-	-
RDS - ? RHD	1	1 : 0	0 : 1	B	94	35	4.68	B	94	-	-	-	-
Diaphragmatic hernia	1	0 : 1	1 : 0	1.0	76	50	1.78	1.0	76	1	1	1	72

19

\* Total number of IDM = 49

TABLE 11 SUMMARY OF 35 INFANTS REFERRED FROM GREATER CAPE TOWN

DIAGNOSIS	No.	Ratio		Onset signs (hrs)	Resp. rate	RR > 60 hrs.	AVERAGE		Weighting (hrs)	Resuscitation	Cyanosis	% Deaths	Av. Age Death (hrs)
		M : F	Prem:Term				Wt. (kg)	RR > 60 hrs.					
Clinical RHD	21	13 : 8	17 : 4	1.8	69	57	1.97	1.8	69	91	91	62	34
NDA	8	8 : 0	5 : 3	2.0	76	51	2.72	2.0	76	87	37	12	79
Pneumothorax	2	2 : 0	0 : 2	B	103	180	3.50	B	103	100	100	0	-
Massive Aspiration	2	2 : 0	0 : 2	?	73	70	3.50	?	73	100	50	50	47
Neonatal Tachypnea	2	2 : 0	1 : 1	5	78	50	2.52	5	78	0	0	0	-

disturbed respiration are shown in Table 12.

The IRDS again accounts for by far the greatest percentage of abnormal findings. Four infants had abnormal radiograms in which the pathology was not identifiable.

TABLE 12 SUMMARY OF RADIOLOGICAL DIAGNOSES

Clinical Hyaline Membrane Disease	62
Neonatal Disseminated Atelectasis	18
Spontaneous Pneumothorax	7
Massive Aspiration	3
Pneumonia	3
Pulmonary Flothera	3
'Abnormal'	4
Normal	8
Diaphragmatic Hernia	1
Unilateral Atelectasis	1
Pleural Effusions	1
Obstructive Emphysema	1
	<hr/>
Total	112

CHMD complicated by Pneumothorax 16.8%

Clinical details of the 8 infants with normal radiograms are given in Table 13. They are 4 with NT, 3 with mild RDS and 1 intracranial haemorrhage.

TABLE 13 CLINICAL DETAILS OF 8 INFANTS WITH NORMAL RADIOGRAMS

Neonatal Tachypnoea	4
Mild RDS	2
Grunting only	1
Intracranial haemorrhage	1

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Table 14 shows the close correlation between the radiological diagnosis and histological findings in 27 infants. Two infants with HMD were not recognised on radiography - one was labelled NDA and the other was regarded as normal. Two of the abnormal films belonged to infants with massive aspiration of squames and meconium respectively.

**TABLE 14 CORRELATION BETWEEN RADIOLOGICAL AND HISTOLOGICAL FINDINGS**

<u>Radiological Diagnosis</u>	<u>Number Autopsied</u>	<u>Pulmonary Histology</u>
Clinical Hyaline Membrane Disease	17	15 Hyaline membranes 2 Resorption atelectasis
Neonatal Disseminated Atelectasis	2	1 Focal atelectasis 1 Hyaline membranes
Massive Aspiration	2	Both aspiration atelectasis
Pneumonia	1	Broncho-pneumonia
Pulmonary Plethora	1	Anomalous pulmonary venous drainage
Normal appearance	2	1 Normal 1 Resorption atelectasis
'Abnormal'	2	1 Aspiration squames 1 Aspiration meconium

### Pathology

Autopsies were performed in only 37% of the deaths in RDS. The results are listed in Table 15.

Total Deaths = 155  
Autopsies = 97 (37%)

**TABLE 15 RDS - AUTOPSY RESULTS**

<u>MAJOR PATHOLOGY</u>		<u>ASSOCIATED FINDINGS</u>	
Resorption atelectasis plus hyaline membranes (38.6%)	- 22	Subarachnoid haemorrhage* - 6 Intra-alveolar haemorrhage - 2 Patent ductus arteriosus - 2 Lung abscess X - 1 Intra-peritoneal haemorrhage - 1	
Resorption atelectasis (15.5%)	- 9	Intra-alveolar haemorrhage - 2 Subarachnoid haemorrhage* - 1 Pleural effusion - 1	
Pneumonia (13.8%)	- 8	Subarachnoid haemorrhage - 2 Pericarditis - 1 Atrial Septal Defect - 1 Congenital syphilis - 1	
Diaphragmatic hernia (3.4%)	- 2	Hypoplastic Left lung - 1 Hypoplastic Right lung - 1	
Massive aspiration: Squames (10.3%)	- 4		
	Meconium - 2		
Intracranial Lesions: (8.5%)			
Cerebral haemorrhage	- 2		
Subarachnoid haemorrhage	- 2		
Toxoplasmosis	- 1		
Intra-alveolar haemorrhage	- 1		
Pleural effusion	- 1		
Subcapsular haemorrhage of liver	- 1		
Septicaemia and focal atelectasis	- 1		
Undetermined	- 1		

\* Subarachnoid haemorrhage - 22.5% of HMD

X Prolonged IPPR therapy

Where there was a combination of lesions the major lesion was classified. Resorption atelectasis ± hyaline membranes was the most common finding and accounts for 66% of deaths from pulmonary pathology. Subarachnoid haemorrhage heads the list of associated pathology, occurring in 22.5% of HMD deaths. Intra-alveolar haemorrhage was also commonly seen. Infection was the cause of death in 10 infants.

#### Electrocardiographic findings

Satisfactory ECGs were recorded at the initial examination in 47 infants. All were done at Groote Schuur Hospital and comprised IRDS mainly. No ECG evidence of hyperkalaemia was present on the initial graphs. The cases were divided into 2 groups according to the praecordial leads - Table 16.

TABLE 16 ECG IN RDS - ASSESSMENT OF PRAECORDIAL QRS COMPLEX

<u>Group</u>	<u>Praecordial leads</u>	<u>GHMD</u>	<u>NDA</u>	<u>Pneumo-thorax</u>	<u>NT</u>	<u>Pleural Effusion</u>	<u>Total</u>	<u>Mortality</u>
I	R > S in V1 and V2	15	3	1	2	-	21	14%
II	R < S or R = S in V1 and/or V2	19	4	2	-	1	26	42%

Group I, with the normal right ventricular dominance of the newborn, had a lower mortality rate than Group II with left ventricular dominance. Assessment of the praecordial P waves in the same groups (Table 17) demonstrates the better survival rates when the P wave is peaked or biphasic. The 3 deaths in Group I were associated with notched or inverted P waves while there were no survivors in Group II with these changes.

TABLE 17 ECG IN RDS - ASSESSMENT OF PRECORDIAL P WAVE

<u>P wave</u>		<u>Survivors</u>	<u>Deceased</u>
<u>V1</u>	<u>V2</u>		
<u>Group I: R &gt; S in V1 and V2</u>			
Peaked or biphasic	Peaked or biphasic	13	0
Peaked or biphasic	Notched	3	0
Notched	Notched	1	1
Notched or inverted	Inverted	1	2
<u>Group II: R &lt; S or R = S in V1 and/or V2</u>			
Peaked or biphasic	Peaked or biphasic	9	3
Peaked or biphasic	Notched	6	3
Notched	Notched	0	2
Inverted	Notched	0	3

CHAPTER 7DISCUSSIONIncidence of RDS

No other figures are available for the incidence of RDS as defined in this study. Dunn (1965) reported a 3.7% incidence of RDS in a selected maternity hospital population where many abnormalities were seen. The incidence in any series will obviously depend on the number of premature infants. The highest incidence of RDS in this survey accompanied the highest incidence of prematurity. The relatively low incidence and higher mortality of RDS in St. Monica's Home and New Somerset Hospital may be due to the fact that some mildly distressed infants were not included in the observations. These two hospitals also do not have resident medical staff with paediatric training.

There is probably no difference in the racial incidence of RDS if allowance is made for the different incidence of prematurity. Many more non-white infants were premature by weight. This has also been found elsewhere in the world (Baird, 1964 and Webb et al. 1962). The assessment of maturity should include the gestational age as calculated from the mother's statement (Gruenwald, 1964a).

Respiratory Distress Syndrome

Only one clinical study, from Toronto, included all the causes of RDS during life (Hanley et al., 1963). Many reports deal only with one or two causes and they will be discussed under the appropriate chapters in Part III.

Hanley et al. (1963) recorded mortality rates between 19 - 76% with an average of 53%. Bauman (1959) found that the fatality rate in the first 7 days of life of the dyspnoeic infant was 60%. Deaths from RDS accounted for 45% of the total and 64% of early neonatal deaths in the maternity hospitals. Early neonatal deaths refer to babies dying within the first 7 days of life.

By including 88% of live-born infants at possible risk in this survey, it was inevitable that the cause of RDS would remain undetermined in many cases. This was especially so in Newbray, Peninsula and St. Monica's Maternity Homes where X-ray facilities were not available. The undetermined group had the usual male preponderance and included a very high percentage of prematures. There was a high mortality and earlier deaths, probably due to the low birth weights (Miller, 1957a, 1963). The clinical picture and course was similar to CHND and like Hanley et al. (1963) one feels that the majority probably fell into the HND category. Some with birth weights below 1.0 kg may have been due to pulmonary immaturity or primary atelectasis (Petter, 1953 and Hanley et al., 1963).

#### Acid-base values

It was impossible in this survey to standardise the time and circumstances of acid-base determinations. The acid-base values will vary with age, degree of anoxia and preceding treatment, if any.

#### Infants of diabetic mothers

Gellis and Hsia (1959) stated that respiratory distress is the single most important finding in the infant of the diabetic mother and that other factors play a relatively unimportant rôle in the morbidity

and mortality of these infants. Their incidence of RDS was approximately 33%. Moore et al. (1960) recorded an incidence of transitional distress in 37%. The high incidence related to gestational age and not low birth weight (Moore et al., 1960). A larger series is needed to confirm or disprove the suggestion here that more females than males are affected. The mortality rate in this series was 33% which is in accordance with the observations of Driscoll et al. (1960) who did not find the case fatality rate to be increased.

#### Radiography

Although there was a very good correlation between the radiological and histological diagnosis, many of the initial films were difficult to classify, particularly those of poor quality. Serial films were of the greatest value in doubtful cases. It is interesting to note that in an attempt to get better films, Smith (1965) advocates lifting the infant to the X-ray table and back again while oxygen is supplied by means of a face mask.

Peterson and Pendleton (1955) described the normal appearance in control infants. A normal or negative radiogram was seen in this survey in one child who subsequently died, with HMD demonstrable at autopsy. This finding is well described by Peterson and Pendleton (1955), Schultze (1958) and Driscoll and Smith (1962). The paediatrician should always be on the alert for the common complication of pneumothorax in CHMD and institute prompt treatment in cases of tension (Smith, 1965).

#### Pathology

The autopsy rate in this survey was unfortunately low. Much can be learned from pathological findings which also serve to confirm

or disprove the accuracy of clinical diagnoses. The high percentage of HMD in early neonatal deaths reported by Arey and Dent (1953), Bound et al. (1956), Benirschke (1960), Sivanesan (1961), Driscoll and Smith (1962) and Butler and Bonham (1963) was confirmed here.

Stahlman (1964) stated that a high percentage of the irreducible minimum of deaths had significant subarachnoid haemorrhage. Intracranial haemorrhage was a complication in one-quarter of CHMD deaths in this survey. Hanley et al. (1963) found intracranial haemorrhage in 24 out of 72 IRDS infants, while Hutchison et al. (1964) recorded an even higher incidence (31 out of 46). According to Avery (1964) this may be due to several factors:

1. Capillary bleeding may be associated with profound tissue anoxia
2. Clotting factors are depressed in severe hypoxia
3. Respiratory effort and grunting may be associated with an elevation of cerebral venous pressure.

Additional factors may be venous engorgement and dilatation which accompanies severe hypercapnia.

The mixed pathology reported here is a typical finding in RDS. Landing (1957) determined the statistical correlation between the different pulmonary lesions.

#### Electrocardiography

The results of this study are in agreement with the statement of Keith et al. (1961) that there is a poorer prognosis with an ECG pattern characterised by a deep S wave in V1. The examination of the P wave confirms the value of the P wave in the assessment of the RDS (Sutin, Horner, Heese and Malan, 1965). About half of the cases were common to both studies.

## P A R T    I X X

### SPECIFIC DISORDERS OF RESPIRATION

Chapter 8	Respiratory rates and patterns in normal infants
9	Neonatal Tachypnoea
10	Clinical Hyaline Membrane Disease
11	Neonatal Disseminated Atelectasis
12	Pneumonia
13	Spontaneous Pneumothorax
14	Massive Aspiration
15	Cerebral Infants
16	Miscellaneous Conditions
17	Intermittent Positive-Pressure Respiration
18	Summary

CHAPTER 8RESPIRATORY RATES AND PATTERNS IN NORMAL INFANTSIntroduction

Before discussion of pathological conditions, it was thought to be of interest and value to record the normal rate and fluctuation of respiration in the first 24 hours of life. The values given here were obtained from normal infants only. Those with respiratory distress were excluded.

Method

The data were obtained from 499 consecutive observation charts with complete records of respiratory rates. Of these, 210 infants were premature by weight, and 289 weighed over 2.5 kg. The values in the first hour after birth and at 3 hourly intervals thereafter were used. The infants were divided into different groups according to birth weight, sex, maternal complications and method of delivery.

All infants were also divided into respiratory groups I, II and III, as follows:

(a) Group I

Infants who breathed at approximately normal rates (between 25 - 55/min.) for the first hour and who showed no significant increase or decrease in subsequent RR. (A significant increase is defined as one in which the mean RR in any period exceeds the mean rate during the first hour by 15/min. or more).

**(b) Group II**

Infants who breathed at comparatively high rates (higher than 55/min.) for the first hour and subsequently showed a decrease to normal rates (25 - 55/min.). This group also contained a few infants who showed a decrease to rates lower than 25/min.

**(c) Group III**

Infants who breathed at high, normal or low rates in the first hour, but in all instances showed a significant increase in their RRs at some time during the first 24 hours.

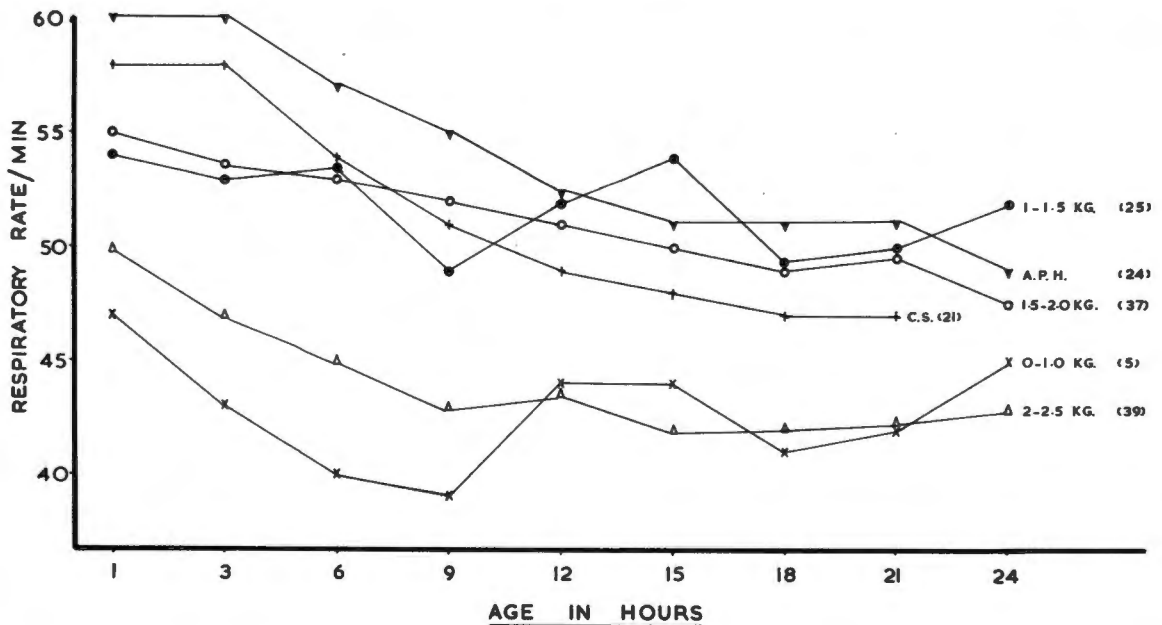
**Results**

**Average normal RR** The mean RR and standard deviation were calculated for all premature and 'term' infants during the first hour and at 6, 12, 18 and 24 hours. These values are shown in Table 18. The rates during the first hour were the same for both premature and 'term' infants: 54 and 53/min. respectively. The rates decreased after this but the fall was slower in 'term' infants. At 24 hours the values were again similar. It will be seen from the standard deviations that there is a wide range of RR at all hours.

**TABLE 18 RESPIRATORY RATES IN NORMAL PREMATURE AND 'TERM' INFANTS**

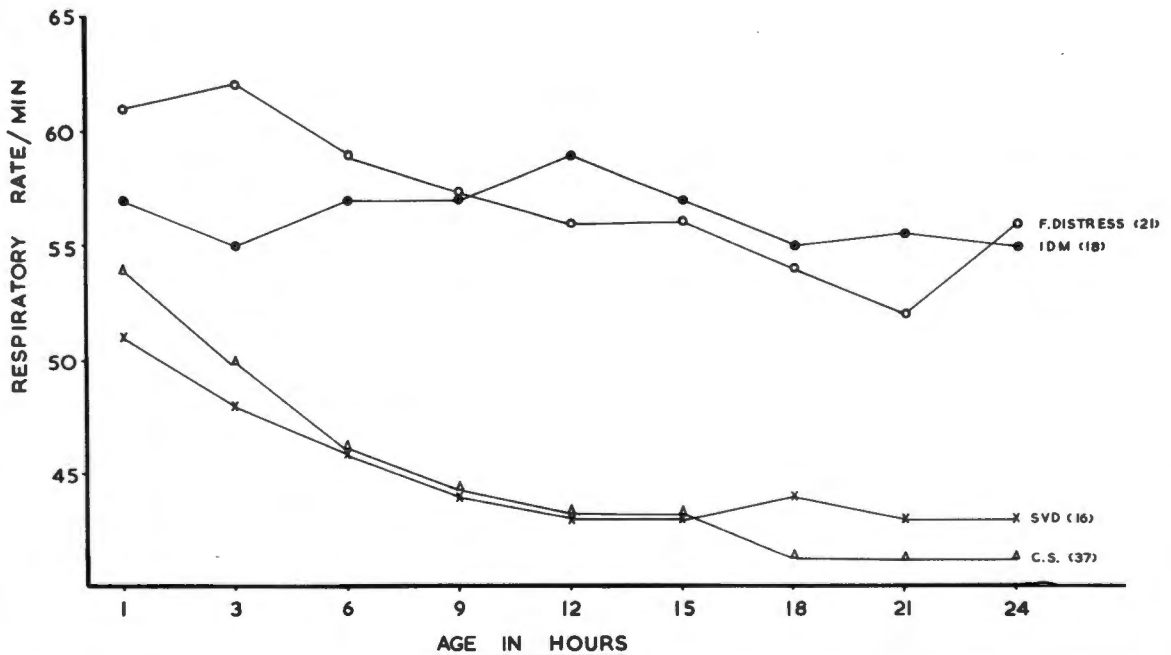
		<u>1st</u>	<u>6</u>	<u>12</u>	<u>18</u>	<u>24</u>
		<u>hour</u>	<u>hours</u>	<u>hours</u>	<u>hours</u>	<u>hours</u>
Prematures	Mean	54	51	48	46	45
	S.D.	14	12	12	11	12
'Term' infants	Mean	53	47	43	44	44
	S.D.	15	13	13	12	12

**Premature infants** The mean RRs over 24 hours were plotted for 6 different categories to determine the effect of weight and complications (Figure 1). The initial and subsequent rates were lower in the smallest (< 1.0 kg) and heaviest (2 - 2.5 kg) weight categories while those between 1 - 2 kg had higher RRs. The lowest values were in < 1.0 kg infants but it must be pointed out that there were only 5 in this category. Higher initial values were evident in Caesarean section delivery and especially antepartum haemorrhage. The graphs for pre-eclamptic toxemia and forceps deliveries were virtually identical with the 2 - 2.5 kg category.



**Fig.1.** Respiratory rates in premature infants in the first 24 hours of life

**'Term' infants** Four categories were plotted here - spontaneous vertex deliveries, Caesarean section deliveries, infants of diabetic mothers and delivery after foetal distress (Figure 2). Foetal distress was defined objectively as occurring in deliveries marked by meconium in the liquor amnii. Although the SVD group started with a mean rate over 50/min., it soon fell to 'normal' values. This was also the case with CS infants. IDM had higher initial rates which were sustained. The values were even higher after foetal distress. Infants born after APH or PET and delivery by forceps, vacuum or breech extraction gave graphs identical with the CS category.



**Fig.2. Respiratory rates in 'term' infants in the first 24 hours of life**

Respiratory groups

The distribution of premature and 'term' infants according to the chosen respiratory groups are shown in Table 19. Even in normal infants there are differences between the premature and 'term' infants. While more premature infants belong to Groups II and III, the majority of 'term' infants fell into Group I.

TABLE 19 DISTRIBUTION OF 499 INFANTS INTO RESPIRATORY GROUPS

<u>Respiratory Group</u>	<u>Prematures</u>	<u>'Term' Infants</u>
I	80 (38%)	147 (51%)
II	87 (41.5%)	102 (35.2%)
III	43 (20.5%)	40 (13.8%)
Total	210	289

Statistical difference between sexes

The hypothesis that there may be a preponderance of females in Groups I and II and of males in Group III was tested in the different categories according to weight and complications. This assumption was true for prematures of 2 - 2.5 kg only ( $P < .05$ ). In all other groups the hypothesis was not substantiated.

Discussion

Although RRs were not counted during crying or feeding, there must inevitably have been subjective observation variations. Periodic breathing was not thought to influence the counting in premature infants as Chernick et al. (1964) found this rhythm on one occasion only under 24 hours of age. Because observation charts were not kept as a routine

on healthy 'term' infants, the number of values obtained for spontaneous vertex deliveries are rather scanty.

The RR in the newborn period has been recorded by Cross and Oppé (1952), Miller (1957), Phillips et al. (1959) and Usher (1961). There was considerable difference in their findings. It was obvious that the range in both premature and 'term' infants is very wide. This led Miller (1957) and Phillips et al. (1959) to divide their infants into 3 different respiratory groups as was done here. The other studies included all infants whereas this study was concerned with normal (non-RDS) infants only.

There was little difference between the mean values for premature and 'term' infants. The rates in premature infants were higher at 6, 12 and 18 hours only. With larger numbers of spontaneously delivered 'term' infants, more noticeable differences may be seen. Usher (1961) recorded an average respiratory rate of 55/min. during the first hour in healthy prematures. His subsequent rates, however, were much higher than those found in this study.

The differences between the premature weight groups were surprising. The slower respiratory rate in the lowest weight group may have been due to the poorer response of the immature respiratory centre to chemical stimuli. It has already been pointed out that there were very few infants in this category. The gestational age was not ascertained here but may prove to be a better guide than weight alone. No other figures for Caesarean section delivery or other complications in prematurity are available for comparison.

The findings in 'term' infants are very much the same as those of Haddad et al. (1956). Gellis and Hsia (1959) also found rapid rates for IDM. The rates for IDM in this study are high even after exclusion of RDS. The presence of meconium in the liquor does not necessarily signify foetal distress (Auld et al. 1961 and Cox, 1963) but was the best objective criterion available. The high respiratory rate with this complication may indicate minimal aspiration. The respiratory rates for such infants have not been recorded previously.

The classification of newborn infants into 3 respiratory groups has been done by Miller (1957) and Phillips et al. (1959). Miller (1957) found that premature infants were divided equally among the 3 groups with relatively more small ones in Group III. He had no deaths in Groups I and II, but 18 out of 73 in Group III which he attributed to HMD (Miller et al., 1958). Phillips et al. (1959) recorded a similar distribution of mortality and pointed out that Group III was the most common pattern under 1.75 kg. Usher (1961) found a rise in RR of more than 20/min after the first hour in 20% of healthy and 70% of RDS infants. Miller (1957) recorded that less than 5% of 'term' infants belonged to Group III.

The incidence of RDS is higher in males than in females. If most RDS infants fall into Group III, one might expect a greater proportion of males in that group, but on the criteria chosen for respiratory grouping no significant difference could be demonstrated. In non-RDS infants the sex does not appear to influence the respiratory pattern. The respiratory groups are, of course, arbitrarily chosen and it may be that some other parameter such as mean rates will show

a sex difference.

### Conclusions

The mean respiratory rates for prematures are slightly higher than for 'term' infants at 6, 12 and 18 hours only. The range of RR is very wide. There is no correlation between rate and the degree of prematurity as judged by weight. Caesarean section and antepartum haemorrhage resulted in higher initial rates in premature infants. The highest rates in 'term' infants were found after foetal distress and maternal diabetes.

More premature infants belong to the respiratory Groups II and III while the majority of 'term' infants fall into Group I. No difference was demonstrable between males and females on this grouping but the possibility that differences do exist is not excluded.

CHAPTER 9NEONATAL TACHYPNOEAIntroduction

The most frequent 'disturbance' of respiration in this survey was a rapid respiratory rate alone. This group was called NT and defined as a RR of more than 60/min maintained for more than 3 hours in the absence of other signs of respiratory distress. Three hundred and thirty-one infants fulfilled these criteria. The further investigation of this group is recorded in this chapter.

Clinical data

The clinical data in NT is shown in Tables 20 and 21. NT was present in 16.6% of premature and 9.5% of 'term' infants respectively. The average incidence for all infants observed was 11.9%.

Premature infants (Table 20)

The incidence of NT in normal vertex deliveries was 16.0%. Higher incidence was found in infants delivered by Caesarean section and breech presentation. The complications of pre-eclamptic toxæmia and antepartum hæmorrhage per se did not lead to a higher incidence. There was no difference between males and females. The onset of  $RR > 60$  was variable and NT obviously includes both those who had a rapid respiratory rate from birth and those who had a rising RR. There is little difference between the average RR values. The usual

TABLE 20 NEONATAL TACHYPNOEA - PREMATURE INFANTS

Complications and Delivery	Number infants observed	Number with NT	% NT	Male	Female	Wt. (kg.)	Onset (hrs)	Resp. rate	Duration (hrs)	Age at 1 mo	Age at death (hrs)	Deaths	AVERAGE		
NVD	624	102	16.0	52	50	1.81	2.3	69	18	7.5	66	3			
IDM	6	1	16.6	1	-	2.43	0	69	34	1.0	-	-			
PET	81	10	12.3	6	4	1.97	2.8	69	29	4.5	-	-			
APH	78	10	12.8	5	5	1.68	1.2	67	18	6.0	-	-			
CS	41	9	22.0	6	3	2.02	1.3	73	13	5.8	-	-			
Forceps Delivery	43	4	9.3	1	3	2.19	1.5	68	11	7.0	-	-			
PET + CS	26	6	23.0	3	3	1.70	1.0	76	33	6.0	60	1			
Breech Delivery	40	10	25.0	7	3	1.96	3.4	68	15	6.3	48	1			
APH + CS	22	8	36.0	3	5	1.85	3.0	71	21	4.0	-	-			
TOTAL	961	160	16.6	84	76	1.86	2.2	68	19	6.3	61	5			

rates were 60 - 80/min but occasionally rates were between 90 - 110. In the majority of infants the RR dropped to below 60 by 24 hours. The duration was prolonged in IDM, PET and PET + CS. Apgar ratings showed a wide range with occasional low values. Chest radiograms obtained in 4 infants with NT revealed no abnormalities.

There were 5 deaths under the age of 5 days. The details regarding these infants are summarised below:

<u>Case No.</u>	<u>Sex</u>	<u>Weight (kg)</u>	<u>Average RR</u>	<u>Duration RR &gt; 60 hrs.</u>	<u>Age Death hrs.</u>	<u>Cause of Death</u>
52	M	1.61	60	23	72	Gastric perforation. Normal lungs
281	M	1.61	74	27	30	Aspiration milk feed
543	M	2.24	62	9	96	Undetermined
569	M	2.06	63	8	48	Undetermined
183	F	1.19	81	60	60	Haemorrhagic disorder

'Term' infants (Table 21)

The overall incidence of NT in 'term' infants was lower than in premature infants. This was particularly apparent when normal vertex deliveries in the 2 groups were compared. The incidence was higher in IDM (especially when delivered by CS), following the complications of neonatal asphyxia and foetal distress, and after breech delivery. The incidence in normal vertex deliveries was lower than in Caesarean section or instrumental delivery. In contrast to premature infants there is a significant difference between the incidence in males and females ( $p < .001$ ). The average age of onset, RR and Apgar ratings were similar to those in Table 20 but the duration of RR > 60 was

TABLE 21 NEONATAL TACHYPNOEA - 'TERM' INFANTS

Complications and Delivery	Number infants observed	Number with NT	% NT	Male	Female	Wt. (kg)	Onset (hrs)	Duration (hrs)	Resp. rate	Apgar at 1 min	Deaths	AVERAGE	
<u>Pre-Eclamptic Toxaemia</u>													
NVD	68	4	5.9	4	-	3.09	1.0	10	64	4.8	-		
IDM	8	1	12.5	1	-	3.85	1.8	20	72	7.0	-		
APH	2	0									-		
CS	65	5	7.7	3	2	2.97	3.6	32	73	2.0	-		
Forceps/VE	140	11	7.8	8	3	3.40	3.0	12	69	6.5	-		
<u>A.P. Haemorrhage</u>													
NVD	30	1	3.3	1	-	3.34	1.0	4	64	2.0	-		
CS	39	3	7.7	3	-	3.24	4.0	10	71	6.0	-		
Forceps	10	0									-		
<u>Caesarean Section</u>													
CS	529	49	9.3	34	15	3.35	2.3	21	69	6.0	-		
IDM	19	5	26.2	4	1	3.93	0.8	19	71	6.4	-		
<u>Instrumental</u>													
VE	602	24	8.0	14	10	3.34	1.8	13	65	6.0	-		
Forceps		24		16	8	3.58	2.0	20	68	6.0	-		
<u>Infant of Diabetic Mother</u>													
	18	2	11.8	1	1	3.72	6.0	33	70	6.0	-		
<u>Neonatal Asphyxia</u>													
	19	6	31.8	3	3	3.18	1.0	17	72	2.3	-		
<u>Foetal Distress</u>													
	62	16	25.8	8	8	3.15	1.0	22	74	4.6	-		
<u>Breech Delivery</u>													
	130	17	13.0	11	6	3.02	0.9	10	70	5.0	-		
<u>Face-Brow presentation</u>													
	8	0									-		
<u>Normal Vertex Delivery</u>													
	58	3	5.1	1	2	3.31	1.3	12	70	5.3	-		
TOTAL	1807	171	9.5	112	59	3.35	2.0	66	15	5.6	0		

shorter. IDM and PHT + CS again showed the longest duration. There were no deaths in the 171 infants with NT.

Acid-base values (Table 22)

In order to evaluate the rôle of the pH and  $PCO_2$  in determining the RR, acid-base values were compared between NT and control infants with RR less than 60/min. There is no significant difference between the 2 groups.

TABLE 22 COMPARISON OF AVERAGE VALUES IN PREMATURE INFANTS WITH AND WITHOUT NEONATAL TACHYPNOEA

Age in hours	<u>Tachypnoea RR &gt; 60</u>			<u>Respiratory rate &lt; 60</u>				
	<u>No. of cases</u>	<u>pH</u>	<u>PCO<sub>2</sub> mmHg</u>	<u>BE mEq/L</u>	<u>No. of cases</u>	<u>pH</u>	<u>PCO<sub>2</sub> mmHg</u>	<u>BE mEq/L</u>
2	9	7.31	46.1	-3.6	13	7.31	44.7	-4.2
4	9	7.33	45.4	-2.7	16	7.33	44.3	-2.5
6	10	7.33	45.0	-1.5	18	7.33	44.0	-2.4
12	7	7.38	38.0	-2.3	16	7.36	40.0	-1.9

Discussion

Although Phillips et al. (1959) regarded the 'normal' respiratory rate as between 31 - 59/min., it is very clear from this survey that a RR of over 60/min must be part of the normal distribution, particularly in premature infants. Fred'hem et al. (1964) stated that a normal limit of frequency of 60/min. may be not only statistically but clinically erroneous.

Cook et al. (1955) wrote:

"The comparative rapid respiratory rate in the infant is not only possible because of a small functional dead space but probably optimal because of elastic and viscous properties of the lung peculiar to the newborn."

They found only a small change in the work of respiration between the rates of 30 - 50/min. (Cook et al., 1957). Miller and Small (1957) recorded the lowest tidal volumes in their respiratory Group III infants and suggested that the RR was increased to maintain effective alveolar ventilation. Nelson et al. (1962) investigated a group of infants who had mild, transient, tachypnea and no other signs of RDS. All presented significant degrees of non-perfusion. In their very thorough study on IDM, Prod'hom et al. (1964) found no difference in the total ventilation in infants with  $RR > 60$  and those with a lower rate. The tachypneic infants presented an extreme of the normal range with altered dead space/tidal volume ratios. The phenomenon of NT is more common in premature infants and may represent a form of structural immaturity.

The higher incidence of NT in certain infants is in accord with the work of other authors. Haddad et al. (1956) recorded higher rates for premature and Caesarean section infants. High rates in IDM have been noted by Haddad et al. (1956), Gellis and Hsia (1959) and Prod'hom et al. (1964). Schaffer (1960) stated that mild forms of the massive aspiration syndrome will have tachypnea only. It is tempting to attribute the higher rates in foetal distress to the presence of

particulate matter in the lungs. Neonatal asphyxia was diagnosed when severe depression was present at birth and is, therefore, a subjective selection of a small number of cases. The association of RR with breech delivery has not been documented previously.

Branning (1942) studied a group of acidotic (hyperpnoeic) infants and found no difference between their acid-base status and that of 'normal' infants. Prod'homme et al. (1964) similarly found no difference in IDM. The acid-base studies here confirm these findings and also show that the tachypnoea does not produce hypocapnia. No  $\text{PaO}_2$  studies were done on NT infants. Miller et al. (1957) found moderate to severe hypoxaemia in their respiratory Group III infants. Schultze (1958) described normal radiograms in infants with persistent tachypnoea only.

The NT deaths in this survey were almost certainly unrelated to pulmonary pathology. The deaths occurred late and in those autopsied were shown to be due to other causes. Any infant with NT alone can therefore be given an excellent prognosis for survival as far as pulmonary adaptation to extra-uterine life is concerned. Persistently slow rates (less than 30) on the other hand have a very poor prognosis (Phillips et al., 1959).

### Conclusions

Sixteen percent of premature infants with normal vertex deliveries have  $RR > 60$  for more than 3 hours. The incidence is higher in Caesarean section and breech delivery. The concept that 'normal' rates are below 60/min. does not, therefore, apply to premature infants.

In NVD 'term' infants the 'normal' rate is, with very few exceptions, below 60/min. As soon as complications of delivery are present the incidence of NT rises. While the sex is not important in prematures, males have significantly higher rates in 'term' infants.

NT carries no increased mortality other than the normal risks associated with prematurity. The tachypnoea is not due to chemical stimulation of the respiratory centre but probably depends on dead space/tidal volume ratios. Infants born by Caesarean section and breech delivery may differ from vertex delivery in the amount of amniotic fluid present in the lungs at birth.

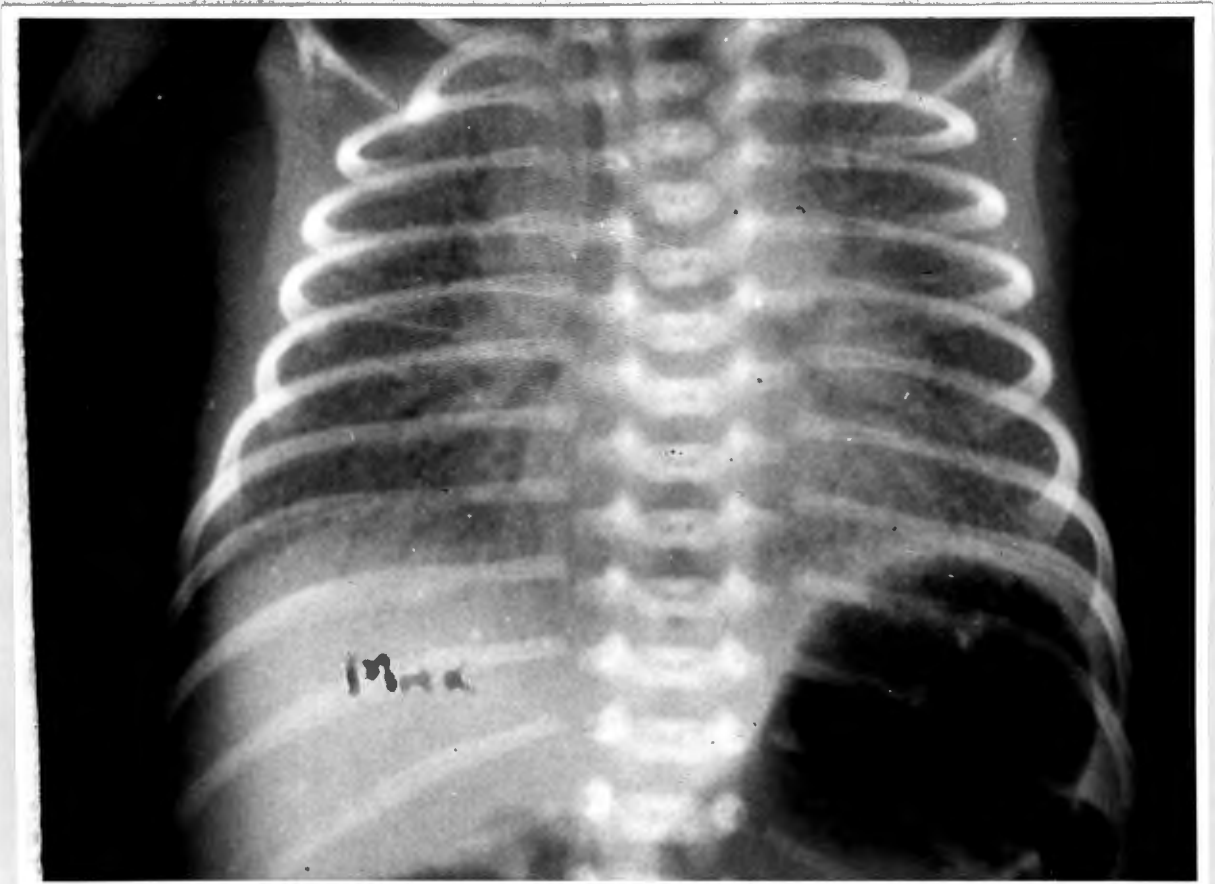
CHAPTER 10CLINICAL HYALINE MEMBRANE DISEASEIntroduction

"No condition in recent years has excited the interest of individuals concerned with newborn infants to quite the extent that HMD has." (Avery, 1964). This is due not only to the high incidence and mortality of this condition but also to the challenge presented to paediatricians, physiologists and obstetricians. The respiratory and cardiovascular systems of the newborn have been intensively investigated in an attempt to elucidate the underlying pathophysiology of HMD. The results in basic knowledge and techniques of investigation which have been gained have been of inestimable value in the better understanding and treatment of all respiratory and cardiovascular problems in newborn infants.

Diagnosis

The diagnosis of CHMD depends on the presence of at least 2 of the 3 criteria of respiratory distress given previously, as well as the identification of a chest radiogram characterised by a reticulogranular pattern and an air bronchogram (Figure 3). In the first few hours of life a radiographic picture of opaque or 'ground glass' lung fields is sometimes seen (Figure 4). This is followed by a finely reticulogranular pattern which becomes coarser with time. The lungs are well expanded with an overall increase in pulmonary density. The reticulogranular pattern is the result of distended alveolar ducts adjacent to focal areas of atelectasis and

exudate (Harris, 1963). Over-distended alveolar ducts may rupture with escape of air into the interstitial tissues and subsequent tracking into the mediastinum or pleura (Craig, 1963).



**Fig. 3** Chest film of CHMD demonstrating the characteristic reticulate-granular pattern and air bronchogram

Pneumothorax was a complication in 16% of cases seen in this survey. The associated air bronchogram is commonly seen since the segmental

bronchi are distended with air because of the combination of the comparatively fixed inspiratory state and the density of the surrounding atelectatic lung.

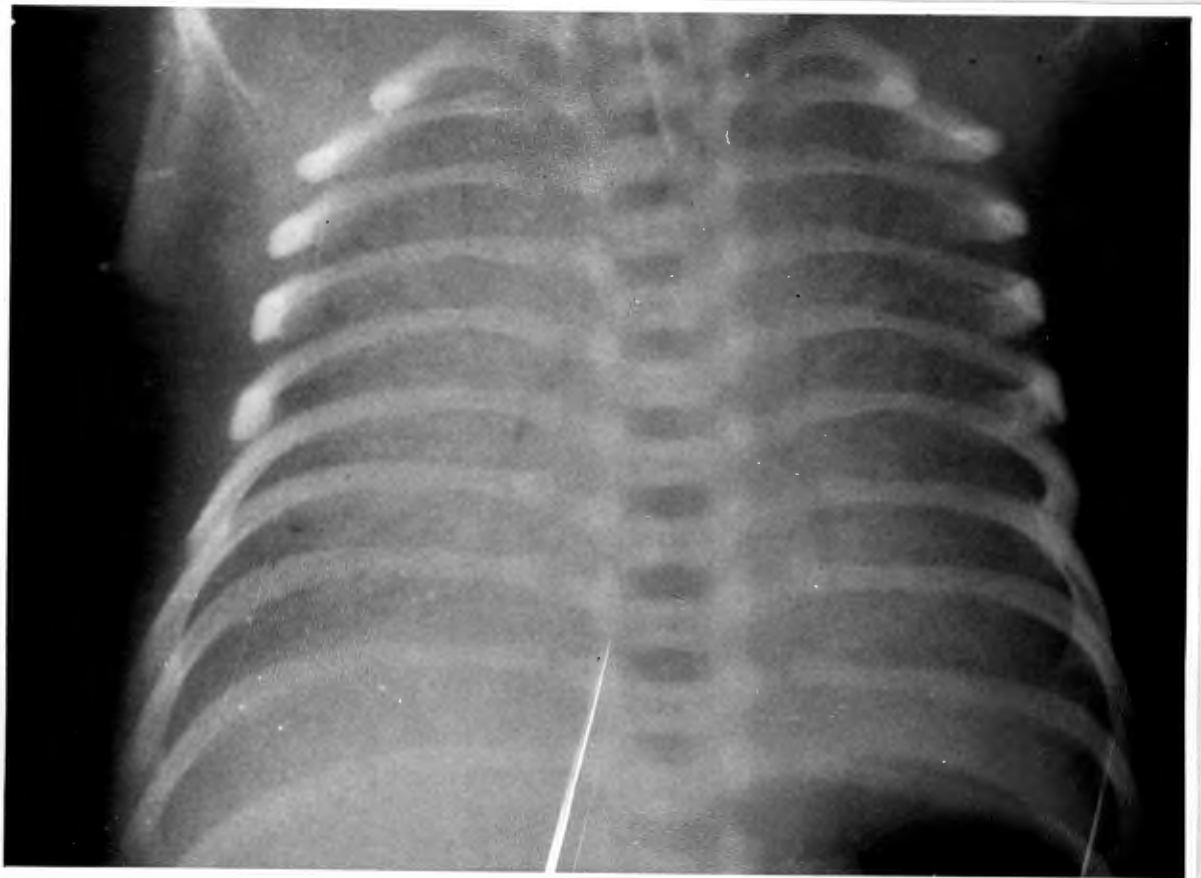


Fig. 4 Chest film of CHMD demonstrating the 'ground glass' appearance of the lung fields

#### Incidence

Live births in the Groot Schuur maternity hospital were analysed to determine on a statistical basis the relationship of CHMD to race, gestational age, sex and maternal factors. The total

live births were 1,889 of which 1,801 were included in the final analysis. The other 88 infants were all large babies with insufficient details regarding gestational age. The following facts were recorded for each infant:

race, sex, weight, gestational age, Caesarean section or vaginal delivery and the presence or absence of the maternal complications of diabetes, antepartum haemorrhage or toxæmia. Gestational age was calculated from the mother's last menstrual period and not corrected after clinical assessment of the stage of pregnancy. In a number of infants a radiogram was not obtained but the clinical course of the disease was judged in retrospect to be sufficiently characteristic to make a confident diagnosis.

The figures were tabulated by the University Computer Centre and the results analysed using the Chi-Square Test for 2 x 2 contingency tables with Yates' correction. Where any expected frequency was less than 5, the exact test for 2 x 2 contingency table was used employing factorials (Bailey, 1959).

Racial incidenceTABLE 23 INCIDENCE OF CHMD IN RACIAL GROUPS

	<u>White</u>	<u>Cape Coloured</u>	<u>Bantu</u>	<u>Total</u>
No. of infants	1,125	579	97	1,801
CHMD	25	29	4	58
< 38 wks <sup>*</sup>	25/175 = 13.1%	28/232 = 12.1%	4/30 = 13.3%	55/437 = 12.6%
< 2.5 kg <sup>†</sup>	25/104 = 22%	25/168 = 14.9%	4/20 = 20%	52/292 = 17.8%
> 38 wks	2/950 = 0.2%	1/347 = 0.3%	0/67 = 0%	3/1,364 = 0.2%
> 2.5 kg	2/1,021 = 0.2%	4/410 = 1%	0/77 = 0%	6/1,508 = 0.4%

\* Difference between races not significant ( $p > .05$ )

† Difference between races not significant ( $p > .05$ )

At first glance there appears to be a considerable variation in the racial incidence but further examination reveals an association of CHMD with the varying racial incidence before term. The latter shows figures for 'prematurity' of 9 - 16% in Whites, 25 - 40% in Cape Coloured and 20 - 30% in Bantu depending on the basis for calculation - weight or gestational age.

The survey shows an average incidence of 13% in the low gestational age group with no significant differences among the 3 races. This is in keeping with the findings of Miller (1963) and Gairdner (1965). Below 38 weeks the total incidence here is almost

identical with the figures published by Driscoll and Smith in 1962 (13%) and by Usher in 1963 (14%). In the heterogeneous population in Cape Town, consisting of different ethnic groups and standards of nutrition and economy, the estimated gestational age is a better guide to the maturity of the fetus than the birth weight. The differences between calculations based on gestational age and birth weight are clearly demonstrated in Table 23 and apply to all three ethnic groups. Baird (1964) has pointed out that a bigger proportion of non-White infants are premature whether judged by weight or by gestational age. This is very obvious in this survey and is certainly exaggerated by the preferential admission of non-White mothers with complicated pregnancies while the majority of White mothers had normal full term pregnancies. The incidence of CHMD does not depend on the total number of births or on the ethnic group, but to a very high degree on the fact of prematurity itself.

#### Maturity

TABLE 24 CHMD - INCIDENCE ACCORDING TO MATURITY

<u>Gestation (wks)</u>	<u>CHMD</u>	<u>Incidence</u>
< 29	10/28	35.8%
29 - 33	28/71	18.3%
34 - 36	13/141	9.2%
37 - 38	4/197	2.0%
> 38	3/1,364	0.2%

The incidence of CHMD fell steeply with increasing maturity. This was also the experience of Dunn (1965) and Usher et al. (1964). While the incidence under 38 weeks was 12.6%, only 0.2% of more mature infants were affected. Over 270 days' gestation, Usher et al. (1964) found only 3 affected infants out of 14,459 deliveries. In the British Perinatal Mortality survey (Butler and Bonham, 1963), 83% of HMD infants had known gestational ages of less than 36 weeks. The most important single predisposing factor is undoubtedly prematurity or immaturity of the foetus. This has been confirmed in experimental HMD in lambs (Reynolds et al., 1965).

#### Sex incidence

TABLE 25 CHMD - INCIDENCE ACCORDING TO SEX

	<u>Male</u>	<u>Female</u>	<u>Significance of difference</u>
< 38 wks	35/213 = 16.4%	20/224 = 9.0%	p < .05
< 2.5 kg	32/129 = 24.9%	20/163 = 12.3%	p < .01

Males were significantly more often affected than females. The statistical significance of a higher incidence in males has also been recorded by Miller (1963). The explanation of this may lie in the lower average gestational age of males as compared with females (Crosse, 1957 and Dawkins, 1964).

#### Caesarean section

Much has been written for and against the association of Caesarean section with CHMD. Although figures in this survey are small, they confirm work in Britain (Butler and Bonham, 1963) and in Canada

(Usher et al., 1964). In all 3 surveys Caesarean section was significantly related to CHMD. This is contrary to the statements of Strang et al. (1957), Moss et al. (1963a) and Gruenwald et al., (1963).

**TABLE 26 CHMD - INFLUENCE OF CAESAREAN SECTION ON INCIDENCE**

<u>Gestation (wks)</u>	<u>Caesarean section</u>	<u>Vaginal delivery</u>	<u>Caesarean section increase</u>	<u>Significance of difference</u>
< 29	2/3 - 33%	9/25 = 36%	0	p > .05
29 - 33	7/11 = 64%	21/60 = 35%	2 x	p > .05
34 - 36	3/24 = 12.5%	10/117 = 8.5%	1.5 x	p > .05
37 - 38	3/32 = 10%	2/165 = 0.6%	16 x	p < .05
> 38	2/109 = 2%	2/1,225 = 0.1%	20 x	p > .05
<b>Total &lt; 38</b>	<b>14/70 = 20%</b>	<b>41/367 = 11.2%</b>	<b>2 x</b>	<b>p &lt; .05</b>

The indication for the Caesarean section is believed to be non-contributory (Usher et al., 1964) although the indications other than antepartum haemorrhage and toxemia were not investigated here. All Caesarean sections were carried out under general anaesthesia.

Antepartum haemorrhage

TABLE 27 CHMD - INFLUENCE OF ANTEPARTUM HAEMORRHAGE  
ON INCIDENCE, CAESAREAN SECTION EXCLUDED

<u>Gestation (wks)</u>	<u>APH</u>	<u>No APH</u>	<u>Significance of difference</u>
< 29	2/16 = 12.5%	7/9 = 12.5%	p < .01
29 - 33	5/21 = 24%	16/39 = 41%	p > .05
34 - 36	2/20 = 10%	8/97 = 8%	p > .05
37 - 38	0/17 = 0%	1/148 = 0.7%	-
> 38	1/72 = 1.4%	0/1,292 = 0%	-
<b>Total &lt; 38</b>	<b>9/74 = 12.1%</b>	<b>32/293 = 10.9%</b>	<b>p &gt; .05</b>

Statistically, antepartum haemorrhage per se is not associated with a higher frequency of CHMD in the infant. This observation has support (Butler and Benham, 1963 and Usher et al., 1964) and opposition (Rogers et al., 1956 and Cohen et al., 1960). Antepartum haemorrhage may lead to a higher infant mortality on the grounds of other pathology such as aspiration of blood or other material (Snyder, 1961), but this is not CHMD. Most workers have been struck by the frequency of association of antepartum haemorrhage with distressed infants. It may be that antepartum haemorrhage jeopardises the infant by inducing premature labour.

Maternal diabetesTABLE 28 HMD - INFLUENCE OF MATERNAL DIABETES ON INCIDENCE

	<u>IDM*</u> <u>Vaginal</u> <u>delivery</u>	<u>IDM*</u> <u>Caesarean</u> <u>section</u>	<u>Controls</u> <u>no diabetes</u>	<u>Significance of</u> <u>difference</u>
< 38 wks	3/7 = 43%	2/2 = 50%	51/428 = 11.9%	p = .015
< 2.5 kg	-	2/5 = 40%	50/287 = 17.4%	p > .05

\* Infant of Diabetic Mother

It is often stated that HMD is the single most important finding in the infant of the diabetic mother (Gellis and Hain, 1959 and Driscoll et al., 1960), but no statistical comparison with control infants is available. In this survey there is a significant difference between the two but the numbers are too small to allow more extensive comment. Only 5 infants of diabetic mothers were less than 2.5 kg while 9 were less than 38 weeks. Farquhar (1962) found no distressed infants over 38 weeks. Although the connection between maternal diabetes and HMD in the neonate is not understood, it has been suggested that the abnormal lipid metabolism in the mother might have a deleterious effect on the formation of surfactant by the foetal lung (Gairdner, 1965).

Maternal toxæmia

Cohen et al. (1960) found a higher frequency of HMD in infants born to mothers with toxæmia. This has not been substantiated by

the present survey or by any other author. On the contrary, maternal toxæmia would appear to protect the foetus from HMD.

TABLE 29 GHMD - INFLUENCE OF MATERNAL TOXAEMIA ON INCIDENCE

	PET Vaginal delivery	PET Caesarean section	Controls No PET	Difference
38 wks.	1/57 = 1.8%	1/14 = 7%	53/366 = 14.5%	No increase
2.5 kg.	1/64 = 1.6%	1/10 = 10%	50/218 = 23%	No increase

Assessment of severity

GHMD has a variable presentation, course and outcome. The distress may vary from transient signs to death within a few hours. The disease often runs a rapid course so that the early condition of the infant may not be an indication of later events. Two typical illustrations of the clinical picture in GHMD are given in Tables 30 and 31. Case 90 illustrates progressive increase in severity with death at 29½ hours while Case 346 shows more severe initial involvement with gradual recovery. Scoring has been done according to the standard index (Appendix iv). In order to discuss the clinical and biochemical findings on a reasonably comparative basis it is necessary to have some system for grading severity.

Infants with GHMD were divided into 4 categories according to their oxygen requirements (Table 32). The assessment was made on the initial examination irrespective of the age or subsequent course. In mild and moderate illness the inspired oxygen requirements were less than 40% ambient oxygen, while in severe cases they were over 40%.

TABLE 30 NO. 90 CHHD - DIED 29½ HOURS

Age (hrs)	Resp. rate	Grunting	Respiration	Oxygen requirement	Air entry	Cryphonations	Oedema	Sternal bulge	Pulse rate	Perkiness	Wt. (kg)	Apneic attacks	Motor response
5	64	++	+	30%	++	-	++	+	140	Good	1.78	-	Fair
8	76	++	++	45%	++	-	++	+	140	Good		-	Fair
15	64	++	++	100%	+	+	++	+	150	Poor	1.76	I 1 60 secs	Poor
17	84	++	++	100%	+	+	++	+	150	Poor		I 1 60 secs	Poor
21	96	++	++	100%	++	+	++	+	148	Poor		-	Fair
24	100	-	+	100%	++	+	++	+	140	Good		-	Fair
27	80	++	+++	100%	++	+	++	+	140	Good		-	Poor
29	72	++	++++	100%	+	+	+++	+	144	Good	1.75	Severe	Poor

TABLE 31 NO. 346 CHND - SURVIVED

Age (hrs)	Besp. rate	Grunting	Respiration	Oxygen requirement	Air entry	Crepitations	Oedema	Sternal bulge	Pulse rate	Respiratory distress	Wt. (kg)	Apnoeic attacks	Keenness of response
4	48	++	+++	?	+	+	++	+	120	Good	2.51	-	Good
9	56	++	+++	65%	+	+	++	+	144	Good		-	Good
15	68	++	+++	65%	+	+	+++	+	144	Good		-	Good
19	70	++	+++	70%	+	+	+++	+	140	Fair		-	Good
25	70	++	+++	70%	++	+	++	+	144	Fair		-	Active
31	76	++	+++	80%	++	+	++	+	144	Good		-	Active
39	78	++	+++	100%	++	++	++	+	144	Good		Short	Good
48	72	++	+++	100%	++	+	++	+	136	Good		Short	Active
55	80	++	+++	100%	++	++	++	+	132	Good		-	Good
61	84	+	+++	100%	+++	+	++	+	152	Good		Short	Good
72	80	-	+++	80%	+++	+	++	+	136	Good	2.52	Short	Active
98	72	-	+++	65%	+++	+	+	-	140	Good		-	Good
103	64	-	++	40%	+++	-	-	-	124	Good	2.41	-	Good

The mild cases were distinguished from moderate illness by the absence of edema, crepitations and a sternal bulge. Severe illness was further subdivided into severe I and severe II. All infants requiring 100% oxygen to maintain normal arterial saturation (or  $\text{PaO}_2$  of about 100 mmHg) were placed in the severe II category.

The major defect in CHMD is one of gaseous exchange in the lungs. This is most strikingly reflected in the oxygen desaturation of the blood. The advent of severe respiratory acidosis is a late indication of imminent death (Hatchison et al., 1962). It would be reasonable, therefore, to grade the severity according to the arterial oxygen tension (Stahlman, 1964 and Boston et al., 1964). In the absence of facilities for measuring oxygen tension and saturation, one could rely on the amount of supplementary oxygen required to relieve cyanosis (Usher, 1963). The drawback of this method is that the  $\text{PaO}_2$  drops to fairly low levels before clinical cyanosis becomes apparent (Warley and Gairdner, 1962). Gairdner (1965) regards the pH as the most useful single measure of respiratory insufficiency while Stahlman (1964) found a high blood lactic acid the best single criterion for non-survival. The lactic acid correlated poorly with the  $\text{PaO}_2$  (Stahlman, Young and Payne, 1962).

Although the division of CHMD into 4 categories would seem unnecessary at first, there is justification for this. The mild group is the most doubtful separate entity. Smith (Eudolph and Smith, 1960) has pointed out that there are very mild grades of the IRDS (HMD). One cannot be sure some even have the disease. Most of these with mild illness would probably be missed unless a chest film were taken.

TABLE 12 IRDS - CLINICAL CLASSIFICATION

Chest radiogram	<u>Clinical Hyaline Membrane Disease</u>				Streaky atelectasis + emphysema Mild - Moderate 17 < 40%
	Mild	Moderate	Severe I	Severe II	
Grading of severity	40%	40%	>40% usually 50 - 70%	100%	
Oxygen requirement	40%	40%	86%	43%	93%
Respiratory rate > 60/min	73%	91%	68	54	72
Average resp. rate/min	70	75	100%	71%	72%
Grunting	50%	91%	100%	86%	50%
Recession	50%	100%	100%	100%	17%
Cyanosis (room air)	23%	91%	100%	86%	11%
Oedema	-	74%	86%	43%	28%
Crepitations	-	43%	76%	43%	6%
Sternal bulge	-	70%	71%	86%	
Apnoeic attacks	0	31%	52%	93%	
Mortality	0	17.3%	57%		
			46.7%		11%
			38.7%		

The work of other authors supports the present grading. Stahlman et al. (1963) used 3 categories; mild, severe-lived and severe-died, later changing mild to moderate illness (Stahlman, 1964). Hutchison et al. (1964) studied 2 groups, mild and severe. Forty percent ambient oxygen was also found to divide the mild from the severe cases. The requirement of 100% oxygen clearly separates some infants into a special category with predictable death in the vast majority (Stahlman, 1964).

#### Clinical findings

The relationship between the 4 categories and the clinical data is shown in Tables 32 and 33.

The infants with mild illness had transient respiratory distress. The respiratory rate was usually raised, but grunting, recession and cyanosis was short-lived. The infants required no treatment other than additional oxygen in one case, and all survived. In the more severe cases the clinical signs compared well with the grading of severity.

(a) Respiratory rate: The highest rates were recorded in moderate illness, often over 100/min. Slow rates (under 60/min) associated with a high oxygen requirement had a poor prognosis. The relationship of the respiratory rate and outcome is shown in Table 34. It will be seen that not only is the average respiratory rate higher in survivors, but the percentage with RR below 60/min. is much lower than in the non-survivors. The serious prognostic import of a slow respiratory rate in the face of severe illness has been well documented (Miller, Behrle

TABLE 33 IRDS - CLINICAL DATA

	<u>Clinical Hyaline Membrane Disease</u>				Neonatal Disseminated Atelectasis	
	MILD	MODERATE	SEVERE I	SEVERE II		
No. of cases	4	23	21	14	18	
Age first investigated (hours)	Average Range	8.0 3 - 12	9.6 2 - 67	7.0 1 - 36	5.6 ‡ - 12	6.7 ‡ - 18
Weight (kg)	Average Range	1.91 1.19 - 2.77	1.93 1.30 - 2.97	1.94 1.24 - 2.97	2.14 1.59 - 3.34	2.69 1.50 - 3.85
Maturity (weeks)	Average Range	33.0 29 - 36	34.0 30 - 39	33.8 28 - 39	33.5 30 - 38	37.3 28 - 40
Apgar (1 min.)	Average Range	8.0 7 - 9	6.6 1 - 9	5.3 1 - 9	4.4 1 - 10	5.0 1 - 9
Sex	Male 3 : Female 2				M 3 : F 1	
Mortality	0	17.5%	57%	93%	11%	
Death (hours)	Average Range	- -	47 21 - 94	36 11 - 71	31 4 - 57	57 36 - 78

and Small, 1958; James, 1959; Phillips et al., 1959; Usher, 1961 and Stahlman et al., 1963).

**TABLE 34 CORRELATION OF RESPIRATORY RATE WITH MORTALITY**

	<u>Respiratory Rate</u>	<u>Survivors</u>	<u>non-Survivors</u>
Clinical HMD	Average	76	54
	< 60/min	4%	42%
RDS - Undetermined	Average	70	45
	< 60/min	12%	73%

At the other end of the spectrum, some of the mild cases never had a respiratory rate over 60/min. Usher (1961) stated that fatal cases had lower rates in the first hour of life. This was not so in this study, as seen in Table 35.

**TABLE 35 CORRELATION OF RESPIRATORY RATES IN FIRST HOUR  
OF LIFE WITH MORTALITY**

	<u>Slow &lt; 60/min.</u>	<u>Fast: &gt; 60/min.</u>
Number	25	12
Survivors	15	6
Mortality *	40%	50%

\* Difference in mortality not significant ( $p > .05$ )

(b) Grunting and recession: There was little difference between the moderate and severe I groups, but the incidence of grunting and recession actually decreased in severe II. Severe retraction is listed by Usher (1961) as being associated with a high mortality. This survey rather confirms the opposite views of James (1959) and Tizard (Rudolph and Smith, 1960) that in very severe illness the infant may be too feeble to have either grunting or retractions.

(c) Oedema and crepitations: The incidence of these two findings rose with the severity and were adverse prognostic signs, especially if present soon after birth. Usher (1961) found a high mortality with early riles and oedema. All the severe cases in the series reported by Hutchison et al. (1964) had oedema.

(d) Apnoeic attacks: As would be expected, these occurred more frequently in the more severely affected infants.

(e) Mortality: This ranged from 0 - 93% and followed the grading of severity. The overall mortality rate was 46.7%. It was not possible to assess the racial influence on mortality because of widely differing conditions of medical and nursing care.

(f) Birth weight and maturity: The severe II group had a slightly higher birth weight but no difference was found in the average gestational ages. The increased weight appeared to be due to infants of diabetic mothers and a higher percentage of Caesarean section deliveries. Tables 36 and 37 show that mortality was not related to birth weight or to the degree of immaturity below 38 weeks. Dunn (1965) recorded no deaths

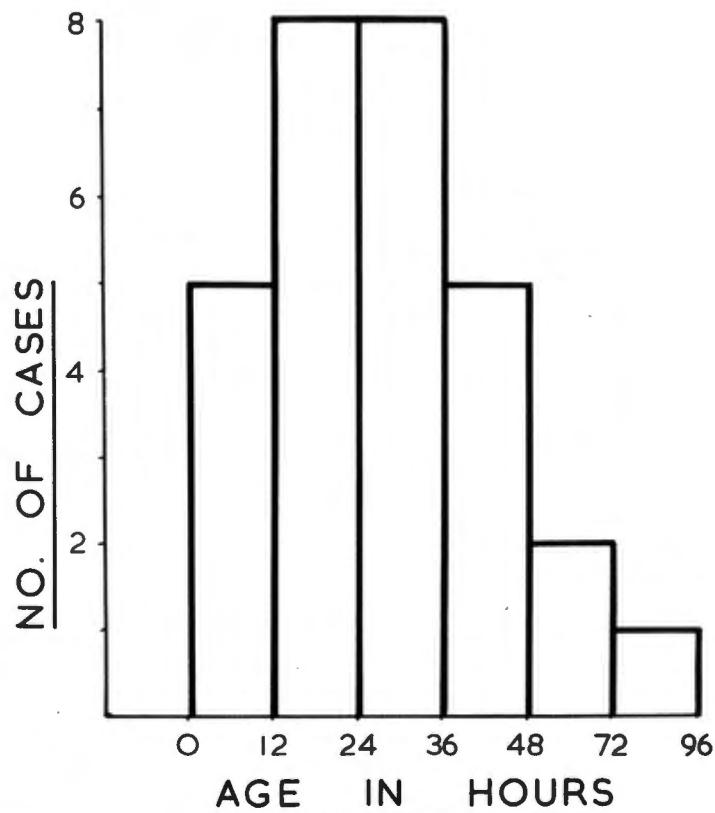
not record the statistical significance.

**TABLE 38** GHMD - SUMMARY OF SEX DIFFERENCES

	<u>Males</u>	<u>Females</u>
Number	39	23
Mortality*	51%	39%
Average weight	1.98 kg.	1.90 kg
Average gestational age	33.5 wks	33.8 wks.

\* Difference between sexes not significant  
( $p > .05$ )

(1) Age of death: The average of death was earlier in the more severe illness. The peak age of death was 30 hours with very few deaths after 48 hours (Figure 5)



**Fig. 5:** Histogram of age of death in GHMD

The improved prognosis with increasing age is demonstrated in Table 39.

**TABLE 39 CHMD - PROGNOSIS<sup>a</sup> ACCORDING TO AGE**

<u>Age in hours</u>	<u>% Estimated survival</u>
Birth	53
12	58
24	67
36	80
48	92
72	97

<sup>a</sup> Only deaths in first 5 days included

Unlike the findings of Stahlman (1964) who stated that it was rare for one group suddenly to go into another, several infants in this study deteriorated rapidly from moderate to severe illness.

The complications of pneumothorax and intracranial haemorrhage were frequently the cause of sudden progression of the illness and death. The stiffened lung in CHMD resists collapse and a small pneumothorax may be present under tension. Bulging of the intercostal spaces will give an indication of the tension. On the other hand, recovery was invariably a gradual process over a period of 2 - 4 days.

Clinical signs of deterioration were:

- (i) Decreasing respiratory rate and effort without biochemical improvement
- (ii) Irregular, sighing respiration
- (iii) Impalpable peripheral pulse
- (iv) Bradycardia
- (v) Persistent hypothermia.

### Acid-base values

The average initial acid-base values for CHMD are given in Table 40. There is good correlation between the acid-base status and the clinical severity. The values for mild illness are within the acceptable range for healthy premature infants (Appendix xxvi). With more severe illness there is a combined respiratory and non-respiratory acidosis which is reflected in the progressive fall in the pH. Although the average  $PCO_2$  is high in severe illness, the values are extremely variable. Boston et al. (1964) emphasized this feature. The extremely low levels of carbonic anhydrase in premature infants (Reutens and Woodford, 1963 and Kaiser, 1964) will lead to accumulation of carbonic acid and increased acidosis. The much greater metabolic acidosis in the severe II group is almost certainly due to non-volatile acids resulting from hypoxia and anaerobic metabolism.

### Biochemistry

The initial biochemical findings are summarised in Table 41. The serum potassium, sodium, chloride and proteins and the blood urea and sugar show no relation to the severity of the condition. Potassium levels over 6.5 mEq/L (Stahlman et al., 1963) were sometimes present in both moderate and severe illness. Usher (1959) found rising values with increasing age. In considering the potassium values, one must remember that the levels in premature infants are higher than in later life. Average normal values of 4.6 - 6.1 mEq/L with a range of 3.8 - 7.2 mEq/L are given by Pincus et al. (1956); Smith (1959); Usher (1959) and Keitel (1959). Sodium, chloride and urea were not materially different from controls, which is in accord with the findings of

TABLE 40 IRDS - ACID-BASE VALUES

	<u>Clinical Kynline Membrane Biocase</u>					<u>Neonatal</u>					
	<u>Mild (1)</u>		<u>Moderate (19)</u>		<u>Severe I (21)</u>		<u>Severe II (13)</u>		<u>Disseminated</u>	<u>Atelectasis (15)</u>	
	Average	7.365	7.234	7.193	7.058		7.274				
pH	Range	-	7.100 - 7.380	6.990 - 7.305	6.805 - 7.250	7.090 - 7.367					
PCO <sub>2</sub> mmHg	Average	39.2	49.6	53.1	68.5	48.4					
	Range	-	25 - 80	33 - 91	35 - 170	31 - 95					
Base Excess mEq/L	Average	-2.8	-7.5	-8.7	-13.5	-6.1					
	Range	-	-3.0 - -13.2	-3.0 - -13.2	-4.5 - -22.8	-1.0 - -10.5					
Buffer Base mEq/L	Average	43.6	39.9	38.2	32.9	43.4					
	Range	-	31.2 - 47.0	29.1 - 46.2	23.4 - 44.5	36.7 - 47.0					
Standard HCO <sub>3</sub> <sup>-</sup> mEq/L	Average	21.7	18.3	17.4	14.4	19.3					
	Range	-	13.1 - 21.6	13.2 - 21.6	9.8 - 20.5	15.0 - 23.0					
Actual HCO <sub>3</sub> <sup>-</sup> mEq/L	Average	21.5	20.1	19.3	17.5	20.8					
	Range	-	10.5 - 30.0	13.1 - 27.0	10.0 - 23.0	15.1 - 25.0					
Age of Determination (hrs)	Average	7	9.6	7.0	5.6	6.7					
	Range	-	2 - 67	1 - 36	4 - 12	4 - 18					

\* Number of estimations

**TABLE 41 - IRDS - INITIAL BIOCHEMICAL FINDINGS**

		<u>Clinical Hyaline Membrane Disease</u>			<u>Neonatal</u>
		<u>Moderate</u>	<u>Severe I</u>	<u>Severe II</u>	<u>Disseminated</u> <u>Atelectasis</u>
$K^+$ mEq/L	Average	6.1	5.4	5.7	5.8
	Range	5.2 - 7.4	4.2 - 10.0	3.8 - 8.3	4.5 - 7.6
$Na^+$ mEq/L	Average	136	137	133	138
	Range	130 - 142	127 - 145	122 - 140	130 - 142
$Cl^-$ mEq/L	Average	94	97	98	105
	Range	91 - 96	86 - 104	88 - 102	103 - 106
Urea mg%	Average	-	38	29	22
	Range	-	10 - 78	19 - 44	15 - 45
Sugar mg%	Average	96	61	83	56
	Range	14 - 308	28 - 116	11 - 227	44 - 88
Total Proteins g %	Average	4.6	4.4	4.3	5.4
	Range	3.9 - 5.7	3.2 - 5.6	3.1 - 5.2	5.3 - 5.6
Albumin g %	Average	2.9	3.2	3.2	3.7
	Range	2.8 - 2.9	2.3 - 3.8	2.3 - 3.7	3.6 - 4.1
Globulin g %	Average	1.4	1.0	0.9	1.7
	Range	1.0 - 1.7	0.3 - 1.7	0.2 - 1.5	1.5 - 2.0
Haematocrit	Average	46%	48%	38%	48%
	Range	40 - 51	44 - 58	31 - 44	-
R - L Shunt	Average	37%	39%	52%	29%
	Range	21 - 65	20 - 56	20 - 84	26 - 32
Age of investigation (hours)	Average	9.6	7.0	5.6	6.7
	Range	2 - 67	1 - 36	1 - 12	1 - 18

Nicolopoulos and Smith (1961), Troelstra et al. (1964) and Payne and Acharya (1965). The variable level of blood sugar reported in the literature is confirmed in this survey. Although no signs attributable to hypoglycaemia were noticed, several of the infants had low levels of blood sugar. The blood glucose levels were presumably even less.

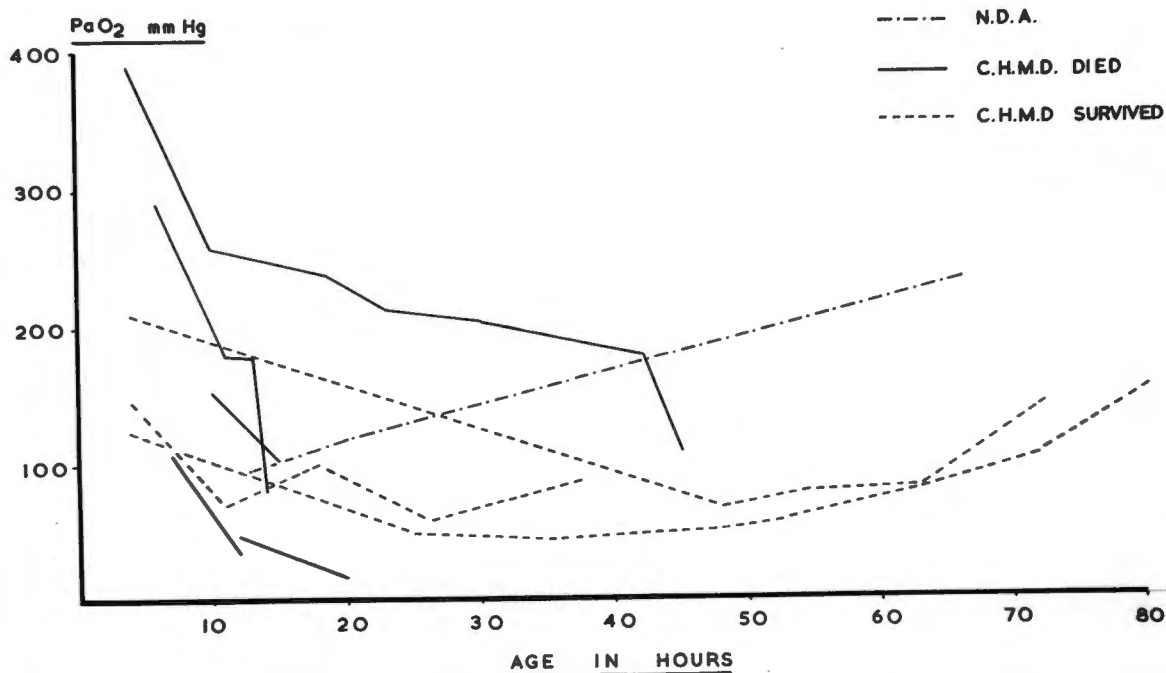
The total serum proteins are low when compared with the normal values of 4.9 - 5.5 g % (Usher, 1961 and Nicolopoulos and Smith, 1961). The protein levels rise with gestational age and birth weight (Geake, 1960 and Gyvia, 1965). Gyvia (1965) also found lower values for boys than girls. Recent estimations have demonstrated that the gamma-globulin fractions are particularly low (Hardie, Heese and Kench, 1965). The average normal haematocrit levels for prematures are 57 - 58% (Pincus et al., 1956 and Nicolopoulos and Smith, 1961). The values in this survey are low, especially in severe II. Nicolopoulos and Smith (1961) found significantly decreased levels in distressed infants at 48 hours only, but Inall et al. (1965) recorded a mean haematocrit of 48% in infants with IRDS. Chu et al. (1965) have pointed out that hypovolaemia will lead to reduction in pulmonary blood flow because of pulmonary vasoconstriction. Inall et al. (1965), however, found no reduction in blood volume.

R - L shunts (Table 41) were calculated from oxygen studies (Appendix xxxiv) and show greater shunts in severe II. There was no difference between the moderate and severe I groups, probably due to the wide range of values. The crucial test of the clinical assessment of severity would be the respective alveolar-arterial oxygen gradients.

Facilities for the direct estimation of  $PO_2$  with an electrode were, however, not available during the early part of this survey. Initial  $PaO_2$  levels were high in a few of the moderate and severe I cases but all fell subsequently. Boston et al. (1964) obtained a good correlation between  $PaO_2$  and subsequent outcome.

#### Hyperoxia test

The ventilation/perfusion impairment which characterises GHMD is best demonstrated by raising the ambient oxygen to 100% and measuring the  $PaO_2$  (Strang and MacLish, 1961 and Nelson et al., 1961). This has been called the hyperoxia test (Prod'hom, 1964). The values in normal infants are between 200 - 400 mmHg (Wang et al., 1963; Nelson et al., 1963 and Prod'hom, 1964). The hyperoxia test was done in most infants in this survey at the initial examination but not always repeated. The control of the  $PaO_2$  at about 100 mmHg appeared more important. The hyperoxia findings are shown in Figure 6. Several infants started in the normal range but there was a continued decrease in all fatal cases. Survivors show stabilisation and then progressive increase. Smith (1964) emphasized the serious importance of a steadily falling  $PaO_2$ . Prod'hom (1964) suggested the use of this test to evaluate the efficacy of any new or old treatment in GHMD.



**Fig. 6: Hyperoxia Test**

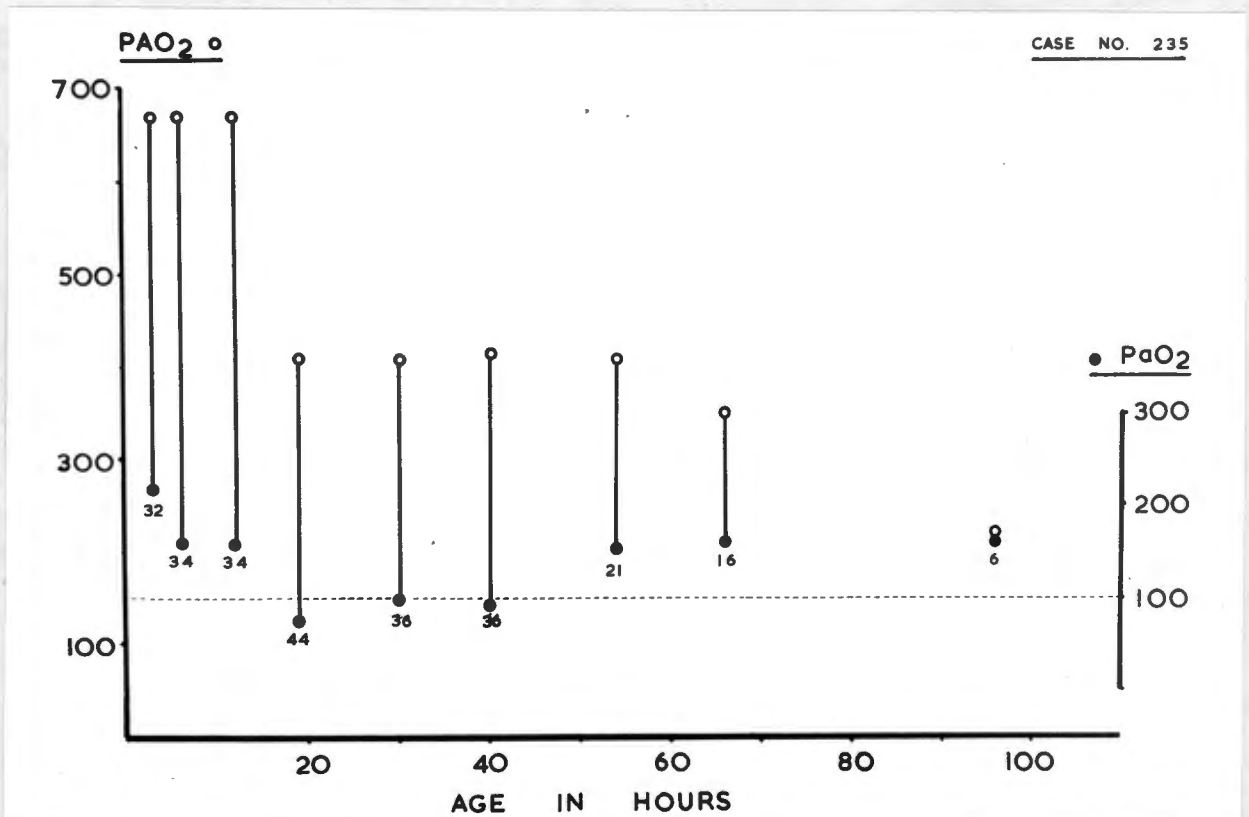
### Specific treatment

(a) Oxygen : As previously mentioned, this is the most important aspect of treatment.

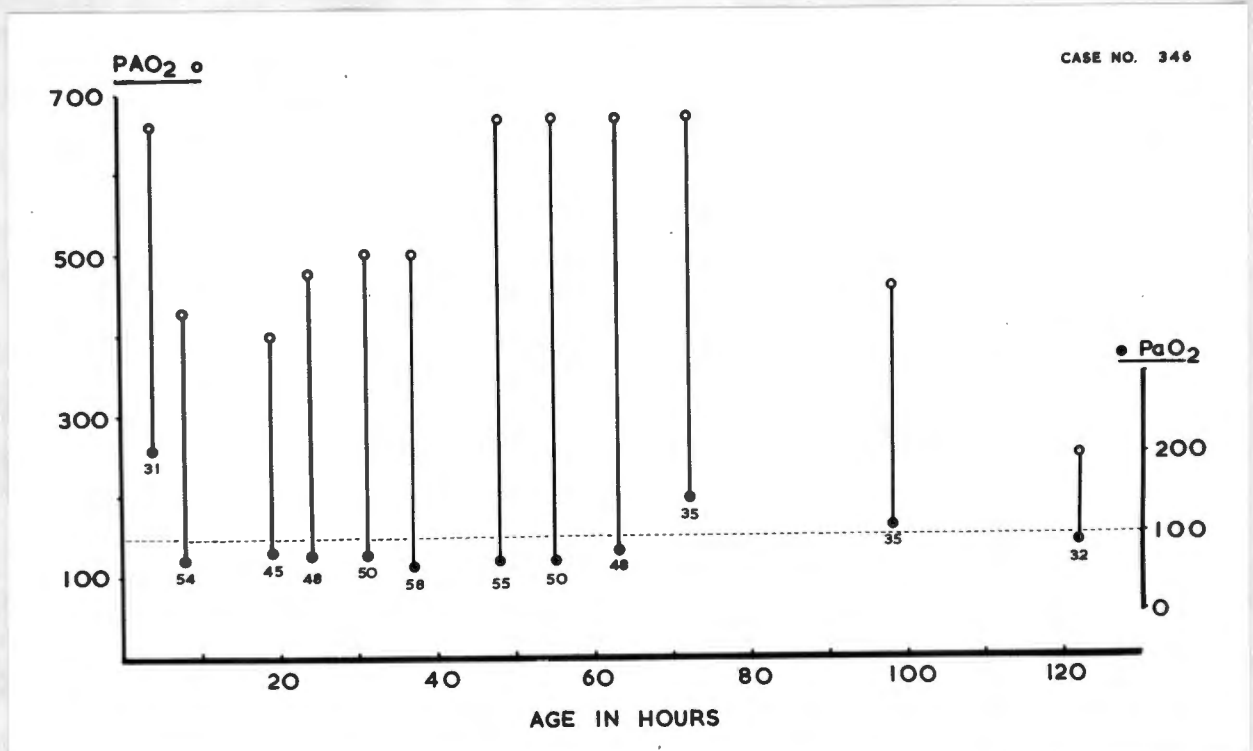
Hypoxia has multiple effects on the infant - reduction in energy-release, exhaustion of liver glycogen, accumulation of non-volatile acids with lowering of pH and available buffer base and cardiovascular disturbances. Anaerobic glycolysis only releases 5% of the potential energy of the glucose molecule. The increased respiratory effort already makes severe demands on the available oxygen and energy so that a vicious cycle is apt to follow (Karlberg and Celander, 1965). A major departure from the normal pH will depress fundamental enzyme activity and cause widespread circulatory and electrolyte disturbances (Mott, 1961; Warley and Gairdner, 1962; Opie et al., 1963; Downing et al., 1965 and Oppé et al., 1965). Hypoxia causes pulmonary vaso-constriction (James and Rowe, 1957; Strang and Macleish, 1961; Cook et al., 1963; Moss et al., 1964 and

Chu et al., 1965) and dilatation of the ductus arteriosus (Born et al., 1956 and Kevaleik, 1963). At a low pH the pulmonary artery is extremely sensitive to hypoxia (Enson et al., 1964). Pulmonary vascular resistance is also increased by asidosis, atelectasis and perivascular pulmonary oedema (Chu et al., 1965; Stern and Lind, 1960 and West et al., 1964).

Sufficient oxygen was given to relieve cyanosis (plus an extra 25%) or to maintain the  $PaO_2$  at about 100 mmHg. This was relatively easy in moderate illness (Figure 7) but more difficult or impossible in severe illness (Figure 8). The calculated R - L shunt is given for each  $PaO_2$  determination.



**Fig. 7** : Alveolar-arterial  $PO_2$  gradient (mmHg) in moderate CHMD. R - L shunt values are given below the  $PaO_2$ .



**Fig. 8:** Alveolar-arterial  $PO_2$  gradient (mmHg) in severe CHMD. R - L shunt values are given below the  $PaO_2$ .

(b) Intravenous fluids : Intravenous fluids were administered in the majority of infants with CHMD (Table 42).

**TABLE 42** INTRAVENOUS THERAPY IN CHMD

	IVF	Dextrose 5% and Levulose 5%	Rheomacrodex*	$NaHCO_3$	Tham
No. of cases	51	42	9	40	5
Survivors	26	24	2	23	1
Mortality	49%	43%*	78%*	42%	80%

\* Low molecular weight Dextran + 5% Dextrose

\* Difference in mortality not significant ( $p > .05$ )

The standard solution used was 5% dextrose plus 5% levulose administered via a scalp vein. This mixture supplied enough sugar without being too irritant to the veins. Tizard (1962), Oaki et al., (1963) and Scott (1965) have reported severe complications following prolonged catheterisation of the umbilical vein. Complications were particularly common following administration of fluid by this route (Scott, 1965). Cort (1962) found that depressed and dying infants had high haematocrit values at 12 hours. She suggested the use of plasma volume expanders to support pulmonary blood flow, maintain renal and acid-base function and relieve the cardiovascular system of the high viscosity. Rheomacrodex was used in 9 infants in this survey but discontinued because there were 7 deaths. The difference in mortality is not statistically significant, however. Better perfusion would result in better oxygenation which could be assessed by means of the hyperoxia test.

The volumes of fluid administered are given in Table 43. The amounts are much less than the 60 - 65 ml/kg/day used by Reardon et al. (1957), Usher (1961), Troelstra et al. (1964) and Gairdner (1965).

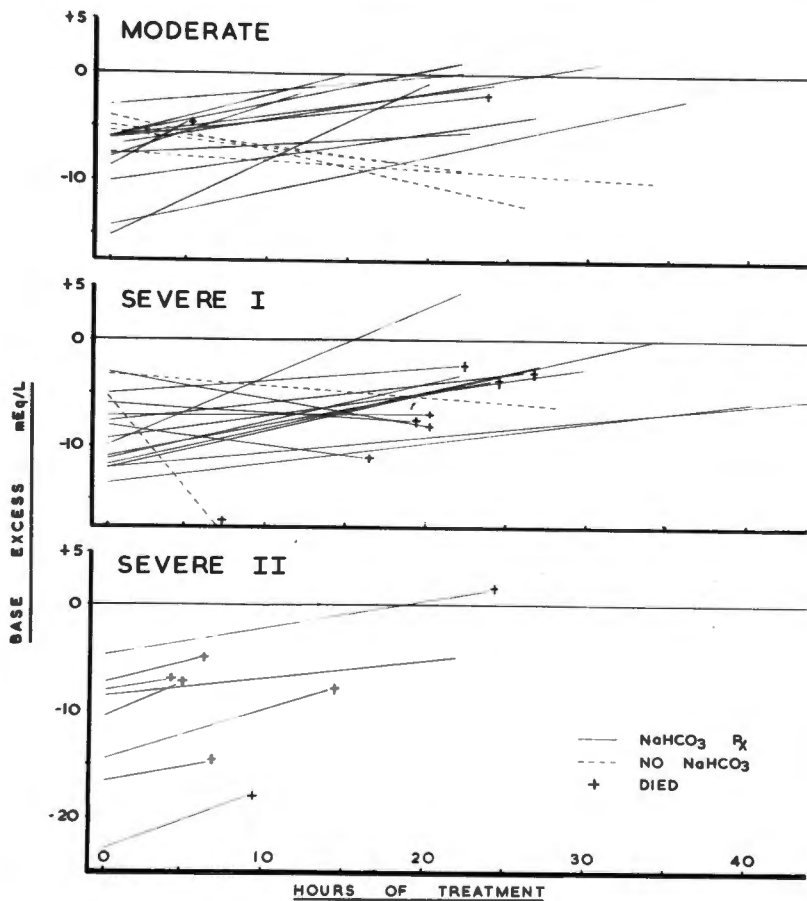
TABLE 43 CHMD - INTRAVENOUS FLUID VOLUMES

	<u>Moderate</u>	<u>Severe I</u>	<u>Severe II</u>	<u>All cases</u>
Average volume ml/kg/24 hrs.	30	28	40	32
Range ml/kg/24 hrs.	29 - 35	22 - 45	33 - 50	22 - 50

Usher (1963) found no signs of fluid overload or cardiac failure. Lower volumes were decided upon because evaporative loss would be

cut down in 100% humidity and the renal function appeared to be impaired in the first 1 - 2 days. The infants do not seem to have suffered any ill effects and diuresis still occurred between 48 - 72 hours (Cort, 1962 and Stahlman, 1964).

(c) Sodium bicarbonate: The amount of sodium bicarbonate given was calculated according to the base excess using a factor of 0.6 x bodyweight in kg. as the amount of body fluid that needs to be buffered (Appendix xxxv). In severe metabolic acidosis, a quarter of this amount was given directly as a 4% solution, while the remainder was administered in the intravenous fluid over the next 24 hours. Figure 9 illustrates the effect of sodium bicarbonate on the metabolic acidosis with this regime.



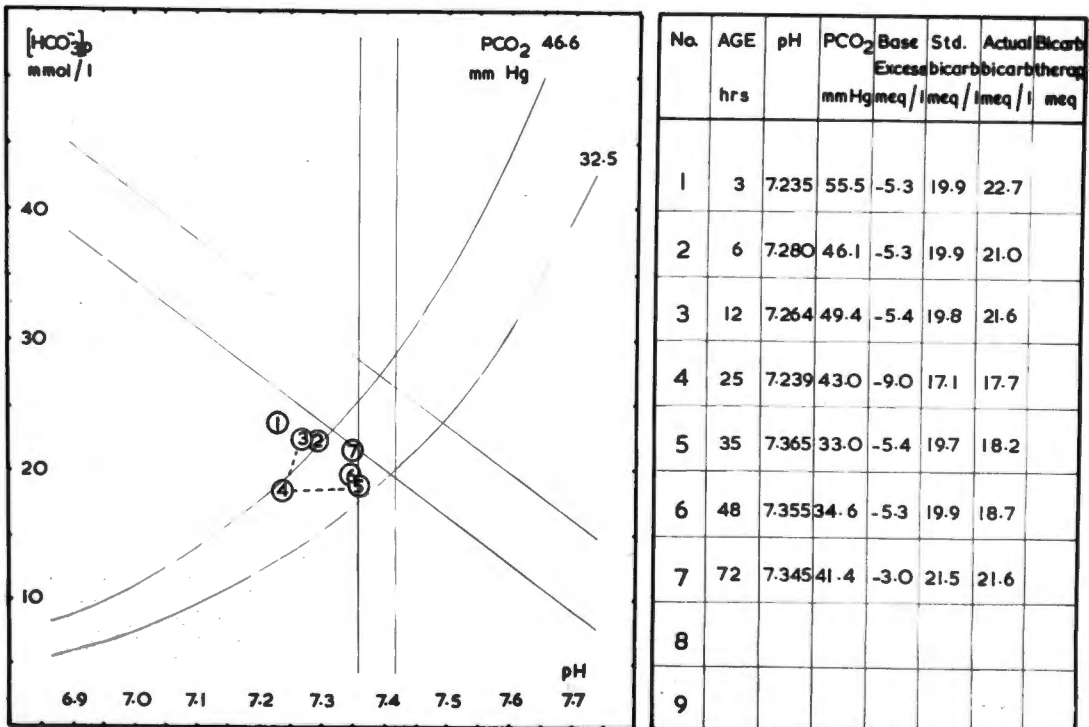
**Fig. 9** : Effect of sodium bicarbonate therapy on metabolic acidosis in CHMD

While the amount is adequate for the moderate and severe I groups, more sodium bicarbonate is required in the severe II group. It may be advisable to give the calculated deficit over a shorter period such as 12 hours. In the early part of the survey a clinical trial was conducted to assess the value of sodium bicarbonate against no alkali. It became apparent from the early results and the literature that one should not withhold alkali from the severely ill infants. The progression of the acidosis in untreated cases is seen in Figure 9.

Moderate illness did not always require sodium bicarbonate as can be seen in the acid-base findings and course in Figure 10.

NAME: BABY L.  
Hosp.Nº: 554

WEIGHT: 2.75 KG.

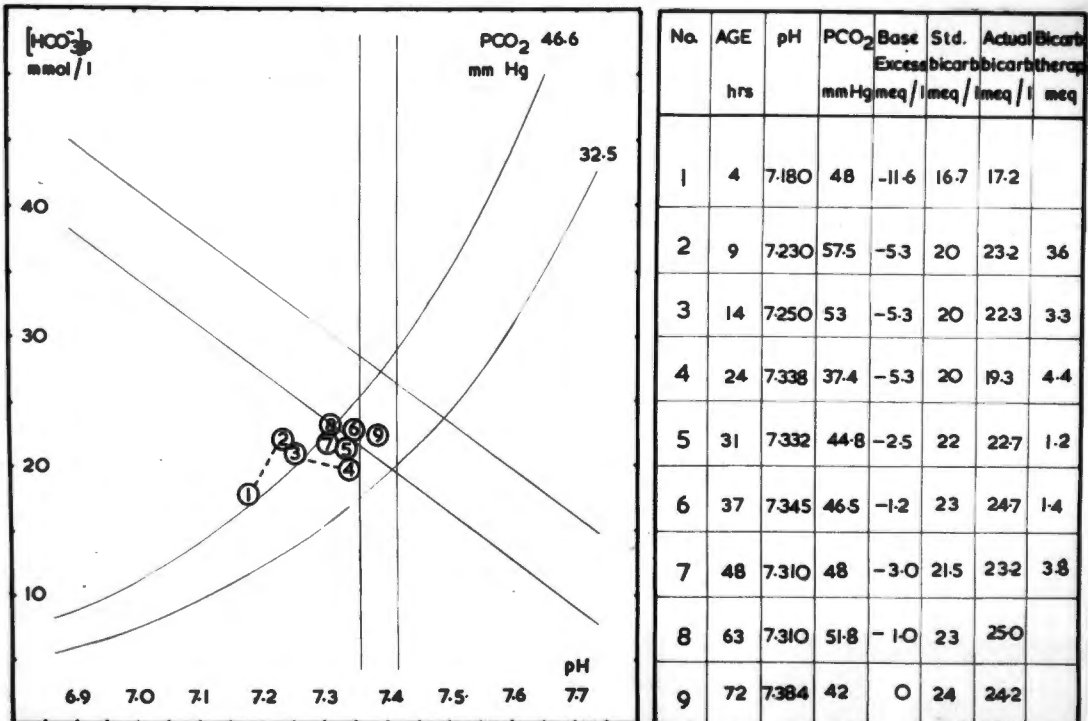


**Fig. 10** : Acid-base findings and course in moderate CHND - no bicarbonate therapy

The pH,  $\text{HCO}_3^-$  co-ordinate system is taken from Siggaard-Andersen (1964). Case No. 346 (Figure 11) demonstrates the gradual return to normal with continuous sodium bicarbonate therapy. Despite adequate correction of metabolic acidosis in Figure 12 the infant died with respiratory acidosis.

NAME: BABY S.  
Hosp.No: 346

WEIGHT: 2.51 KG.

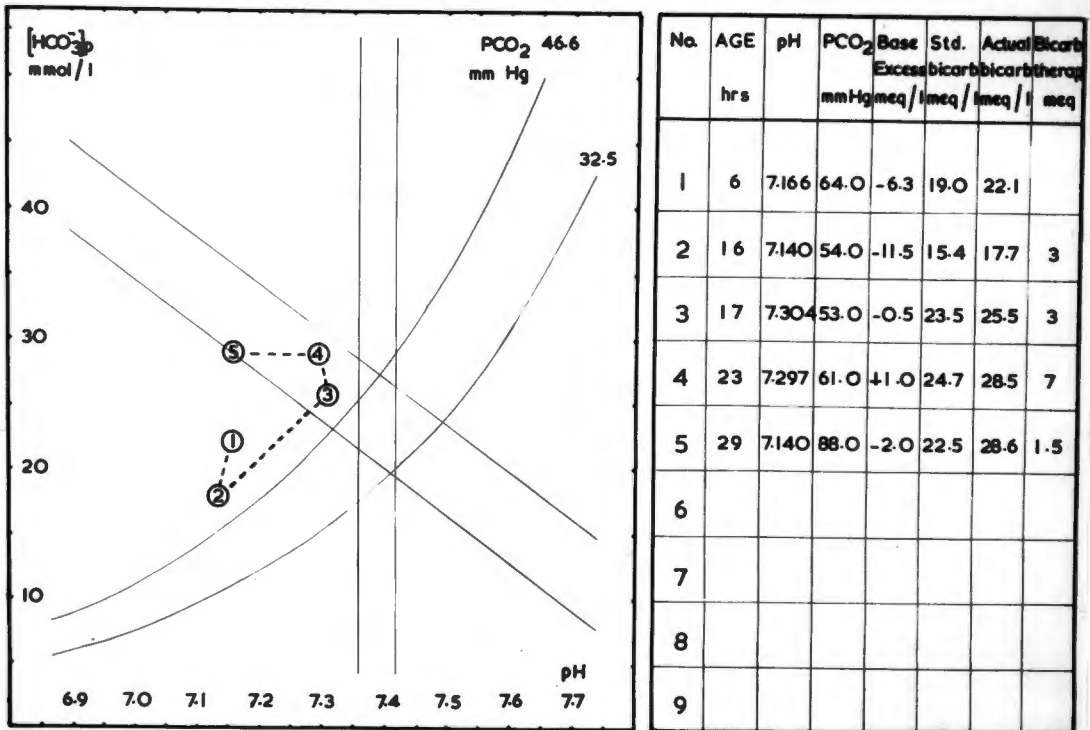


**Fig. 11** : Acid-base findings and course in severe CHMD with recovery

The physiological basis for the correction of metabolic acidosis and reversal of its effects on metabolism and circulation is sound. Usher (1961, 1963) stressed the importance of early treatment. Stahlman (1964) gained the impression that the earlier management is started, the more benign the course is likely to be. The only survivors in the high risk group of Boston et al. (1964) were those who received early and vigorous bicarbonate therapy.

NAME: BABY D.  
Hosp. No: 90.

WEIGHT: 1.78 KG.



**Fig. 12 : Acid-base findings and course in severe CHND with fatal outcome**

Usher (1961a), Stahlman (1964), Hutchison et al. (1964) and Smith (1965) calculated the amount of sodium bicarbonate according to the pH value while Deliveria-Papadopoulos et al. (1964) estimated the base deficit. Oypé et al. (1965) criticised the calculations according to the base excess in that this can only achieve partial correction of the pH, unless alveolar ventilation also improves. Stahlman (1964) estimated 60% of body weight to be water and gave the bicarbonate over a few hours. Hutchison et al. (1964) corrected 3% of body weight in one injection and then repeated the readings  $\frac{1}{2}$  - 1 hourly. Smith (1964) administered bicarbonate in a slow drip.

Troelstra et al. (1964) found sodium bicarbonate to be more effective than Tham in metabolic acidosis and without side effects. The production of metabolic over-correction does not seem to be harmful. Sodium bicarbonate produces an increase in  $CO_2$  levels, cardiac output, cardiac rate and cardiac work and a decrease in peripheral and pulmonary vascular resistance (Maxwell et al. 1959 and Rowe et al. 1964). Intra-arterial injection of sodium bicarbonate caused marked flushing of the lower limbs on several occasions.

(d) Tham

Tham was administered as a 0.3 molar solution to only 5 infants. One responded dramatically with rise in pH and fall in  $PCO_2$  from 86.0 to 40.5 mmHg. In the others, neither Tham nor sodium bicarbonate could improve the acidosis. In such severe cases no amount of buffer can compensate for the gross hypoxia that must be present. Gupta (1965) recently reported good response in 2 HMD infants treated with Tham. The marked rise in  $PaO_2$  was attributed to increased pulmonary perfusion (Nahas, 1962). Hatchison et al. (1964) concluded that Tham has no advantages over sodium bicarbonate in the treatment of metabolic acidosis and that the risks such as respiratory depression, hypoglycaemia and local irritation outweigh any advantages. Most clinicians reserve the use of Tham for patients with severe respiratory acidosis or a pH below 7.10.

(e) Insulin and Digoxin

In the early part of the survey insulin and digoxin were given routinely in severe cases. No untoward effects were noted, but on the other hand no improvement could be established. Insulin is best given

in the dosage of 1 unit/2 - 4 g. glucose intravenously whenever potassium reaches high levels. Stahlman (1964) adds insulin if the potassium is above 6.0 mEq/L but this figure is rather low for the newborn, 6.5 or 7.0 mEq/L being more realistic values. In this survey 11 infants had initial potassium levels over 6.5 mEq/L and 22 below this figure. There was no difference in the mortality between the groups ( $p > .05$ ).

Digoxin dosage should be carefully calculated at not more than .05 mg/kg body weight (Levine and Blumenthal, 1961 and Stahlman, 1964). Half may be given intramuscularly stat and the rest over 24 hours. Stahlman (1964) regards a pulse rate of over 150/min. as an indication, as would be cardiac failure. According to Usher (1961) the pulse rate in IRDS is 10% faster than in healthy premature infants, in which case recordings of 150/min. would be common. The pulse rates in this survey usually varied between 120 - 144/min.

#### (f) Blood transfusion

Finally, 10 ml of blood taken from a compatible donor, in a plastic syringe, was injected directly into the umbilical arterial catheter on a few occasions. This should be a routine therapeutic procedure if the haematocrit is below 40%.

#### Recovery period

Some interesting features were noticed in infants who survived. About half became jaundiced. The average age of onset was 62 hours with a range of 27 - 108 hours. Recession and tachypnoea persisted for up to 7 days in the most seriously ill infants with persistent radiographic changes consisting of very coarse and irregular opacities. This is in

agreement with the experience of Stahlman (1964) who also noted that cardiac murmurs often appeared in the convalescence but eventually disappeared. Weight loss was greater than in healthy prematures and continued for 4 - 7 days. This loss occurred despite high caloric feeds (Usher, 1961 and Beard et al., 1963).

Quite a remarkable finding has been the frequently raised  $PCO_2$  in the recovery period. The rise was never very high and occurred at a time when the infant was improving and the  $PaO_2$  had returned to normal. The only reference in the literature is that of Stern (1964) who recorded the same phenomenon. Stahlman (1964) stated that very ill infants had abnormal blood gases for many days but presumably included  $PO_2$  and  $PCO_2$ .

Ileus with vomiting used to be a problem in some cases but was not seen in the latter part of the survey. Usher (1961) also had difficulty with paralytic ileus and one wonders whether the routine use of insulin could be implicated in some way. No serum potassium levels were done and all cases improved spontaneously. Glycerine suppositories were tried with fairly good results. It seems advisable to commence oral feeding with small amounts frequently, via a stomach tube.

No planned follow-up was conducted on the infants in this survey. Those who were seen later appeared to be well and healthy. Shepard et al. (1964) reported that 48% of infants at follow-up had significant radiological changes compatible with pulmonary fibrosis. Daves (1965) wrote: "There is reason to suspect that some of the children

who recover may yet bear the scars of respiratory distress in their lungs and brains."

### Conclusions

CHMD is the most common cause of respiratory distress in newborn infants. Premature delivery is by far the most important factor in the pathogenesis of this condition. The calculated gestational age is a better guide to the maturity of the fetus than birth weight. Emphasis of treatment should be directed towards possible prophylaxis at or before birth in high risk infants. The low serum globulin levels warrant further investigation into a possible immunological basis for CHMD. The low haematocrit values suggest haemorrhage into the lungs on the same basis. A controlled trial with cortisone would appear justifiable.

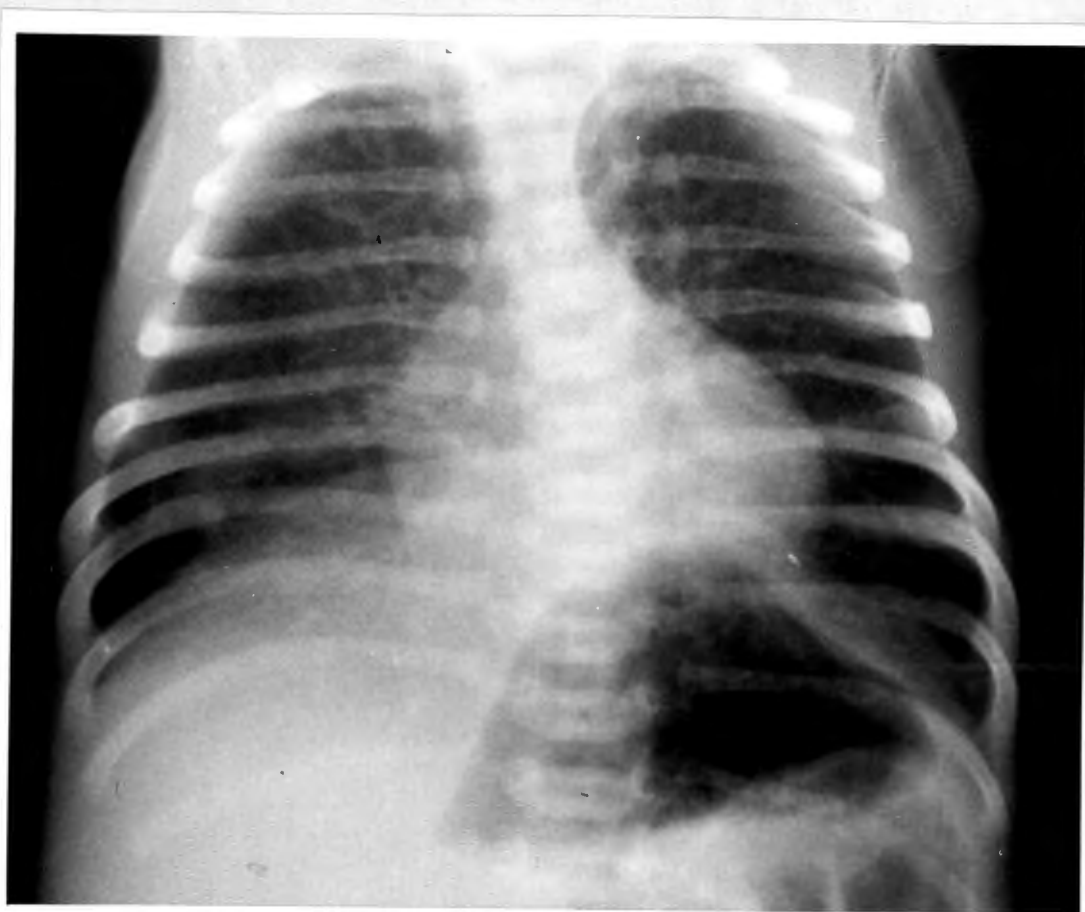
Assessment of severity based on the oxygen requirements is a very good clinical guide to prognosis. Measurement of  $\text{PaO}_2$  is of tremendous value in controlled oxygen treatment and the best biochemical criterion of the progress of the infant. Early metabolic treatment will make the difference between survival and death in moderately severe illness. Severely affected infants succumb in spite of available therapy. Once the infant has reached 48 hours of age the prognosis is very favourable. The raised  $\text{PCO}_2$  during the recovery period requires further investigation.

CHAPTER 11NEONATAL DISSEMINATED ATELECTASISIntroduction

Although an aspiration syndrome, here called NDA, has only recently been suggested as an entity in IRDS, it has long been noted that there were milder cases of 'HMD' which did not have the characteristic radiographic features of CHMD. Prod'hom (1964) and Prod'hom et al. (1965) documented a most thorough study of the pathophysiology of IRDS, dividing their cases into Types I and II. This differentiation between the types was based on lower R - L shunts and normal functional residual capacity in Type II. The radiological findings in this group corresponded very closely to the radiological description of NDA given by Kettler, Malan and Heese, (1964). The striking feature about NDA has been the rapid improvement and low mortality.

Diagnosis

The radiographic appearance of NDA is characterized by streaky atelectasis in the distribution of the bronchial tree, general emphysema and absence of a marked air bronchogram (Figure 13). This radiographic appearance was seen in 18 infants with RDS.



**Fig. 13** : Chest film of NDA demonstrating streaky atelectasis with emphysema and absence of air bronchogram

The contrasting radiological features of NDA and CHMD are shown in Figure 14. Two infants had other pathology associated with the radiological picture of NDA - nasal obstruction requiring an oral airway in one and acute blood loss (Hb. 9 g%) in the other.

**Clinical findings**

The clinical findings in NDA are given in Tables 31 and 32. They are included with CHMD for comparison. NDA comprises 22.5% of the

NDA - 18 CASES			CHMD - 62 CASES	
		AIR BRONCHOGRAM		
		OPACITY OF LUNGS		
		GRANULARITY		
		SEGMENTAL ATELECTASIS		
		EMPHYSEMA		
		EXTRA-PULMONARY AIR		

**Fig. 14** : Evidence of radiological signs:  
 black = prominent signs;  
 hatched areas = doubtful signs

infants with IRDS and differs from CHMD in several aspects although they were indistinguishable on initial clinical examination.

Half of the infants were cyanosed in room air, but the environmental oxygen requirement was more than 40% in only one of them. The respiratory rate was well over 60/min. in the vast majority. Grunting and recession were present in 72% of cases. The incidence of oedema, crepitations, sternal bulging and apnoeic attacks was notably lower than in CHMD. Prod'homme et al. (1965) also recorded less oedema and no rales. The mortality was 11% - autopsy showed that one, in fact, had HMD while the other died of a pneumonia

peritonitis and septicæmia with focal areas of atelectasis.

Prod'hom et al. (1965) had no deaths in their Type II, the corresponding group of their series.

Both studies showed the gestational maturity and birth weight to be greater in NDA. It is interesting to note that there were more females in the study of Prod'hom et al. (1965) while the present survey follows the usual male preponderance in neonatal respiratory distress. The low Apgar score at one minute suggests depression with possible aspiration of material.

The typical clinical picture and progress of NDA is shown in Table 44. The air entry, in contrast with CHMD, was never markedly diminished in these infants.

#### Investigations

(a) Acid-base values (Table 39) : NDA occupied an intermediary position between mild and moderate CHMD which corresponds to the clinical assessment of severity.

(b) Biochemistry (Table 40) : Potassium, sodium, chloride, urea and sugar are not materially different from CHMD or normal values. The total protein levels are higher than CHMD and approximate those of normal infants. It is interesting to speculate that the higher gamma globulin levels are also a pointer to the different etiology. The difference in R - L shunts between NDA and CHMD is in agreement with the findings of Prod'hom (1964).

(c) Hyperoxia: Only one NDA infant was investigated according to this method and is included in Figure 6. The initial  $PaO_2$  was low but

TABLE 44 NO. 80 NDA - SURVIVED

Age (hrs)	Resp. rate	Grunting	Resonance	Oxygen requirement	Air Entry	Crepitations	Oedema	Sternal bulge	Pulse rate	Peripheral pulse	Wt. (kg)	Apnoeic attacks	Neuro-muscular tone
1½	52	++	++	7	++	-	++	-	120	Good	2.84	-	Good
3	60	++	++	35%	++	-	++	-	120	Good		-	Good
5	65	++	+	35%	+++	-	++	-	128	Good		-	Good
8	76	-	+	30%	+++	-	++	-	130	Good		-	Good
20	80	-	+	30%	+++	-	+	-	140	Good		-	Good
44	64	-	-	-	+++	-	-	-	140	Good		-	Good

rapidly rose to over 200 mmHg. Fred'hem (1964) found all their Type IX infants to be in the normal range.

Treatment

Cyanosis was easily relieved with low concentrations of ambient oxygen. Only one infant (shown in Figure 6) required more than 40%. Intravenous fluids and sodium bicarbonate were given to 5 infants. The metabolic acidosis was easily corrected in all 5 and some required less than the calculated amount of sodium bicarbonate to replenish the base deficit. The acid-base values and treatment in NDA is illustrated by Case No. 240 in Figure 15.

NAME: BABY P.  
Hosp.Nº: 240

WEIGHT: 2.35 KG

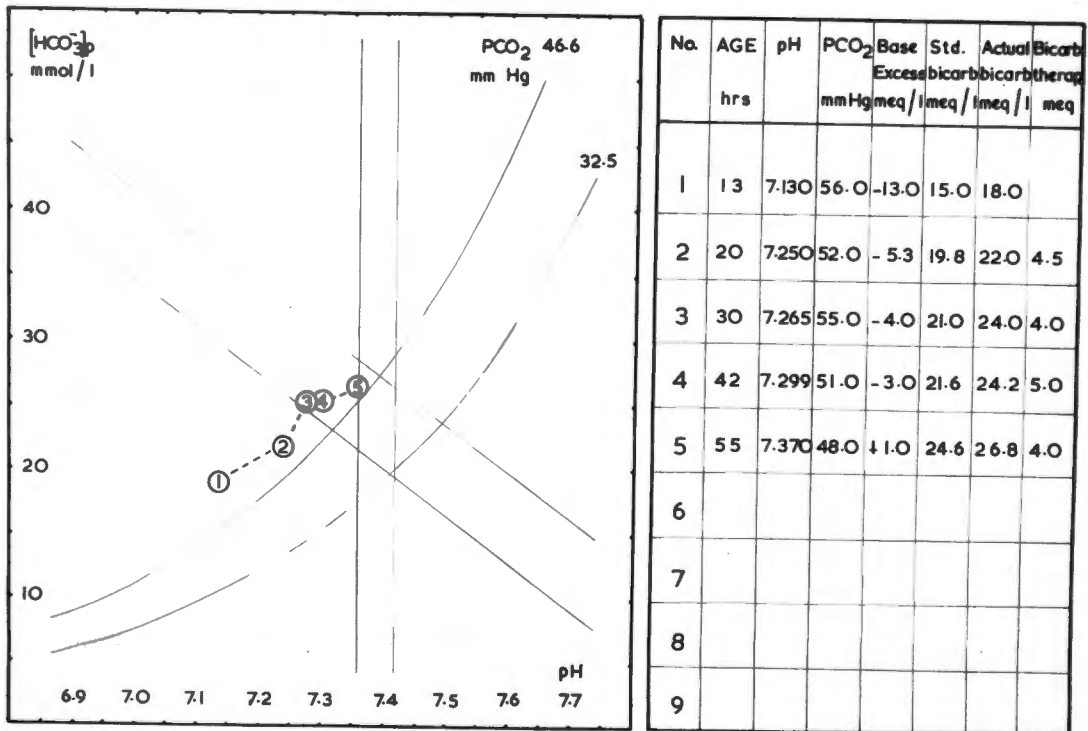
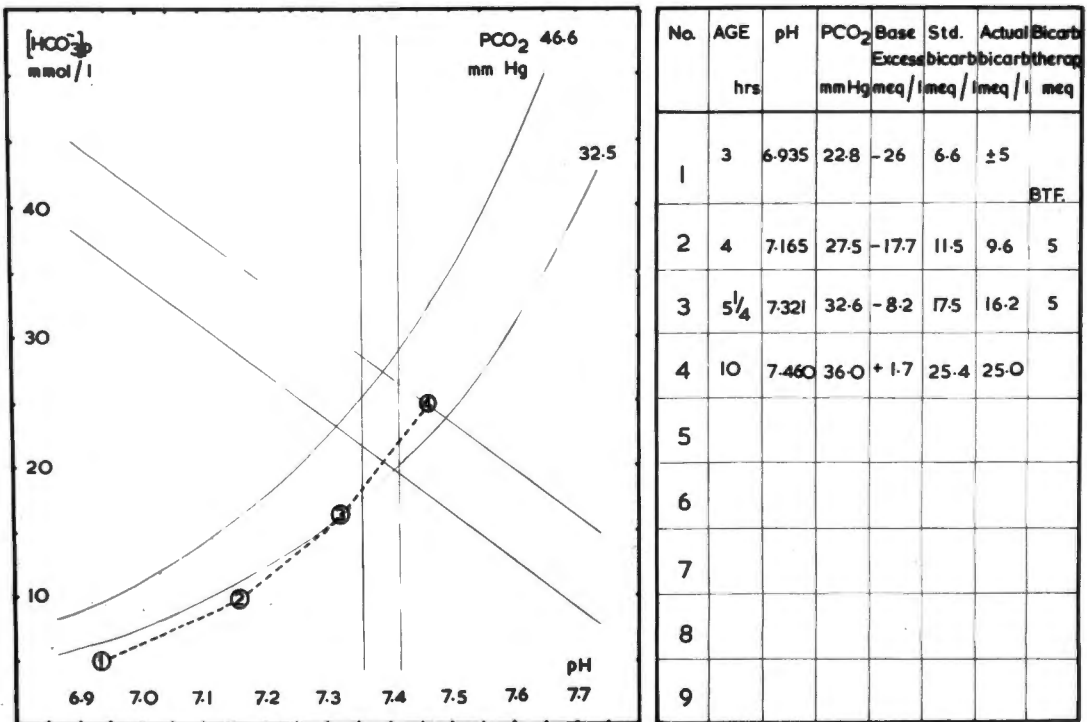


Fig. 15 : Acid-base findings and course in NDA

This infant (Figure 15) subsequently developed septicaemia and died. The acid-base values returned to normal spontaneously in all the others with the exception of the infant who died of HMD and another where there was associated blood loss. The dramatic response in the latter to blood transfusion and sodium bicarbonate is shown in Figure 16.

NAME: BABY L.  
Hosp. No: 234.

WEIGHT: 3.85 kg.



**Fig. 16 :** Acid-base findings and course in NDA with acute haemorrhage

**Discussion**

There is an obvious clinical overlap between this condition and milder forms of CHMD. Radiology is most helpful but occasionally

one finds a coarse reticulogranular pattern that could be either NDA or CHMD. Smith (1964) suggested that these might be mild HMD. It is hardly necessary to stress the value of serial films in doubtful cases. Prod'hom et al. (1965) found that one of their Type II infants had an 'HMD' radiogram. Similarly, one 'NDA' infant in this survey had hyaline membranes at autopsy. Hutchison et al. (1964) found that not all their mild cases had significant radiographic changes. Stahlman (1964) recorded hyper-aeration in the first 6 hours in moderate illness. The films were frequently not characteristic of CHMD. It is interesting to speculate that in some of their cases the respiratory distress could have been due to NDA.

The single most helpful investigation in these infants is the calculation of the R - L shunt on 100% oxygen. In differentiation of NDA from mild or moderate CHMD one would still have to rely on radiology and the clinical course unless pulmonary ventilation studies are done to measure functional residual capacity. Few centres will be able to emulate the careful studies of Prod'hom et al. (1965).

Much more difficulty is experienced in formulating a clear concept of the pathology. Schaffer (1960) stated that the massive aspiration syndrome covers a whole range of pathology. One may get either segmental or disseminated atelectasis. Avery (1964), discussing the role of aspiration of clear fluid in the causation of respiratory distress, came to no definite conclusion. In the case of the infant who died from pseudomonas septicaemia at 78 hours, the upper lobes were expanded but there were areas of atelectasis in the middle and lower lobes. The alveolar ducts were normal and no particulate matter, squames or hyaline membranes were seen.

An interesting observation in NDA is the absence of pneumothorax. Spontaneous pneumothorax is usually associated with massive aspiration syndromes. There is generalized emphysema in NDA and one would have expected rupture of some of the over-distended alveoli.

### Conclusions

The author believes there is good justification for separating NDA from CHMD. Whether NDA is an aspiration syndrome or merely a variant of CHMD in more mature infants remains to be seen. Only detailed investigations in a large number of infants will clarify the position. The normal serum protein values found here would exclude any suggestion of an immune reaction. The differentiation is a very useful guide for the clinician who has to assess each case, decide on therapy and deal with anxious parents. When the radiological picture of NDA is present in an infant with RDS one can predict recovery with complete confidence.

CHAPTER 12PNEUMONIA

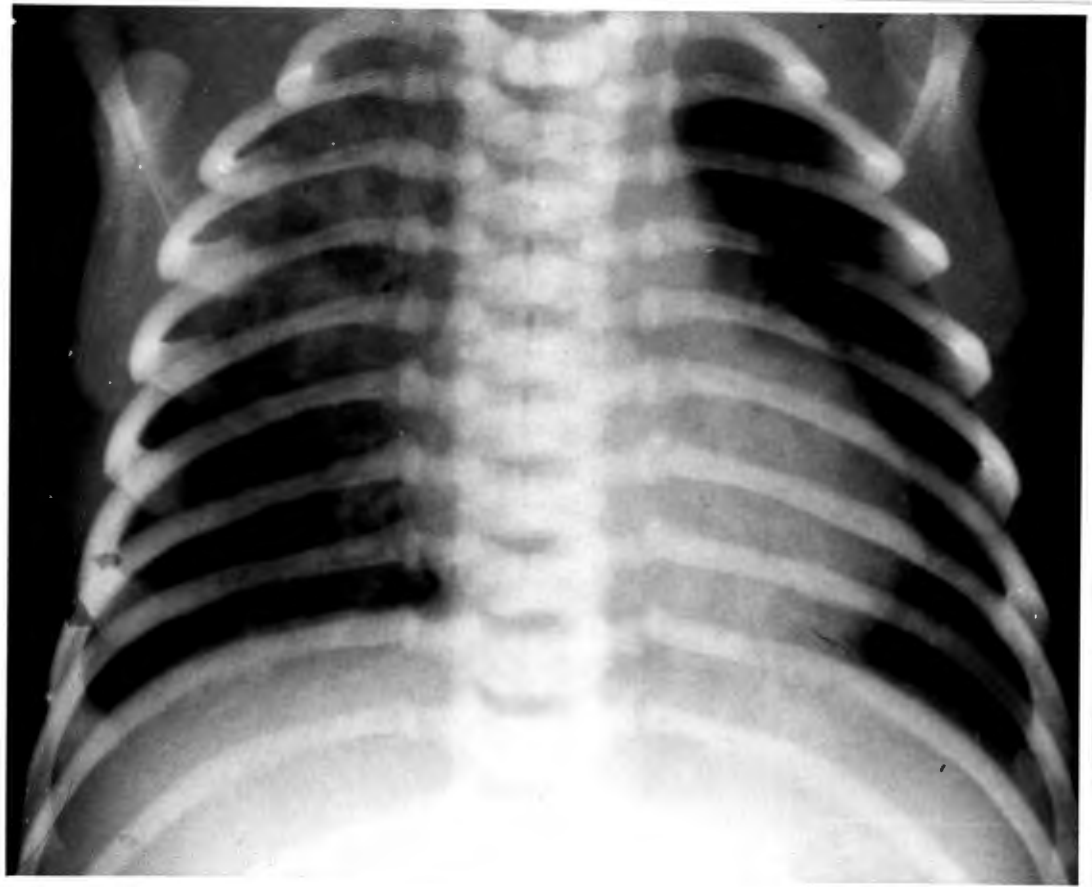
Pneumonia, acquired in utero or in the early neonatal period, is the commonest serious infection in newborn infants. It remains one of the principal causes of death. Blanc (1959) wrote: "Of all the main causes of neonatal death, infection would appear to be the easiest to eliminate." A knowledge of the predisposing conditions and clinical features are, therefore, of importance to anyone responsible for the care of newborn infants.

Clinical findings

Congenital pneumonia was diagnosed in 13 newborn infants in this survey (Table 8). The basis for diagnosis was variable - 3 on radiology, 2 at the bedside without radiographic support and 8 at autopsy. An example of the radiographic appearance is shown in Figure 17. None were intensively investigated. The high mortality (69%) is a reflection of the large number of autopsy diagnoses. The incidence of pneumonia in deaths from RDS was 13.8%.

Pneumonia was more common in males and in premature infants. Signs of respiratory distress appeared soon after birth and are probably indicative of ante- or intra-partum infection. The respiratory rate varied from 42 - 96/minute with a mean of 60/min. Grunting was present in 89% of cases, cyanosis in 69% and recession in only 38%. Focal crepitations were present in 2 cases. The average duration of signs

was 37 hours and the average age of death 34 hours. At autopsy associated pathology was subdural haemorrhage, pericarditis, atrial septal defect and congenital syphilis. Organisms were isolated at autopsy from 2 infants - streptococcus and klebsiella respectively. No umbilical cords, placentae or membranes were examined histologically.



**Fig. 17** : Chest film of congenital pneumonia

#### Discussion

The coarse, diffuse pulmonary mottling of bronchopneumonia on radiography may resemble the late stages of HMD (Steiner, 1954). An interlobar fissure is frequently evident in normal infants and

should not be interpreted as infection without parenchymal involvement (Peterson and Pendleton, 1955). Confirmation of the diagnosis was most often sought from other evidence of infection in the amnion, placenta or nose of the infant (Blanc, 1959; Benirschke, 1960 and Driscoll and Smith, 1962).

The autopsy incidence of pneumonia in the first week of life is reported as 12.2% (Bound et al., 1956 and Sivanesan, 1961) and 13.3% (Butler and Bonham, 1963). The incidence in this survey (13.8%) is much the same. The deaths in the series of Sivanesan (1961) occurred on the 3rd - 5th day, but were much earlier here.

In the discussion of pneumonia in the literature, no mention is made of the sex incidence. The usual male preponderance was found in this survey. The increased incidence in premature infants is in accordance with the reports of Blanc (1959) and Benirschke (1961). Usher (1961) recorded that pneumonia usually presented with tachypnea and cyanosis and little or no grunting and retraction. Schaffer et al. (1955) and Driscoll and Smith (1962) also stated that retraction was not a prominent sign as was the experience here. Grunting, on the other hand, was the most consistent sign and is recorded by James (1959) and Schaffer et al. (1955). Usher (1961) mentioned focal râles as a feature of pneumonia.

There are no reports of ventilation studies on newborn infants with pneumonia. Boda and Muranyi (1962) found that hypercapnia was an exceptional occurrence in infants with pneumonia as there was a tendency to hyperventilate. One acid-base determination was done on

an asyanotic infant in this survey. The values were pH 7.439,  $PCO_2$  31.5 and BE -2.0.

The most important associated obstetrical features are maternal pyrexia and prolonged rupture of the membranes (Anderson et al., 1962). The incidence of pneumonia closely correlates with that of premature rupture of the membranes, but the association is not consistent. On the other hand the association of pneumonia with the placental lesions of amniotic infection is practically constant (Blans, 1959). The vast majority of neonatal pneumonias are thought to be of intra-uterine origin (Bernstein and Wang, 1961). Schaffer et al. (1955) stated that where the pregnancy had been normal the infants were frequently premature.

It seems reasonable to investigate and observe infants born after rupture of membranes for more than 24 hours. Cultures should be taken from the nose and throat. Anderson et al. (1962) regarded a maternal temperature of  $99.6^{\circ}F$  and rupture of membranes for more than 36 hours as absolute indications for antibiotic therapy. Others would prefer to wait if the infant is vigorous and well. Treatment should consist of wide-spectrum antibiotics to cover both gram negative and positive organisms. In this survey ampicillin and cloxacillin were used together.

**Conclusions**

Congenital pneumonia is the commonest infection in the newborn period and is responsible for 13.8% of deaths in RDS. Male and premature infants are at greater risk. Signs of RDS in an infant born after rupture of the membranes for more than 24 hours requires prompt and vigorous antibiotic therapy. The antibiotics should be effective against both gram negative and positive organisms. Focal crepitations and marked recession are uncommon findings. Radiology and histological examination of the placenta and membranes will help to differentiate between pneumonia and CHMD.

CHAPTER 13SPONTANEOUS PNEUMOTHORAXIntroduction

Spontaneous pneumothorax is said to be more common in the newborn period than at any other time during childhood. Although an infrequent cause of respiratory distress, it is important to recognise and assess this condition as in cases of tension pneumothorax prompt treatment can be life saving. The detection of pneumothorax in newborn infants will depend on a high index of suspicion plus a knowledge of the predisposing factors and physical findings. In addition to the usual features of respiratory distress these infants may have characteristic signs. Confirmation of the diagnosis rests on the availability of radiographic facilities or direct aspiration in cases of emergency. Pneumo-mediastinum is included under the title of pneumothorax as it is probably a variant of the same underlying pathology (Lubchenco, 1959).

Clinical findings

Seven cases of asymptomatic spontaneous pneumothorax were seen in this survey. Five of these infants were born in the maternity hospitals and the other two were referred from Greater Cape Town. The incidence in the maternity hospitals was 0.05%. The clinical details of the 7 infants are set out in Table 45. In none of them were resuscitative measures employed at birth and they all survived.

The radiological findings are shown in Table 45 and one case

TABLE 45 DETAILS OF INFANTS WITH SPONTANEOUS PNEUMOTHORAX AND PNEUMOMEDIASTINUM

Serial No.	Sex	Birth wt. (kg)	Age at 1 min.	Obstetrical Factors	Delivery	Signs first noted	Radiological findings		Treatment	Cleared in:
							Thorax	mediastinum		
17	M	3.39	3/10	Ruptured membranes 48 hours	Vacuum	5 hrs	R & L	+	Antibiotic	4 days
71	F	3.51	7/10	Postmature. Fetal distress. Meconium liquor ++	Forceps	1 hr	R (tension)	-	Tube drain R Antibiotic	12 days
232	M	2.89	7/10	Rapid delivery of body	Normal vertex	1 hr	L	+	None	2 days
273	M	2.83	-	Postmature. 15 min delay with head	Breech	1 hr	L	+	None	6 days
311	M	3.37	5/10	Face presentation	Forceps	1 hr	L	+	None	3 days
393	M	2.58	7/10	Normal	Normal vertex	1 hr	-	+	Antibiotic	4 days
611	M	4.17	-	Cord around neck. Facial petechiae. Meconium liquor ++	Normal vertex	Birth	L	+	Antibiotic Ba.NCO <sub>3</sub>	14 days

\* Counsel. L.U.L.

is demonstrated in Figure 18. Some degree of pneumomediastinum was present in all except Case 71. Consolidation of one lobe was seen in Case 393. Case 611 had the accepted radiological picture of meconium aspiration (Peterson and Pendleton, 1955). Pneumothorax is often incorrectly diagnosed on the presence of skin folds on the chest film. Such folds or lines usually extend beyond the margins of the parietal pleura. If there is any doubt the film should be repeated.



**Fig. 18 :** Chest film demonstrating spontaneous pneumothorax on the left side

The clinical signs and their relative frequencies are summarised in Table 46. Tachypnoea, up to 130/min. was seen in all the infants. A prominent chest bulge was present in 6 cases. The bulge was on the same side as a unilateral pneumothorax in Cases 71, 232, 273 and 311. In Cases 17 and 611 there was central sternal bulging. In Case 393 no bulge could be detected. The presence of a chest bulge in association with other signs led to the correct diagnosis prior to radiology in 5 instances.

**TABLE 46 PNEUMOTHORAX - CLINICAL PRESENTATION**

RR > 60	100%
Chest bulge	
Cyanosis	86%
Recession	
Grunting	
Decreased AE	71%
Irritability	57%
Cardiac signs	43%

Central cyanosis was present shortly after birth in 6 cases. The cyanosis was prolonged in Cases 71 and 611; in the others it was of a few hours' duration. Recession was a constant finding but much less severe than that seen in infants with CHMD.

Five infants had persistent grunting and decreased air entry. Diminished air entry on the side of the chest bulge was found in 4 cases. In the fifth, the air entry was initially decreased on the side opposite

to the pneumothorax but became equal after 2 hours. Unusual irritability and restlessness was present in 4 cases. Cardiac signs were not helpful in this study, a shift of the cardiac impulse being detected in only one child. In two others, the heart sounds were faint, with occasional crepitations over the sternum.

#### Acid-base values

The acid-base findings in 6 of the infants are given in Table 47.

**TABLE 47 PNEUMOTHORAX - ACID-BASE BIOCHEMISTRY**

<u>Serial number</u>	<u>Age in hours</u>	<u>pH</u>	<u>PCO<sub>2</sub> mmHg</u>	<u>BE mEq/L</u>	<u>BB mEq/L</u>	<u>Standard HCO<sub>3</sub><sup>-</sup> mEq/L</u>	<u>Actual HCO<sub>3</sub><sup>-</sup> mEq/L</u>
17	12	7.457	25.0	-2.5	47.0	22.0	17.5
	15	7.460	26.0	-4.4	44.8	20.5	17.0
71	2	7.184	55.0	-9.3	38.5	17.2	19.2
	4	7.400	38.0	-1.0	48.0	23.2	22.0
273	12	7.362	30.8	-7.2	36.8	18.2	17.0
	19	7.372	39.5	-2.1	45.5	22.2	22.1
311	24	7.370	34.0	-5.0	40.6	20.0	19.0
	13	7.376	38.9	-2.2	47.0	22.2	22.0
393	8	7.395	35.5	-2.8	42.6	21.6	21.0
611	31	7.150	48.6	-11.2	33.4	15.3	16.4
	47	7.347	46.2	-0.6	44.9	23.3	24.4

Case 17 presented with a respiratory alkalosis associated with a very high respiratory rate. The PCO<sub>2</sub> rose to 35 mmHg at 77 hours. In Case 71 there was prompt return from a combined acidosis to normal values after needle aspiration of a tension pneumothorax. Cases 273, 311 and 393 were essentially normal. Case 611 was a severely ill infant

with meconium aspiration who was given sodium bicarbonate intravenously to correct the non-respiratory acidosis. The arterial oxygen tension was measured in this infant only and was found to be 72 mmHg while breathing 45% oxygen.

#### Treatment

Tension pneumothorax developed in Case 71 and required emergency aspiration. This was followed by underwater drainage through a chest catheter for 12 days, with complete recovery. Antibiotics were used when infection was suspected or thought to be an additional risk. No treatment other than the routine nursing care and observation was necessary in 3 cases. A sterile tray with needles, taps and syringe was kept at the side of the incubator in case of tension pneumothorax. Additional oxygen was given when cyanosis was present.

#### Discussion

The incidence of symptomatic spontaneous pneumothorax of the newborn in this survey is 0.05%. This figure corresponds to those of Harris and Steinberg (1954), Howie and Weed (1957), Lubchenco (1959) and Chernick and Avery (1963). It has been pointed out that the radiological incidence is much higher than would be suspected from clinical signs. Emery (1956) has estimated that a variable amount of interstitial air, causing no symptoms, would occur in perhaps 1 out of every 200 normal full-term infants, i.e. 0.5%. The high incidence of pneumomediastinum in this study is not surprising, as it has been shown experimentally that the mediastinal pleura requires less tension to rupture than the visceral pleura (Hamman, 1939).

There were many similarities between this study and those reported by Howie and Weed (1957) and Chernick and Avery (1963). The vast majority of their infants had birth weights over 2.5 kg. in contrast with the hyaline membrane group. None of the infants in this study was premature by weight. There was a strong male preponderance. In most instances the onset of distress occurred shortly after birth, if not in the delivery room itself. Several infants were born by complicated deliveries. In such cases there is presumably a greater risk of aspiration of foreign material.

The association of meconium and mucus aspiration in the pathogenesis of pneumothorax has been discussed by Chernick and Avery (1963) and Emery (1956). The high transpulmonary pressure across the lung with the first few breaths may rupture some alveoli while others are still atelectatic due to aspiration of foreign material. The development of pneumothorax after over-vigorous resuscitation with positive-pressure respiration clearly belongs to a separate etiological group (Emery, 1956 and Ostalay and Beard, 1963).

In this study the presence of a chest bulge, either unilateral or central, has been a prominent feature. The finding of a unilateral chest bulge, decreased air entry on the same side, tachypnea and cyanosis, is virtually diagnostic of a pneumothorax. Heald and Wilder (1949) recorded a marked precordial bulge with almost absent heart sounds in infants with pneumomediastinum. Prosser (1964) mentioned over-distension and fixation of the chest as signs of interstitial emphysema. Vines (1963) also recorded decreased air entry and distant heart sounds, but did not mention bulging of the chest wall.

Radiological confirmation of a clinical diagnosis of pneumothorax is imperative. The signs may be identical in cases of infantile lobar emphysema (Leape and Longino, 1964).

Several infants displayed unusual irritability and more attention should perhaps be paid to this sign. It seems to be an important feature of pneumothorax in premature infants (Lubchenco, 1959). In this study the cases with irritability had the highest respiratory rates, 80 - 130/min. It is uncertain whether this should be attributed to anoxia or the irritant effect of air within the mediastinum. Extra-pulmonary air within the chest is probably painful or at least a source of discomfort. Lubchenco (1959) noted an improvement in the irritability after oxygen administration. This may have been an expression of the more rapid absorption of loculated air while breathing higher concentrations of oxygen as demonstrated by Chernick and Avery (1963). Case 611 showed marked irritability and tachypnoea with a  $\text{PaO}_2$  of 72 mmHg.

Except for those with tension pneumothorax and meconium aspiration the infants showed little disturbance of their acid-base balance. The only other available figures for pH,  $\text{PCO}_2$  and BE are those of 2 cases recorded by Prosser (1964). One infant had HMD and the other a tension pneumothorax with acid-base figures similar to those of Case 71 in this study.

The principles and practical aspects of treatment have been fully discussed by Chernick and Avery (1963). They stressed the value of high ambient oxygen to facilitate the absorption of the air. Vines (1963) drew attention to the importance of negative suction

drainage where there is underlying lung disease. This was not applied in the patient with tension pneumothorax but it would probably have shortened the period of absorption.

### Conclusions

Symptomatic spontaneous pneumothorax is an uncommon cause of RDS but prompt treatment can be life saving in cases of tension. The affected infants are mature and often postmature with a history of difficulties during the delivery. A unilateral chest bulge is the most characteristic finding. Associated with decreased air entry on the same side, tachypnoea and cyanosis, it is virtually diagnostic of pneumothorax. Radiological examination is imperative. The acid-base balance was only disturbed in cases of tension and meconium aspiration. High ambient oxygen will facilitate the absorption of loculated air. Immediate needle aspiration followed by water-seal drainage through a catheter is necessary if tension develops. The mortality from this condition should be negligible provided it is recognised early and treated properly.

CHAPTER 14MASSIVE ASPIRATIONIntroduction

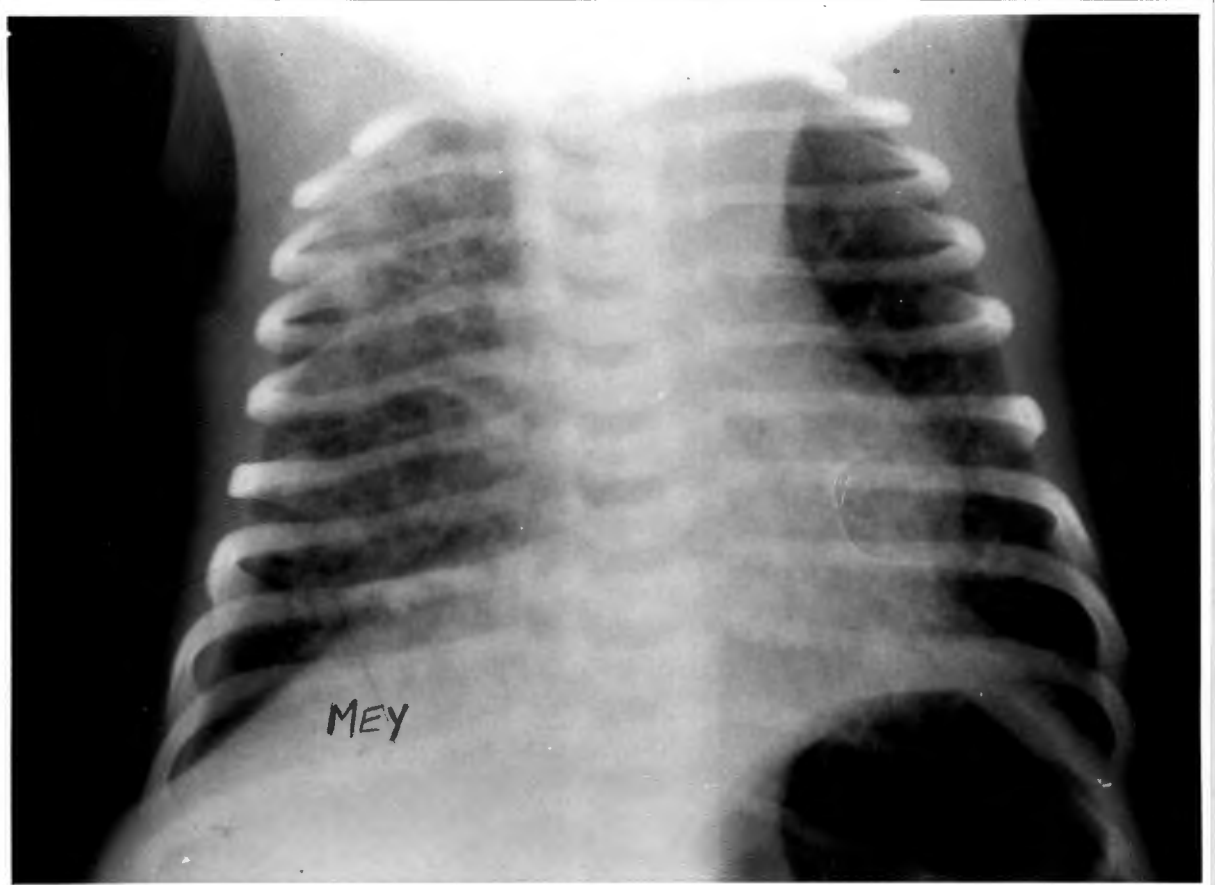
Inhalation of particulate matter suspended in amniotic fluid causes irregular obstruction to the bronchial tree that interferes mechanically with inflation of the lungs with resultant focal atelectasis and ectasia. Particles such as squamous cells and meconium are readily apparent in the airways and alveoli at autopsy of some infants whose clinical course is characterized by laboured breathing from birth and abundant râles in the lung fields. On the other hand, squamous cells may be present in alveoli without causing serious respiratory difficulty (Avery, 1964).

Massive aspiration refers to those infants in whom it was felt that aspiration of amniotic fluid and its particulate matter was responsible for illness and death.

Diagnosis

As in respiratory distress due to pneumonia and pneumothorax, a knowledge of the predisposing factors and clinical features should lead the medical attendant to suspect massive aspiration. Radiology will confirm the presence of pulmonary abnormality. There is usually a hyper-expanded chest with flattened diaphragms and coarse, non-uniform areas of atelectasis and emphysema. In meconium aspiration, the bilateral coarse infiltrations and interspersed foci of lobular hyperaeration produce a honeycomb appearance (Figure 19). Diagnosis in

this survey was made on the clinical and radiological appearance in 3 cases and at autopsy in 4 cases, 2 of whom had abnormal but not characteristic radiograms.



**Fig. 19** : Chest film of massive meconium aspiration

#### Clinical findings

Massive aspiration was present in 7 infants in this survey. (Tables 8 and 11). It was not possible to determine the incidence, as many of the milder forms were not investigated and did not come to autopsy. Males again predominated over females but only 2 were premature infants. Three were meconium-stained at birth and the average Apgar score at 1 min. was 3.5.

The respiratory rate tended to be slow with an average of 55/min. Grunting was heard in all cases with an average duration of 21 hours. Although recession was also present in all, the severity was usually mild or moderate. Cyanosis, on the other hand, was a severe problem. The signs of respiratory distress persisted for over 5 days in the one survivor. Two infants had general edema and one had bilateral pleural effusion in addition to the edema. Thoracentesis produced a yellow sterile fluid with a few cells and protein of 2.3 g %. The average age of death was 34 hours and the high mortality was due to the selection of cases. Histology revealed aspirated squames in 4 and meconium in 2 infants.

Acid-base determinations in 2 infants showed a combined acidosis with average pH 7.160,  $PCO_2$  of 61.3 and BE -9.3 Treatment was conducted along the usual lines for RDS.

### Discussion

The radiological appearance in massive aspiration syndromes has been documented by Peterson and Pendleton (1955), Hanley et al. (1963), Stahlman (1964) and Avery (1964). No figures are available on incidence. Schaffer (1960) stated that in his experience it was the most common cause of respiratory distress. In contrast with the findings in this survey, Stahlman (1964) stated that the birth weight was usually over 2.5 kg. Two small infants (1.33 and 1.47 kg. respectively) had aspiration atelectasis in this survey. Marked aspiration was recorded by Sivanesan (1961) in infants over 2.0 kg. only. In the literature (Peterson and Pendleton, 1955; Clifford, 1957; Hanley et al., 1963 and Stahlman, 1964), the majority of infants had

features of postmaturity such as wrinkled and peeling skin and meconium staining. The presence of meconium is significantly associated with depression at birth (Auld et al. 1961). The low Apgar scores here are in agreement with the experience of Stahlman (1964).

The clinical signs, especially tachypnoea, may persist for days or weeks (Avery, 1964). The respiratory rates in this survey are slow when compared with those reported by Hanley et al. (1963) and Stahlman (1964). This again suggests exclusion of the milder forms (Schaffer, 1960). Persistent grunting was invariably present which was not the experience of Usher (1961). Other investigators agree that retraction is mild (Schaffer, 1960; Usher, 1961 and Hanley et al., 1963), but that cyanosis is difficult to alleviate (Stahlman, 1964). Rales may or may not be heard on auscultation (Schaffer, 1960; Hanley et al., 1963 and Avery, 1964). Mortality figures vary from 39% to over 50% in severe cases (Clifford, 1957; Schaffer, 1960; Hanley et al., 1963 and Stahlman, 1964). No figures are given for the age of death. Hanley et al. (1963) found aspirated maternal blood in addition to keratinised squamous cells and meconium.

Usher (1962) found the major biochemical disturbance to be a severe metabolic acidosis with an elevated  $PCO_2$  in some infants. A combined acidosis was reported by Stahlman (1964) as was the finding here. Avery (1964) advocates aspiration of the stomach of all infants who are meconium stained at the time of birth. The larynx should be inspected with a laryngoscope and any meconium removed by suction. Stahlman (1964) used intravenous glucose and buffers and digitalised all infants.

Pneumothorax is a relatively common complication (Peterson and Pendleton, 1955; Schaffer, 1960; Usher, 1962 and Stahlman, 1964) and requires constant vigilance to prevent tension. The association between aspiration and spontaneous pneumothorax is discussed in the previous chapter. Schaffer (1960) regarded cor pulmonale as an occasional complication while Stahlman (1964) regarded it as very common. The oedema found here was thought to be a manifestation of cardiac failure.

### Conclusions

Aspiration of amniotic fluid ± particulate matter may cause a whole spectrum of conditions including transient distress after Caesarean section, NT and NDA. Massive aspiration was used to describe the respiratory distress caused by aspiration of large amounts of squames and meconium. The classical case of massive aspiration is a mature or postmature infant with signs of foetal distress such as meconium staining. They are often depressed at birth and require prompt recognition and supportive therapy. The mortality is high and pneumothorax is a common complication. Recognition and prevention of foetal distress in utero should be the main aim. Prevention of further aspiration at the time of birth is a logical approach. Treatment should be directed towards correcting anaemia and acidosis and treating cardiac failure.

CHAPTER 15CEREBRAL INFANTSIntroduction

Disturbance of cerebral function is often reflected in disturbances of respiration. Cerebral damage in the newborn infant may be due to intracranial haemorrhage or anoxia, sustained before or during delivery. Intracranial haemorrhage is, of course, a frequent secondary complication of RDS, but this chapter concerns infants with primary cerebral lesions.

Diagnosis

The diagnosis of cerebral disturbance was made on the presence of certain signs and confirmed in some by spinal puncture.

The clinical signs were:

Irritability  
Twitches  
Convulsions  
Apnoea  
Full fontanelle

Primary pulmonary pathology was thought unlikely in the absence of marked grunting, recession and cyanosis. One radiographic examination showed normal lungs. Autopsies on RDS infants added two unsuspected cases of intracranial haemorrhage.

Presentation

Twenty-one infants were labelled 'cerebral' on the above criteria.

The presentation of respiratory disturbances in these infants was as follows:

Neonatal Tachypnoea	- 12
RDS	- 6
Apnoea attacks	- 1
Cyanosis (slow RR)	- 1

#### Clinical findings

Males outnumbered females and even more striking was the fact that there were no females with intracranial haemorrhage. Only 4 infants were premature by weight. The majority of the deliveries were complicated - 6 forceps deliveries, 4 vacuum extractions, 4 breech deliveries and one Caesarean section for foetal distress. The indications for instrumental deliveries were not determined. Foetal distress, other than meconium in the liquor, may have been indications for intervention (Cox, 1963). The low average Apgar score of 3.4 is indicative of cerebral depression. The RR was variable with an average rate of 68/min. The majority were rapid with two very slow rates in infants who died at 8 and 12 hours respectively. The average duration of tachypnoea was 3½ hours. Grunting occurred in 7 infants, but lasted longer than 4 hours in only two. Recession was virtually absent and cyanosis almost invariably associated with severely depressed infants.

Acid-base determinations in tachypnoeic infants showed values in the normal range with low  $PCO_2$  levels. One determination was done soon after an apnoeic attack and the findings were:

pH 7.145,  $PCO_2$  41.0 and BE -13.5.

No  $PaO_2$  studies were carried out.

The mortality was 33%. Death occurred late in most infants at an average age of 72 hours. Autopsy showed 2 subarachnoid and 2 cerebral haemorrhages. One infant had developed hydrocephalus and histology demonstrated extensive toxoplasmosis of the brain. The two depressed and cyanosed infants had incomplete expansion of the lungs. No neurological follow-up was made of any of the survivors.

### Discussion

Confirmation of the clinical diagnosis of cerebral irritation or damage may be very difficult. Focal signs such as convulsions or a bulging fontanelle suggest intracranial pathology but do not distinguish haemorrhage from the cerebral oedema of asphyxia (Avery, 1964). A lumbar puncture is not uncommonly traumatic. Normal newborn infants may have red cells in the cerebrospinal fluid and one may get normal fluid in spite of gross cerebral damage. Radiology will help to exclude pulmonary pathology (Steiner, 1954). One should always remember to investigate the possibility of hypoglycaemia and hypocalcaemia in infants with twitching and apnoeic attacks.

Tizard (1964) stated that males greatly exceed females in intracranial haemorrhage which is also the case here. Both Tizard (1964) and Donald et al. (1958) emphasized that intraventricular haemorrhage is mainly confined to extreme prematurity. The 2 infants with subarachnoid haemorrhage in this survey weighed 1.67 and 1.73 kg. respectively. Donald et al. (1958) thought asphyxia was the primary cause of the lesion and not trauma.

According to Usher (1962) the respiratory disturbance is usually hyperventilation rather than laboured respiration. This was

the usual finding here. Gross haemorrhage and increased intracranial pressure are likely to be associated with respiratory depression (Avery, 1964) and led to early death in 2 infants.

### Conclusions

Only severe intracranial lesions with cerebral depression cause RDS as defined in this survey. The majority of 'cerebral' infants have tachypnoea with respiratory alkalosis. Males outnumber females especially in cases of intracranial haemorrhage. Premature infants are at greater risk for intraventricular haemorrhage. There is a high incidence of instrumental and breech deliveries. Asphyxia and trauma were probably both causative factors.

The diagnosis is based on clinical signs of central nervous irritability or depression in the absence of pulmonary or biochemical abnormalities such as hypoglycaemia or hypocalcaemia. Confirmation of a diagnosis of intracranial haemorrhage should be sought by lumbar puncture. Treatment is that of the underlying pathology.

CHAPTER 16MISCELLANEOUS CONDITIONS

In 15 infants RDS was due to miscellaneous conditions as shown in Table 48. Most of these are well recognised causes of respiratory distress and each will be discussed briefly.

TABLE 48 RDS - MISCELLANEOUS CONDITIONS

<u>Condition</u>	<u>Cases</u>	<u>Deaths</u>
Congenital heart disease	4	3
? Hyaline membrane disease	3	1
Acute haemorrhage	2	2
Diaphragmatic hernia	2	2
Pulmonary haemorrhage	1	1
Pleural effusion	1	1
Unilateral atelectasis	1	0
Meningocele	1	0

Congenital heart disease

Four infants, 2 males and 2 females, were seen with respiratory distress due to congenital heart disease. The respiratory distress was characterised by tachypnoea and cyanosis with minimal recession and absent grunting. The mean respiratory rate was 73/min and persisted for days, or weeks in one case. The cyanosis was often disproportionately severe for the degree of distress and retraction (Hanley et al. 1963 and Avery 1964). Hanley et al. (1963) also stated that grunting is rarely present. They found the infants to be vigorous and well for 24 - 48 hours after birth, with sudden onset of signs.

The chest radiogram was abnormal in the 3 infants investigated. Pulmonary plethora was marked in Case 3 and is illustrated in Figure 20. This infant was catheterised and shown to have a Tetralogy of Fallot with anomalous pulmonary venous drainage. Harris (1963) and Gairdner (1963) have both pointed out that the fine mottling produced by severe pulmonary congestion may suggest primary pulmonary disease.

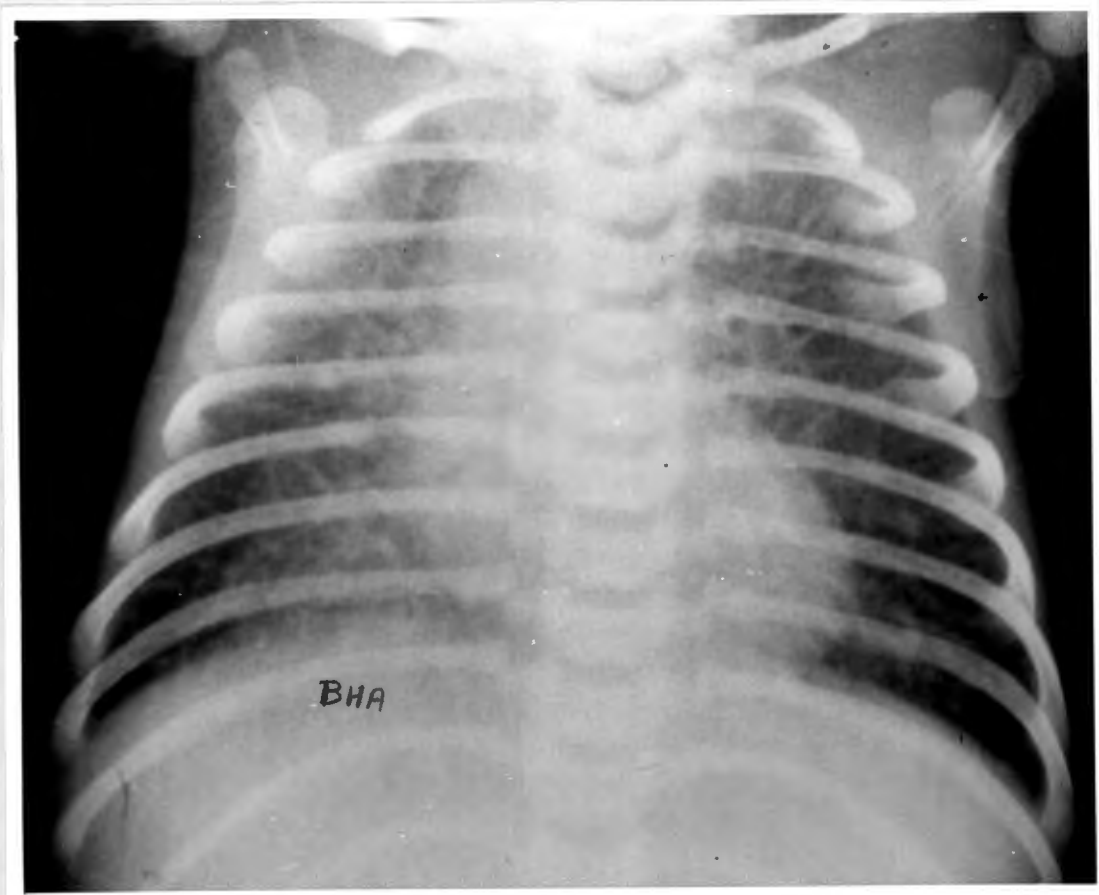


Fig. 20: Chest film of anomalous pulmonary venous drainage

Hanley et al. (1963) stated that auscultation of the heart is of limited value in differential diagnosis. They found that a QR

pattern in lead  $V_1$  was always associated with a cardiac lesion and that transposition of the great vessels, aortic atresia, coarctation of the aorta and pulmonary atresia accounted for 62% of congenital heart disease. The neonatal mortality in this survey was 75% and that of Hanley et al. (1963), 76%.

Congenital heart disease was an infrequent cause of respiratory distress in this survey. It may well be that many only presented signs for the first time after 24 hours. Although always raised in the differential diagnosis, the other causes of RDS are more important.

#### ? Hyaline membrane disease

In 3 infants the final diagnosis was not established despite radiographic examination and an autopsy in one of them.

Case 265 weighed 1.70 kg and presented with classical signs of RDS and severe acidosis (pH 7.07,  $PCO_2$  50.0, BE -16.8). The chest radiogram was abnormal but could not be defined more clearly. She recovered following general and metabolic therapy.

Case 170, 4.08 kg., was born of a diabetic mother and presented with tachypnoea and grunting. The radiogram was normal and the acid-base balance only mildly disturbed. He received no treatment and made an uneventful recovery.

Case 498, 2.75 kg., presented a different problem. She was born normally and had tachypnoea and cyanosis from birth. The chest film showed the characteristic features of CHMD. A combined acidosis (pH 7.188,  $PCO_2$  55.4, BE -8.2) was present initially. The tachycardia and cyanosis, only relieved by a high concentration of oxygen, persisted

until death at the age of 28 days. Histology revealed alveoli and alveolar ducts distended by a protein-rich oedema fluid. Many alveoli showed haemorrhage and desquamated cells plus histiocytes. The bronchi had patchy areas of ulceration and desquamation of epithelial cells. It was thought that the infant had HMD with secondary changes due to the oxygen therapy (Bruns and Shields, 1954; Berfenstein et al., 1958 and Cedergren et al., 1959). There was, in addition, a patent ductus arteriosus.

#### Acute haemorrhage

Two infants died from acute blood loss - one from a subcapsular haemorrhage of the liver and the other from multiple sites. The clinical presentation with tachypnoea, grunting, cyanosis and recession was similar to pulmonary causes of RDS. Usher (1962) and Stahlman (1964) have stressed that the clinical features and acid-base values may closely resemble infants with CHMD. The lack of immaturity, pallor and falling haemoglobin should aid the differential diagnosis.

Blood replacement produces a dramatic effect with decreasing respiratory effort and cessation of grunting (Stahlman, 1964). Usher (1963) stated that it may be necessary to give sodium bicarbonate to control acidosis. The effect of treatment on acid-base metabolism has already been illustrated in Figure 16. Acute haemorrhage and shock in the newborn has a high mortality, but is completely reversible with early treatment. It is, therefore, extremely important to recognise this condition.

#### Diaphragmatic hernia

Diaphragmatic hernia was the cause of respiratory distress in

2 infants. Both were premature and both were females. One never established adequate respirations and died at 4 hours. At autopsy there was a defect in the right posterior aspect of the diaphragm with herniation of bowel and a hypoplastic right lung. The other weighed 1.78 kg. and had tachypnoea, recession and cyanosis from shortly after birth. Radiology showed bowel in the left thorax. The bowel was reduced and the hernia closed surgically but she died post-operatively. The left lung was also hypoplastic at autopsy.

The associated pulmonary hypoplasia is a major obstacle in successful surgical repair. In an attempt to improve ventilation one often causes rupture and a pneumothorax. Ree and Stephens (1956) and Sabga et al. (1961) found hypoplastic lungs in nearly all cases of diaphragmatic hernia autopsied.

Although the diagnosis of a diaphragmatic hernia may be suspected clinically when a scaphoid abdomen and bowel sounds in the chest are present, radiology will reveal the true state of affairs. Contrast media may occasionally be required to delineate bowel from pulmonary cysts.

#### Pulmonary haemorrhage

Pulmonary haemorrhage not associated with other pathology was found in one infant only at autopsy. The infant weighed 1.81 kg. and presented with tachypnoea and cyanosis. Death occurred at 5 hours.

Pulmonary haemorrhage was a fairly common pathological finding in other studies (Claireaux, 1958; Ahvenainen, 1959; Sivanesan, 1961 and Hanley et al., 1963). Although found with other lesions, Landing (1957) noted a statistically significant association with acute pneumonia

only. It would appear that the diagnosis cannot be made during life (Hanley et al., 1963). Very little is known about pulmonary haemorrhage and the etiology is obscure (Avery, 1964). The absence of other features of bleeding would not support a diagnosis of a haemorrhagic tendency.

#### Pleural effusion

Bilateral pleural effusions with pulmonary atelectasis were found at autopsy in one infant. The pregnancy was complicated by hydramnios and the infant born at term.

Severe distress, with a RR of 35/min. and severe cyanosis was present from birth. An additional feature was generalised oedema and death ensued at 10 hours. This case was identical with one described under massive aspiration, except that no particulate matter was demonstrable here. The pleural fluid was not examined at autopsy.

Schaffer (1960) described a case with bilateral pleural effusions shortly after birth. Perry et al. (1963) found only 13 reported cases and stressed the importance because of dramatic relief afforded by prompt thoracentesis. Schaffer (1960), Perry et al. (1963) and Avery (1964) all agreed that these were early cases of chylothorax and that the fluid only becomes chylous after milk feeds. The pathogenesis is unknown.

Danks and Stevens (1964) recently described a case of RDS with a very high haematocrit who had a massive pleural effusion. Whether the case in this survey was an early chylothorax or due to cardiac failure is debatable.

#### Unilateral atelectasis

One premature infant, delivered by Caesarean section, had all the signs of RDS from birth. Acid-base determinations showed pH 7.170,

$PCO_2$  58.0 and BE -9.5. The right lung was collapsed on radiography. She was treated with oxygen and intravenous fluids with spontaneous expansion of the affected lung over the next 2 days. Bronchoscopy was not performed, but the most likely cause would have been a large plug of mucus obstructing the bronchus.

#### Meningoencephalitis

This infant (2.74 kg.) presented with tachypnea associated with mild grunting, recession and cyanosis. The tachypnea persisted for 5 days but the other signs cleared after 3 - 4 hours. No radiographic examination was made and he survived.

CHAPTER 17INTERMITTENT POSITIVE-PRESSURE RESPIRATIONIntroduction

Assisted ventilation by means of a mechanical respirator is the logical approach to respiratory failure in newborn infants. This was first employed by Donald and Lord in 1953. In the ensuing years, relatively few reports of the use of respirators in respiratory distress were published (Donald et al., 1958; Benson and Colander, 1959; Galgan et al., 1960; Stahlman et al., 1962 and Heese et al., 1963). Warley and Gairdner (1962) advocated sternal traction in very small infants. The disappointment rate was often very high.

Recent publications indicate great interest in this form of therapy as well as improved results. The problems of assisted ventilation in immature infants with abnormal lungs are indeed many, and only careful monitoring of such infants will provide some of the solutions.

Indications

IPPR was used in terminal CHMD in 21 infants in this survey. There were 13 terminal CHMD infants in the neonatal respiratory unit and all were put on to respirators. IPPR was also tried in 6 infants in the Groote Schuur Hospital Maternity section and in 2 infants at Red Cross War Memorial Children's Hospital. In the other 8 deaths, it was not attempted because of lack of equipment and facilities. IPPR was not employed in any of the other conditions of RDS.

Any one of the following was considered a possible indication for IPPR :

1. Apnoea > 1 min.
2. PaO<sub>2</sub> < 40 mmHg in 100% oxygen.
3. PCO<sub>2</sub> > 80 mmHg.
4. pH < 7.10.

The indications listed in the literature are given in Table 49.

TABLE 49 NBS - INDICATIONS FOR VENTILATORY AID

	<u>Malan</u>	<u>Stahlman 1964 (a)</u>	<u>D-Papadopoulos et al. 1964</u>	<u>Robertson et al. 1964</u>	<u>Syer<sup>*</sup> 1964</u> <sup>3/5</sup>
Apnoea	> 1 min.	+	+	+	
PaO <sub>2</sub> mmHg <sup>x</sup>	< 40	< 30			< 40
PCO <sub>2</sub> mmHg	> 80	> 75			> 80
pH	< 7.10				
Cardiac			arrest	arrest	Rate < 80 or > 160
Respiratory rate					< 30 or > 120
Central cyanosis					In 100% O <sub>2</sub>

\* Personal communication . 3/5 = Any 3 criteria

x In 100% ambient oxygen

The major criterion seems to be apnoea. Apnoea may occur suddenly or following premonitory signs such as slowing of the RR, irregular and sighing respiration, and short apnoeic attacks. The onset and duration of apnoea in CHMD was analysed in Table 50. Only 2 survivors had apnoea lasting more than 1 min. while this was the most

common presentation of failure in non-survivors. Excessive handling and removal from oxygen may initiate apnoea. Short apnoeic spells were relatively common in survivors, especially after 48 hours.

TABLE 50 CHMD - OCCURRENCE OF APNOEIC ATTACKS

AGE IN HOURS	SURVIVORS (33)		NON-SURVIVORS (29)	
	<u>Number with Apnoea</u>		<u>Number with Apnoea</u>	
	<u>Short</u>	<u>&gt;1 min.</u>	<u>Short</u>	<u>&gt;1 min.</u>
0 - 6	1	-	4	4
6 - 12	3	1*	4	6
12 - 18	2	1	3	4
18 - 24	1	-	3	2
24 - 36	1	1*	4	2
36 - 48	1	1*	1	1
48 - 72	3	-	-	2
72	3	-	-	1

\* Apnoea in the same infant

A  $\text{PaO}_2$  of 40 mmHg corresponds to an arterial saturation of 73% (at pH 7.40 and  $\text{PCO}_2$  40 mmHg) and represents severe cardiopulmonary insufficiency. Using the same conversion factors (Severinghaus, 1958), a  $\text{PaO}_2$  of 40 mmHg at 7.10 or  $\text{PCO}_2$  80 mmHg will only give a saturation of 57%. Karlberg and Colander (1965) found that below  $\text{PaO}_2$  40 mmHg, available buffer base gradually declined. Oypé et al. (1965) stated that a  $\text{PCO}_2$  above 75 mmHg cannot be tolerated for long periods and some means of ventilation becomes necessary. A raised  $\text{PCO}_2$  is always accompanied by hypoxia. Treatment with oxygen, however, raises the  $\text{PCO}_2$  level compatible

with life (McNicol and Campbell, 1965). In this survey, a  $PCO_2$  of 80 mmHg or a  $pH < 7.10$  were never indications for IPPR without associated apnoea and/or  $PaO_2$  below 40 mmHg.

These indications are late signs and it would be in the infant's interest if the necessity for assisted ventilation could be predicted earlier.

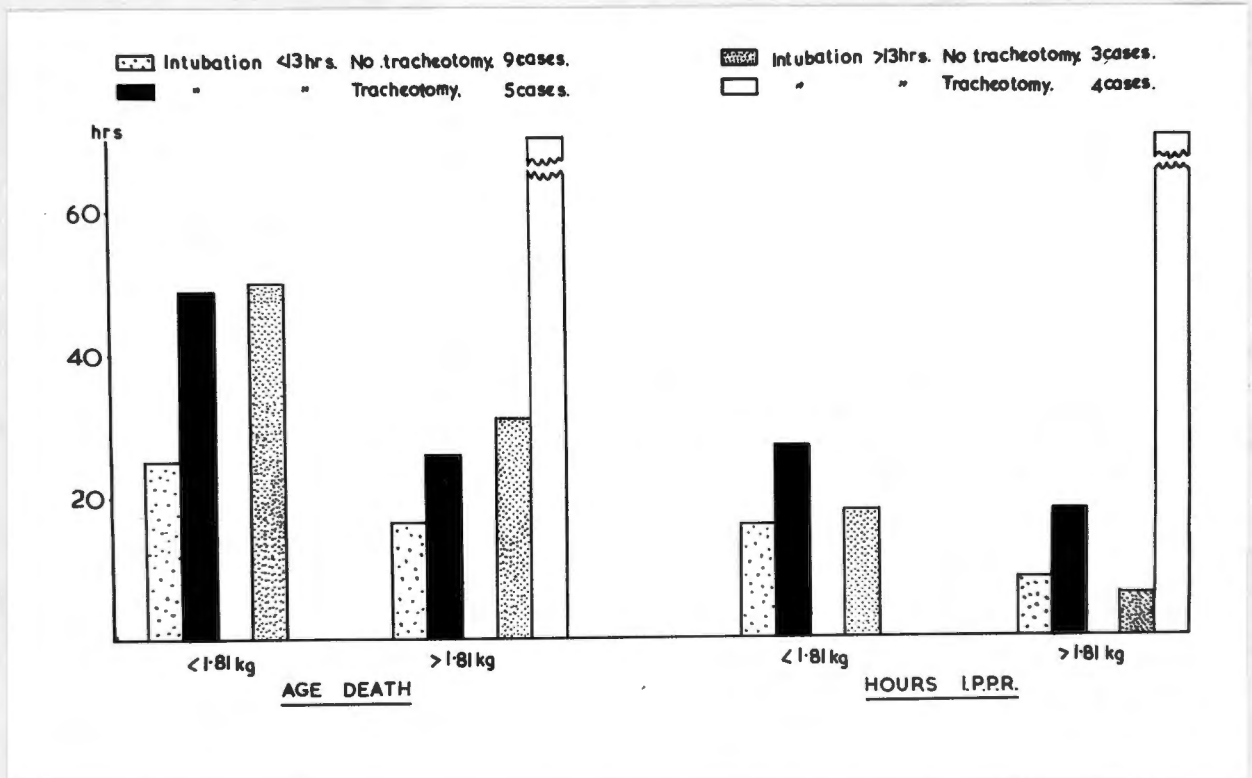
#### Procedure

As soon as an indication for IPPR was present, the infant was intubated and pumped by hand until connection to a respirator. Several respirators were tried: Radcliffe, Engström and Bird Mark 8. Muscle relaxants were given in the earlier cases but discontinued later. Tracheostomy was performed in 9 infants. The decision regarding tracheostomy was rather arbitrary and reserved for those who were doing well on the respirator.

#### Results

Out of 21 cases, only 1 infant survived. The results are illustrated in Figure 21.

The infants of 1.81 kg. (4 lbs) and over appeared to be a better risk but, with 4 exceptions, did not live any longer than those who were below 1.81 kg. The most severe illness required intubation under 13 hours and these infants died earlier. Although not strictly comparable, infants with tracheostomy survived longer than those without tracheostomies. The most favourable outcome was associated with infants over 1.81 kg. requiring IPPR after 13 hours. The average age of intubation for non-survivors was 14 hours.



**Fig. 21: IPPR in CHMD**

Three infants survived for more than 3 days (Table 51)

**TABLE 51 IPPR - INFANTS SURVIVING THREE DAYS**

Serial Number	Wt. (kg)	IPPR begun (hours)	Tracheostomy (hours)	Duration IPPR	Outcome	Diagnosis
148	1.92	24½	26½	19 days	Died 20 days	HMD
497	2.49	48	56	48 hrs.	Survived	HMD
518	2.97	24	72	24 days	Died 25 days	HMD + Pneumothorax + Pneumonia

All were over 1.81 kg. and stopped breathing 24 hours or more after birth.

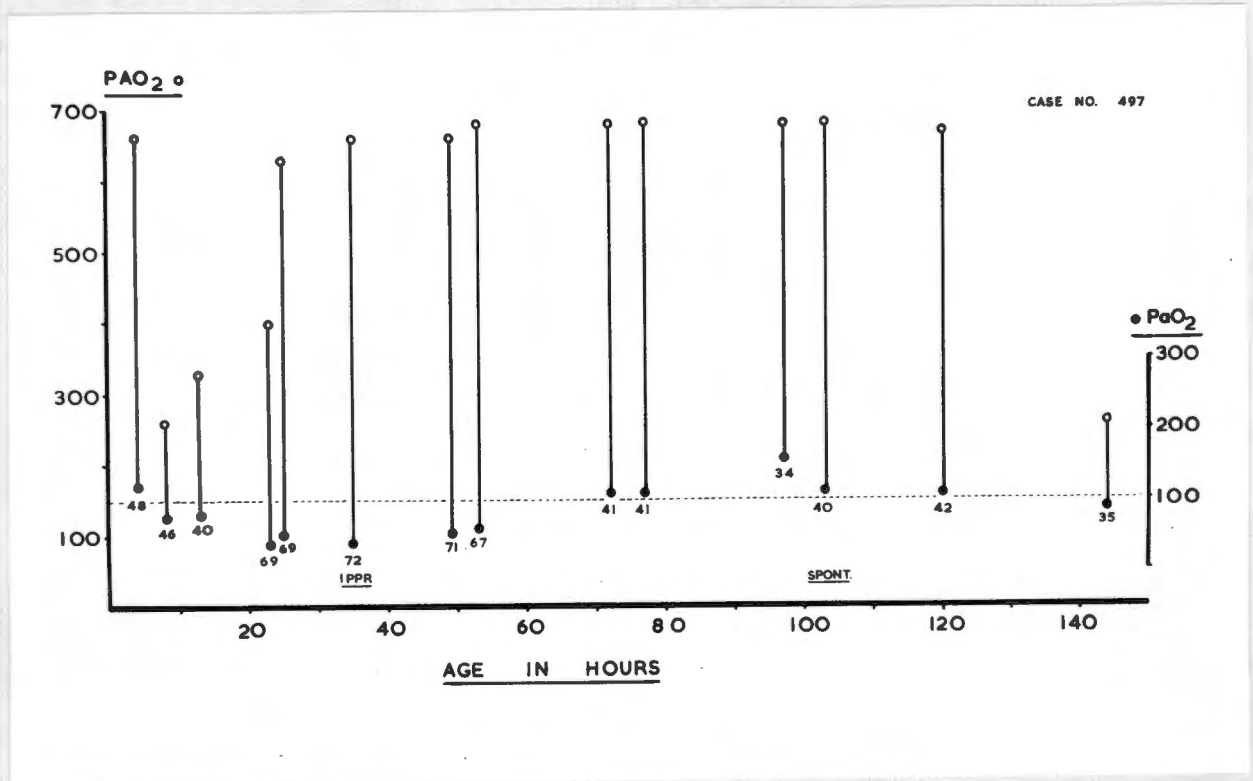
Case 148 lived for 20 days and had gross pulmonary changes at autopsy.

These were swollen and distorted alveolar lining cells, some hyaline membranes, loss of bronchiolar epithelium and extensive fibrosis. Case 497 had sudden apnoea at 48 hours. Ventilation was assisted for 48 hours and the infant successfully weaned from the Bird respirator. Detubation was extremely difficult due to tracheal stenosis and was only accomplished at 3 months. He died suddenly at 6 months, presumably from kinking of the trachea. Case 518 was complicated by a pneumothorax causing apnoea. He responded well to IPPR and drainage but developed a pneumococcal pneumonia. He remained on IPPR for 24 days before dying from multiple lung abscesses.

All 3 infants in Table 51 were ventilated with the Bird Mark 8 respirator. The advantages of the Bird were patient triggering, variable flow rates and rapid respiratory rates. The results in this survey favour the Bird and not a volume-cycled respirator with or without the use of curare. The cause of death was usually respiratory failure, but some died of pneumothorax, cerebral haemorrhage and cardiac embarrassment. Two infants died of blocked endotracheal tubes and another because the tube had gone down the right main bronchus. The majority of infants improved on ventilation and then deteriorated after a variable period.

The effect of assisted ventilation on the  $PO_2$  gradient is shown in Figure 22. It will be noticed that there was minimal initial improvement in either the  $PaO_2$  or R - L shunt. Both values deteriorated on resumption of spontaneous respiration. The effect on acid-base metabolism, on the other hand, is quite striking (Figure 23). Not only was the  $PCO_2$  lowered from 57 - 41.5 and, subsequently, to 28 mmHg, but the metabolic

acidosis was also corrected. The changes after discontinuance of the Bird are demonstrated.



**Fig. 22** : Alveolar-arterial  $PO_2$  gradient (mmHg) in severe CHMD treated with IPPR. R - L shunt values are given below the  $PaO_2$

### Discussion

The results of ventilatory assistance will obviously depend on the indications for such therapy. Recent survival rates are:

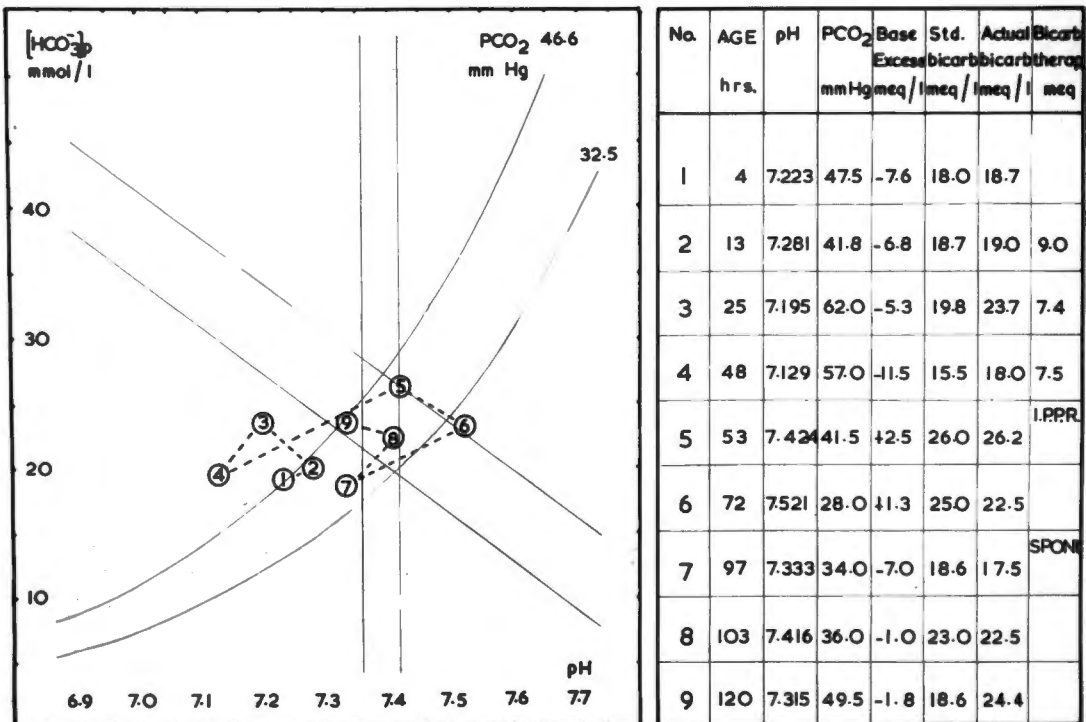
Deliveria-Papadopoulos and Swyer (1964)	- 1/18
Stahlman (1964)	- 11/25
Fearon et al. (1964)	- 7/22
Tunell et al. (1965)	- 6/34
Thomas et al. (1965)	- 11/18

The survivors of Fearon et al. (1964) were all over 1.80 kg. and older than 24 hours when assistance was required. Similarly, the survivors

in the series of Deliveria-Papadopoulos and Swyer (1964) and Thomas et al. (1965) were over 28 and 27 hours respectively. This finding suggests that those who survived were able to maintain spontaneous respiration for much longer and probably became apnoeic from exhaustion rather than from pulmonary changes too gross to support life.

NAME: BABY D.  
Hosp. No: 497.

WEIGHT: 2.49 KG.



**Fig. 25** : Acid-base findings and course in severe CHMD treated with IPPR

Although most workers performed tracheostomies (Hensen and Gelander, 1959; Heese et al., 1963 and Fearon et al., 1964) there seems to be an increasing preference for plastic endotracheal (or nasotracheal) tubes (Thomas et al., 1965). Tracheostomy may become necessary for adequate aspiration of bronchial secretions but leads to many more

complications, one of which is tragically illustrated in this survey. The advantage of tracheostomy in this series may be entirely due to the selection of cases. Whatever method is favoured, adequate humidification is an absolute necessity (Sara, 1965).

Stahlman (1964) stated that a pressure-controlled respirator was safer than a volume-controlled system. Fearon et al. (1964) and Thomas et al. (1965) used Bird and Bennett respirators respectively. Donald et al. (1958) were convinced that artificial respiration should operate on the principle of augmenting existing respiratory effort, if any. The results with the patient-triggered Bird respirator were better in this survey than with the use of curare and a volume-cycled respirator. When dealing with low compliance, the higher respiratory rate possible with the Bird (60 - 80) is more physiological. Mouth pressure should be kept as low as possible to minimise circulatory complications (Stahlman, 1964 and Avery, 1964) and pneumothorax. Fearon et al. (1965) listed their causes of death under technical and medical complications. Infection must rank as the major risk in prolonged IPPR. More than half the recoveries of Fearon et al. (1965) had pneumonia. The threat of resistant gram negative infection in the newborn is well recognised (Shallard and Williams, 1965).

The effect of IPPR in this survey confirms the reports from others that although one can reduce the  $PCO_2$  to satisfactory levels, there is less success in maintaining a normal  $PaO_2$  (Stahlman, 1964; Deliveria-Papadopoulos and Swyer, 1964; Fearon et al. 1964 and Gairdner, 1965). In an attempt to improve the  $PaO_2$ , the  $PCO_2$  was lowered to below

25 mmHg on a few occasions. Robertson et al. (1964) ventilated one infant for a month with a successful outcome, while Stahlman (1964) usually weaned the infants on the 3rd - 5th day when the  $PaO_2$  approached 150 mmHg. She stated that the chances of getting a viable and cerebrally intact baby diminished after that time. The use of a neuromuscular block will obscure the ability of the infant to manage without assistance. Thomas et al. (1965) stressed the importance of hourly physiotherapy in the recovery phase. The extensive changes found in the lungs of Case 148 were attributed to unresolved HMD, the effect of IPPR and prolonged high concentration of oxygen.

The poor results in this survey are a reflection of the attempt to use IPPR in the majority of terminal CHMD cases including those not in the neonatal respiratory unit.

### Conclusions

Until more is known about the efficacy of assisted ventilation in improving distribution/perfusion disturbances in CHMD, the rationale of IPPR must be to prevent death from neuromuscular exhaustion in the presence of sufficient gas exchange surface to support life (Deliveria-Papadopoulos and Swyer, 1964 and Smith, 1965). These infants would appear to be over 1.80 kg. and able to maintain spontaneous respiration for more than 24 hours.

This method of treatment is completely dependent on continuous well-trained, experienced nursing and medical supervision with 24-hour facilities for biochemical determinations. It cannot, therefore, be embarked upon as routine in general hospitals and must, for the time being, be limited to a research project in specialised neonatal respiratory units.

CHAPTER 18SUMMARY

This survey has covered the problems of diagnosis, investigation and treatment of respiratory distress in newborn infants in Cape Town. The results emphasise the importance of respiratory disorders in the newborn and help to identify the infants at risk.

Five criteria were chosen for the diagnosis of RDS. At least 2 of them should be present before a positive diagnosis is justified. Grunting was the most constant sign of RDS but to be significant should be present 3 hours after birth. A rapid respiratory rate alone does not signify respiratory distress.

There was little difference between the mean respiratory rates of healthy and 'term' infants. The values in prematures were slightly higher at 6, 12 and 18 hours only. There was no correlation between respiratory rate and the degree of prematurity as judged by birth weight. While the majority of 'term' infants fell into Group I, more of the premature infants belonged to respiratory Groups II and III.

The most frequent 'disorder' of respiration was Neonatal Tachypnoea which is defined as a respiratory rate of more than 60/min. for more than 3 hours in the absence of other signs of respiratory distress. Neonatal tachypnoea was present in 16% of premature infants but only seen in 'term' infants when maternal diabetes or complications of delivery were present. This condition carried no increased morbidity or mortality.

The incidence of RDS in the maternity hospitals was 2.44%. There was a close association with birth before term as judged by weight. While male infants were significantly affected more frequently than females ( $p < .01$ ), no difference in incidence could be detected between the racial groups. The mortality rate in RDS was 50%, accounting for 64% of early neonatal deaths.

Clinical hyaline membrane disease was the most important cause of respiratory distress and occurred in 12.6% of all live-born infants of less than 38 weeks' gestation. The incidence was significantly higher in males, infants of diabetic mothers and after delivery by Caesarean section. The clinical and biochemical findings were related to the ambient oxygen requirements. Early and vigorous therapy with supplementary oxygen and intravenous sodium bicarbonate would appear to offer the best recovery rates at present. Intracranial haemorrhage and pneumothorax were common complications of CHMD.

A radiological appearance suggestive of an aspiration syndrome was called Neonatal Disseminated Atelectasis. In the initial stages these infants closely resemble those with mild-moderate CHMD but recovery is more rapid. Whether this is a separate entity or CHMD in more mature infants is uncertain.

Congenital pneumonia is the commonest infection in the newborn period and was responsible for 13.8% of deaths in RDS. Male and premature infants are at greater risk.

The incidence of symptomatic spontaneous pneumothorax was 0.05%. A unilateral chest bulge was found to be a most important diagnostic sign. Provided it is recognised early and treated properly, the mortality from this condition should be negligible.

Massive aspiration is caused by the aspiration of large amounts of amniotic fluid and meconium. The mortality in this condition is high, with pneumothorax a notable complication. Recognition and prevention of foetal distress in utero should be the main aim.

Intracranial lesions and congenital heart disease were rare causes of RDS in the first 24 hours of life.

Intermittent positive-pressure respiration was of very limited value in terminal CHMD and would appear to aid some infants who would otherwise die from neuromuscular exhaustion. Experience has shown that these infants weigh at least 1.80 kg. and are able to maintain spontaneous respiration for more than 24 hours.

The live births in the Republic of South Africa in 1963 were 77,900 White; 100,317 Cape Coloured and 275,402 Bantu. To define the problem of neonatal respiratory distress in South Africa, the findings of this survey were extrapolated to the above figures. The following results were obtained:

Premature births (all races)	46,820
Infants with CHMD	8,325
Total number with RDS	10,890
Deaths in RDS	5,445

As a result of the work of this thesis, the author makes the following suggestions.

- (a) The calculated gestational age is a better guide to the assessment of maturity than the birth weight. This is of particular importance in South Africa with its heterogeneous population.
- (b) Maternity units can no longer be regarded as adequate without radiological facilities suitable for the newborn. "Indeed, it is so essential that it would be obvious neglect to care for infants in an institution where chest films were not available 24 hours a day." (Avery, 1964).

- (c) Much valuable information can be obtained from autopsy in RDS and errors in future diagnosis and management avoided. Lack of material for pathological consideration handicapped this study and the importance of autopsy is stressed.
- (d) Special units should be established to provide intensive care for infants with RDS and other neonatal problems. Fixed monitoring equipment, ventilatory aids and experienced nursing and physician care should be readily available (Stahlman, 1964).
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## PART IV

### APPENDIX

Charts for recording clinical observations

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Acid-base and oxygen values in infants with RDS

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Bibliography

**CHARTS FOR RECORDING CLINICAL OBSERVATIONS**

YAW  
D







INDEX FOR RECORDING CLINICAL OBSERVATIONS

<u>Grunting</u>	0	None
	+	Audible with stethoscope only
	++	Audible to naked ear
<u>Recession</u>	+	Costal retraction only
	++	Costal plus xiphoid retraction
	+++	Marked xiphoid retraction with abdominal elevation, "see-saw".
	++++	"See-saw" with exhausted appearance, often with slower, sighing respiration
<u>Air Entry</u>	0	None
	+	Poor, but easily detectable
	++	Fair, diminished from normal
	+++	Good, normal
<u>Oedema</u>	+	Filling in of palmar spaces
	++	Puffiness of dorsum of hands and feet
	+++	Generalized to whole body

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**CLINICAL DATA OF INFANTS WITH RDS**

## GRUNTING

Case No.	Maternity hospital	Sex	Race	Complication	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Grunting (hrs)	Recession	Cyanosis	Outcome	P.M.	Remarks
177	PMH	M	C	APH	1.81	9	B	42	18	-	-	S		
223	NSH	M	C	-	1.70	-	1/2	42	4	-	given O <sub>2</sub>	S		
248	PMH	M	C	APH	2.43	9	1/2	48	4	-	-	S		
263	MMH	F	E	-	1.53	2	1/2	51	6	-	-	S		
264	GSH	M	C	-	1.36	2	1	44	4	-	given O <sub>2</sub>	S		
305	GSH	M	C	APH	0.90	2	2	49	7	+	given O <sub>2</sub>	S		Septic abortion
318	NSH	M	C	-	1.13	6	1	40	4	-	given O <sub>2</sub>	D49	No	Cleared on O <sub>2</sub>
331	NSH	M	C	-	0.93	6	1	40	6	-	given O <sub>2</sub>	D72	No	
394	NSH	F	C	PET CS	0.93	6	B	37	9	-	given O <sub>2</sub>	S		
469	GSH	F	C	-	0.85	-	1/2	44	5	-	-	S		
539	StM	M	C	-	1.42	8	1	44	5	-	-	S		
635	StM	M	C	-	1.76	10	1/2	56	7	-	-	S		
594	PMH	M	B	APH	2.26	2	1/2	48	4	-	given O <sub>2</sub>	S		
198	PMH	M	B	CS	2.58	2	1/2	52	7	-	-	S		Hydrocephalus
388	PMH	M	C	CS	3.91	3	1/2	51	4	-	-	S		
475	PMH	F	C	PET CS	3.29	2	1/2	41	5	-	-	S		Intubated at birth
488	GSH	F	E	CS	2.83	7	1/2	36	12	-	given O <sub>2</sub>	S		Cleared on O <sub>2</sub>
553	PMH	F	C	CS	4.00	2	B	51	3	-	given O <sub>2</sub>	S		
526	StM	F	B	Foetal distress Breech	2.71	-	?	42	7	-	-	S		
222	PMH	M	C	-	2.72	7	1	43	5	-	given O <sub>2</sub>	S		Cleared on O <sub>2</sub>
220	PMH	M	C	-	3.94	5	B	44	5	-	-	S		
411	PMH	F	C	-	2.95	9	1	46	4	-	-	S		
562	PMH	F	C	-	3.09	9	B	40	3	-	-	S		

\* E = European, i.e. White

GRUNTING AND NEONATAL TACHYPNOEA

Case No.	Maternity hospital	Sex	Race	Complication	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Duration (hrs)	Grunting (hrs)	Recession	Cyanosis	Outcome	Remarks
330	PMH	M	C	-	1.96	9	5	68	12	3	-	given O <sub>2</sub>	S	
355	GSH	F	C	APH	2.21	7	6½	85	23	3	-	-	S	
379	GSH	M	E	-	1.87	6	3	72	19	3	-	-	S	
383	PMH	M	C	-	2.18	7	11	71	15	4	+	given O <sub>2</sub>	S	
430	PMH	M	C	-	1.44	7	5½	73	19	5	+	-	S	4 apnoeic attacks
442	PMH	F	C	-	1.95	10	7	64	4½	8	-	-	S	
522	StM	F	C	-	1.70	1	6½	68	10	8	-	-	S	
566	GSH	F	C	APH	1.27	5	17	68	22	5½	-	given O <sub>2</sub>	S	
597	GSH	F	C	CS	1.92	7	3½	62	8	4	-	-	S	
162	MMH	M	E	CS	3.34	2	9	64	13	4½	-	-	S	Sternal bulge
474	GSH	M	E	CS	2.96	6	8	79	16	7	-	-	S	
636	PMH	F	B	CS Foetal distress	3.61	7	6	77	20	3	-	-	S	
625	PMH	M	C	-	2.72	7	22	68	18	20	-	-	S	Oedema 38 weeks

CLINICAL HYALINE MEMBRANE DISEASE

Case No.	Materiality	Sex	Race	Complications	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Duration (hours)	Grunting (Hours)	Recession	Cyanosis	X-ray	ECG	Outcome	P.M.	Remarks
1	GSH	F	E	-	1.19	8	6	80	88	-	+	+	+	-	D94	No	No investigations
49	GSH	M	E	-	2.09	7	4	86	44	4	+	+	+	+	S		
50	GSH	M	C	-	1.19	-	4	71	96	-	+	-	+	+	S		
78	GSH	M	E	-	1.70	1	1 1/2	76	100	27	++	+	+	+	S		
98	GSH	M	C	CS	1.24	6	1 1/2	61	17	5	+++	+	+	+	S		
77	GSH	F	C	APH	1.61	6	B	52	IPPR	9	++	+	+	+	D16	Yes	Bilat. pneumothoraces
124	PMH	M	B	-	1.78	8	1 1/2	78	85	5	++	+	+	+	S		
135	GSH	M	E	APH	1.61	6	B	41	IPPR	-	++	+	+	+	D34	Yes	
132	PMH	M	C	-	1.47	9	1	62	37	8	+	+	+	+	S		
145	GSH	F	E	-	1.98	3	B	?	IPPR	-	-	+	+	-	D4	Yes	IPPR from birth
134	GSH	F	E	-	1.78	4	B	60	66	++	++	+	+	+	D66	No	Congenital abnormalities
158	PMH	M	C	-	1.53	6	1 1/2	85	3	2 1/2	+++	+	+	-	S		
169	GSH	M	E	-	2.02	2	B	66	7	1	+++	+	+	+	D13	No	Difficulties from birth
150	GSH	M	E	-	1.61	9	B	75	96	-	++	+	+	+	S		Pneumothorax
179	PMH	M	C	-	1.64	7	B	70	120	12	++	+	+	-	S		
190	GSH	M	E	-	1.33	-	B	73	IPPR	11	M++	+	+	+	D35	No	Second in family
202	GSH	F	E	Forceps	2.35	9	1	94	54	40	++	+	+	+	D70	No	
203	MMH	F	E	CS	1.58	1	6	75	22	17	++	+	+	+	D54	Yes	Subarachnoid haemorrhage
295	GSH	F	E	CS	1.89	1	1	88	144	53	+++	+	+	+	S		
296	GSH	F	E	CS	1.81	1	1	74	144	36	++	+	+	+	S		
308	GSH	F	B	-	1.30	-	<6	61	96	12	++	+	+	-	S		Admitted 6 hours
310	GSH	F	E	APH	2.07	7	1 1/2	79	63	6	++	+	+	+	S		
313	GSH	M	C	APH	1.97	6	1 1/2	92	38	9	+++	+	+	+	D38	Yes	
347	GSH	F	E	CS	1.78	6	1	82	47	20	+	+	+	+	S		
235	GSH	F	E	CS	2.04	2	1 1/2	83	150	8	++	+	+	+	S		
236	MMH	M	E	-	1.73	6	1 1/2	79	120	19	++	+	+	+	S		
464	GSH	M	E	APH	1.80	8	B	72	144	12	++	+	+	+	S		
465	MMH	M	E	PET	1.36	3	B	54	IPPR	6	+++	+	+	+	D49	Yes	
479	GSH	M	E	CS	1.36	6	B	40	IPPR	6	++	+	+	+	D19	Yes	
496	MMH	M	E	-	2.04	6	1	80	36	16	+	+	+	+	S		

Continued

CLINICAL HYALINE MEMBRANE DISEASE (continued)

Case No.	Maternity Hospital	Sex	Race	Complications	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Duration (hours)	Grunting (hours)	Recession	Cyanosis	X-ray	ECG	Outcome	P.M.	Remarks
497	GSH	M	E	CS	2.49	5	B	79	48	48	++	+	+	+	S		IPPR 48 hours
517	GSH	F	C	CS	1.39	5	B	46	44	38	++	+	+	+	D44	No	
529	GSH	F	C	PET	1.92	6	1	90	144	36	++	+	+	+	S		Oxygen turned off
568	MMH	M	E	CS	2.21	6	B	65	18	18	++	+	+	-	D18	Yes	
608	GSH	M	E	CS	2.35	3	B	77	25	25	++	+	+	-	D31	No	? I - C Haemorrhage
28	GSH	M	C	CS	2.86	4	1½	26	IPPR	2	-	+	+	+	D8	No	Hyperventilated
147	GSH	M	C	IDM	3.29	10	B	45	IPPR	14	+++	+	+	+	D57	No	
233	GSH	F	C	PET	3.26	8	10	73	6	14	-	+	+	+	D35	No	
518	GSH	M	E	CS	2.97	9	B	66	24	24	++	+	+	+	NND	Yes	Pneumothorax IPPR 24 days
554	GSH	M	E	CS	2.75	7	1	96	72	24	++	+	+	+	S		
301	GSH	F	C	IDM	2.79	8	5	47	-	5	-	-	+	-	S		
403	GSH	F	C	IDM	2.35	6	1	72	61	27	++	+	+	+	S		
480	GSH	F	C	IDM	1.92	7	6	78	50	-	-	+	+	+	S		

NEONATAL DISSEMINATED ATELECTASIS

Case No.	Maturity	Sex	Race	Complication	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Duration (hrs)	Grunting (hrs)	Recession	Cyanosis	X-ray	ECG	Outcome	Remarks
2	GSH	F	E	-	1.81	-	< 9	64	28	18	+	+	+	+	S	
146	GSH	F	C	-	1.95	7	2	49	-	-	+	+	+	-	S	
79	PMH	M	C	-	1.50	7	8	72	30	30	+	-	+	-	D38	HMD at autopsy
131	PMH	F	C	CS	2.89	9	2	63	24	-	++	+	+	+	S	Nasal obstruction
80	GSH	M	C	IDM CS	2.84	3	1 1/2	68	45	8	+	+	+	+	S	
242	GSH	F	E	IDM CS	3.40	1	1 1/2	68	13	2	-	+	+	+	S	
130	PMH	M	C	Foetal distress	3.34	4	1/2	85	31	-	+	-	+	+	S	
494	GSH	M	E	-	3.37	3	4	90	44	++	-	-	+	-	S	
136	NSH	M	C	neonatal asphyxia	3.63	1	B	70	36	20	-	+	+	-	S	
199	GSH	M	E	APH	2.01	8	9	62	6	2	+	+	+	-	S	Slow initial resp. rate

HYALINE MEMBRANE DISEASE - AUTOPSY DIAGNOSIS

27	PMH	M	C	-	2.29	5	B	45	4	-	+	+	-	-	D4	
29	PMH	M	C	-	1.53	7	B	44	-	7	+	-	+	-	DL44	Normal X-ray
144	GSH	M	B	APH CS	1.13	6	1	76	12	2	-	+	-	-	NND	Infection
353	GSH	M	C	APH	1.47	6	B	23	13	4	-	+	-	-	DL3	
441	GSH	M	C	-	1.36	-	B	30	4	2	-	+	-	-	D4	
172	PMH	F	C	CS	2.75	1	B	42	6	-	-	+	-	-	D6	
376	PMH	M	B	forceps	3.40	3	2	69	32	25	+	+	-	-	D34	
641	NSH	M	C	VE	3.13	9	B	32	12	8	-	+	-	-	DL2	Subarachnoid haemorrhage
293	GSH	M	C	APH	2.83	1	1	60	23	2	-	+	-	-	D24	Twitches
484	GSH	M	C	APH	1.13	1	B	49	30	-	++	+	-	-	D30	Subarachnoid haemorrhage
582	PMH	M	C	APH CS	1.93	1	1/2	66	21	21	++	+	-	-	D21	

RESPIRATORY DISTRESS SYNDROME - UNDETERMINED

Case No.	Material	Sex	Race	Completion	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Duration (hrs)	Grunting (hrs)	Recession	Cyanosis	Outcome	Remarks
4	GSH	M	C	-	0.96	-	2	?	25	++	-	+	D27	Normal X-ray
9	PMH	F	C	-	1.70	-	3	71	60	2	+	+	S	
41	StM*	F	C	-	1.58	10	2	68	28	3	+	-	S	Grunting short period
43	NSH	M	C	-	1.30	2	15	64	18	24	-	+	D120	Apnoeic attacks
60	GSH	M	C	APH	2.01	3	6	52	9	-	+	+	D14	
66	PMH	M	C	PET	1.58	4	B	46	9	3	+	+	D9	Apnoeic attacks
108	GSH	F	C	APH	1.38	2	B	20	3	-	+	+	D3	
109	PMH	M	C	CS	1.72	6	B	34	12	10	-	+	D12	
111	NSH	M	C	PET	2.06	7	2	67	48	++	-	+	D51	
157	PMH	M	C	-	1.31	6	1 1/2	40	4	5	+	+	D5	
159	PMH	M	C	APH	1.58	5	1	69	25	8	-	-	S	
160	PMH	M	C	-	0.85	4	B	36	5	5	+	+	D5	
173	PMH	F	C	-	0.85	3	B	40	29	29	+	+	D29	Apnoeic attacks
174	PMH	F	C	-	1.50	3	B	28	11	11	+	+	D11	Apnoeic attacks
192	StM	M	C	-	2.21	10	3	53	57	47	+	+	D60	2 apnoeic attacks
208	PMH	F	C	-	2.18	8	6	63	43	7	-	+	S	
214	PMH	M	C	-	0.96	3	B	31	10	9	+	+	D10	
215	PMH	M	C	PET	1.19	4	4	82	30	8	+	+	S	
238	PMH	F	C	APH	1.05	6	2	36	9	6	+	+	D9	
249	PMH	F	C	APH	1.75	7	1 1/2	100	120	12	++	+	S	NaHCO <sub>3</sub> Treatment
258	NSH	M	B	CS	1.42	4	1	52	27	27	-	+	D28	
261	NSH	F	C	CS	1.07	-	< 5	48	17	5	-	+	D22	
275	NSH	F	C	-	0.91	-	B	48	5	5	-	+	D5	
278	PMH	M	C	-	1.76	8	6	81	48	11	+	-	S	
282	MMH	F	E	-	1.13	9	B	40	8	8	+++	+	D8	
284	GSH	F	E	PET	1.33	1	B	57	9	3	-	+	D9	Apnoeic attacks
309	NSH	F	C	CS	1.81	2	1 1/2	29	48	6	-	+	D48	Oedematous. Avertin
328	PMH	F	C	APH	1.70	3	2	79	13	6	+	+	S	Mother morphia
329	PMH	F	C	-	1.47	5	B	48	-	++	+	+	D32	
332	NSH	M	B	-	1.71	2	1	44	5	5	-	+	D6	
333	NSH	M	C	APH	2.25	2	1	52	21	++	-	+	D22	
334	NSH	F	B	APH	1.84	2	1	63	144	27	-	+	S	

Continued

RESPIRATORY DISTRESS SYNDROME - UNDETERMINED (Continued)

Case No.	Maternity hospital	Sex	Race	Completion	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Duration (hrs)	Grunting (hrs)	Recession	Cyanosis	Outcome	Remarks
338	NSH	M	C	-	2.24	6	B	47	32	++	-	+	D32	
339	NSH	M	C	-	1.22	5	B	39	10	8	-	+	D10	
340	StM	F	C	CS	1.47	6	2	69	26	-	+++	+	D35	Oedematous
345	PMH	M	C	APH	1.39	7	B	43	7	7	+	+	D7	
356	GSH	M	E	APH	0.79	6	B	26	6	-	+	+	D6	
373	StM	F	C	-	1.07	4	B	34	10	10	+	+	D10	
378	PMH	F	C	APH	0.82	1	B	20	3	-	-	+	D3	
381	GSH	M	B	-	1.16	0	B	41	8	8	+	+	D8	4 short apnoeic attacks
382	GSH	M	E	-	2.43	7	†	63	24	++	-	-	S	
385	PMH	M	C	-	2.09	6	†	68	6	5	++	given O2	S	Rapid improvement
397	NSH	F	C	-	2.44	2	B	32	5	4	-	+	D5	
401	GSH	M	C	APH	1.56	7	2	57	18	-	-	+	S	9 short apnoeic attacks
410	PMH	M	C	APH	1.47	2	B	52	13	13	+	+	D13	Oedematous
412	GSH	M	C	-	0.65	0	B	26	7	7	-	+	D7	
431	PMH	M	C	-	2.15	9	2	81	90	14	+	-	S	Twin
432	PMH	F	C	-	1.41	10	B	65	20	20	+++	+	D20	
433	PMH	M	C	-	2.14	7	B	64	24	21	-	-	S	
455	MH	F	E	PET CS	1.22	1	B	42	8	3	-	+	D8	
466	GSH	M	C	APH	1.36	1	B	50	12	-	+++	+	D12	
467	GSH	M	C	-	1.02	1	B	34	5	4	+	+	D5	
486	NSH	M	C	-	1.07	10	B	62	23	14	+	+	D23	
487	NSH	M	B	APH	1.41	2	B	50	14	11	-	+	D14	
493	PMH	M	C	-	1.47	4	B	54	13	8	+	+	D13	
501	GSH	M	C	APH	1.75	2	B	28	15	++	+	+	D15	Frequent apnoeic attacks
502	PMH	M	C	-	1.61	5	B	73	60	10	-	+	S	12 short apnoeic attacks
503	PMH	M	B	-	2.43	5	3	99	48	-	-	+	S	
516	GSH	M	C	-	1.53	1	1	45	22	20	++	+	D23	
531	MH	M	E	APH CS	2.49	8	B	67	5	4	+	+	D7	
532	GSH	F	C	-	0.71	1	B	32	10	10	++	+	D10	
533	PMH	M	C	PET	1.05	1	B	68	14	14	++	+	D14	
540	NSH	M	C	-	1.48	9	B	44	15	9	-	+	D15	
545	NSH	F	C	APH	1.25	2	B	62	38	8	-	+	D38	Apnoeic attacks
547	PMH	F	C	-	1.13	6	2	60	20	8	-	-	D37	
564	GSH	M	C	-	2.06	4	B	44	-	8	+	+	S	

Continued

RESPIRATORY DISTRESS SYNDROME - UNDETERMINED (continued)

Case No.	Age	Sex	Race	Color of skin	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Duration (hrs)	Grunting (hrs)	Recession	Cyanosis	Outcome	Remarks
565	GSH	F	C	PET	0.73	7	B	20	8	8	+	+	D8	
570	PMH	F	C	-	0.91	1	<6	48	8	8	-	+	D14	
580	PMH	M	B	-	2.02	7	†	68	24	9	+	+	S	Oedema ++ NaHCO <sub>3</sub>
581	PMH	M	B	-	2.13	8	1	70	28	4	+	+	S	Oedema ++ NaHCO <sub>3</sub>
584	GSH	F	C	-	1.53	2	1	68	28	3	++	+	S	
585	GSH	M	C	CS	1.81	3	B	72	60	19	++	+	S	
592	PMH	F	C	APH	1.43	3	B	40	3	3	+	+	D3	
592	PMH	M	C	PH	2.26	9	B	68	42	3	+	+	S	
600	PMH	F	C	-	1.44	3	B	61	17	17	+++	+	D17	
616	NSH	M	C	-	1.28	6	1	50	27	27	+	+	D28	
617	PMH	M	C	-	1.33	8	†	43	8	3	-	+	D9	Apnoeic attacks
618	PMH	M	C	-	1.13	5	9	72	6	12	+	+	S	
619	PMH	M	C	CS	2.28	8	B	70	60	32	-	+	S	
620	GSH	F	E	-	1.05	1	1	34	40	-	-	+	D41	Oedematous
621	GSH	F	B	-	0.73	8	1	52	26	13	-	+	D27	
622	GSH	F	C	-	1.10	8	B	45	16	6	-	+	S	
626	MMH	F	E	-	2.46	3	3	89	84	26	++	+	S	
629	PMH	M	C	-	0.90	2	B	42	13	7	-	+	D13	Oedematous
633	NSH	M	C	APH	1.07	8	†	48	49	++	-	+	D49	
634	NSH	F	C	APH	2.06	3	B	53	26	26	++	-	S	
61	StM	M	C	CS	2.55	10	2	82	98	27	++	+	S	NaHCO <sub>3</sub>
551	PHM	M	C	CS	3.63	1	1	73	36	14	-	+	S	Early rupture membranes
122	GSH	F	E	CS	3.98	8	2	62	17	7	-	-	S	
368	PMH	M	C	Forceps	1.30	4	4	61	25	24	++	+	D36	Frequent apnoeic attacks
335	NSH	F	C	IDM	3.17	10	-	>60	81	++	-	+	D81	Pyrexia. Twitches
314	PMH	F	C	APH	2.72	1	†	41	8	-	-	+	D8	Apnoeic attacks
317	NSH	M	C	APH	2.72	6	3	46	19	18	-	+	D19	Meconium liquor
439	PMH	F	C	-	2.72	7	2	71	33	20	-	+	S	Oedematous
155	NSH	M	B	-	4.28	2	2	71	70	30	-	+	S	Cardiac failure. Chesty. Postmature. Meconium liquor)
360	StM	M	B	-	2.86	1	1	73	96	++	-	+	S	Hypoglycaemia

PNEUMONIA

Case No.	Sex	Race	Complication	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Duration (hrs)	Grunting (hrs)	Respiration	Cyanosis	X-ray	ECG	Moocoino	P.M.	Remarks
14	PHH	F	C	2.83	5	6	57	48	50	-	-	-	-	D54	Yes	'Cerebral'
46	PHH	F	B	2.18	2	B	60	8	3	+	+	-	-	D8	Yes	Cong. syphilia
63	PHH	M	C	4.42	7	5	85	91	-	-	-	+	-	S	-	-
64	PHH	M	C	1.30	9	‡	70	27	4	-	-	-	-	S	-	Offensive liquor
120	MHH	M	E	2.77	1	‡	68	24	-	-	-	-	-	S	-	Pyrexia. Rales ++
211	PHH	M	B	1.55	4	‡	49	48	24	+	+	-	-	D48	Yes	A.S.D.
260	MHH	M	E	2.66	9	3	63	23	15	+	+	-	-	D26	Yes	Pericarditis. Strept.
302	NSH	M	C	5.11	10	B	96	48	++	-	+	+	-	S	-	-
504	PHH	M	C	2.38	1	B	56	6	4	-	+	-	-	D6	Yes	Subarachnoid haemorrhage
505	StM	M	C	1.81	5	B	42	58	26	+++	+	-	-	D58	Yes	Klebsiella
419	GSH	F	C	1.47	2	B	22	3	++	-	+	-	-	D3	Yes	Atelectasis
628	GSH	M	B	1.36	6	‡	57	54	28	++	+	+	-	D54	Yes	-
643	PHH	F	C	2.99	2	B	42	47	4	-	+	-	-	D47	Yes	Subdural haemorrhage

PNEUMOTHORAX

17	PHH	M	C	3.41	3	7	80	41	-	-	-	+	-	S	-	-
71	GSH	F	E	3.51	7	B	65	180	-	+	+	+	+	S	-	Pleural drainage
232	MHH	M	E	2.89	7	2‡	68	48	1	+	+	+	-	S	-	-
311	MHH	M	E	3.57	5	‡	73	37	3	+	+	+	+	S	-	-
393	GSH	M	C	2.58	7	‡	77	24	3	+	+	+	+	S	-	-

MASSIVE ASPIRATION

Case No.	Maternal Hospital	Sex	Race	Completing status	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Duration (hours)	Grunting (hours)	Recession	Cyanosis	X-ray	ECG	Outcomes	P.M.	Remarks	
316	NSH	M	C	-	2.63	5	6	29	74	48	+	+	+	-	D80	Yes	Rales ++ Oedema +	
358	GSH	F	E	PET APH	1.47	5	1	62	14	18	+	+	+	-	D33	Yes		
525	StM	F	C	Foetal distress	3.41	-	B	65	15	15	+	+	-	-	D15	Yes	Meconium +	
572	StM	M	B	-	1.33	2	2	35	11	4	+	+	-	-	D11	Yes		
610	PMH	M	C	-	3.26	2	B	46	24	18	++	+	+	+	D24	Yes	Oedema + Pleural effusions	
<u>CONGENITAL HEART DISEASE</u>																		
3	GSH	F	C	-	1.90	6	3	64	3	-	-	+	+	+	NND 29	Yes	Fallot and A.P.V.D.	
48	PMH	M	C	Foetal distress	2.69	5	B	86	31	-	+	+	-	-	D31	No	Parasternal murmur ++	
243	GSH	M	E	PET	2.95	2	1	82	144	-	-	-	+	+	S	No	P.D.A. Failure	
370	NSH	F	C	-	2.94	-	B	60	120	-	-	+	+	+	D120	No	? Transposition	

CEREBRAL INFANTS

Case No.	Sex	Race	Mode of Delivery	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Duration (hrs)	Grunting (hrs)	Recession	Cyanosis	X-Ray	ECG	Outcome	P.M.	Diagnosis	Remarks
10	M	C	Forceps	4.26	1	14	93	> 10	-	-	-	-	-	S		Neonatal Tachypnoea	Blood in C.S.F.
596	M	E	-	1.73	2	B	38	8	4	±	+	-	-	D8	Yes	RDS - I-C Haem.	
129	M	E	Forceps	3.74	8	B	46	24	-	-	+	-	+	S		Apnoeic attacks	Blood in C.S.F.
138	F	B	PET	3.29	2	†	87	6½	1	-	-	-	-	S		Neonatal Tachypnoea	Apnoea. Twitches
140	M	B	Forceps	3.34	1	< 15	63	24	-	-	-	-	-	S		Neonatal Tachypnoea	Bloody C.S.F.
161	M	B	Breech Forceps	3.17	1	1	60	48	4	+	+	-	-	S		RDS - 'Cerebral'	Tone ++. Twitches Intubated. Cardiac massage. Twitches ) Bloody C.S.F. ) Apnoea
181	F	C	Forceps	2.86	2	1½	61	28	-	-	-	-	-	S		Neonatal Tachypnoea	Twitches
254	M	B	V.E.	4.05	2	†	88	4	++	-	-	-	-	ND7	Yes	RDS - Cerebral haem.	Twitches
292	M	E	V.E.	3.34	7	B	65	60	-	-	-	+	-	S		Neonatal Tachypnoea	C.S.F. heavily blood-stained. ) Twitches )
390	F	C	Forceps	3.26	6	4	100	27	1	-	-	-	-	S		Neonatal Tachypnoea	Tone ++ ) Cerebral cry )
408	F	C	Forceps	4.42	0	B	44	-	-	+	+	-	-	S		Cyanosis	Twitches
438	M	C	V.E.	3.40	5	2	77	30	-	-	-	-	-	S		Neonatal Tachypnoea	Twitches. Clear CSF
607	M	C	V.E.	3.29	1	†	66	72	25	-	+	-	-	S		RDS - 'Cerebral'	Convulsions. Clear CSF
85	F	B	CS Foetal diastress	2.09	2	B	48	-	-	-	+	-	-	D56	No	Cerebral damage	Apnoeic spells ) Convulsions ) Bradycardia )
65	M	C	Breech	4.80	2	1½	71	> 24	-	-	-	-	-	S		Neonatal Tachypnoea	Very irritable
392	M	C	Breech	4.36	1	2½	67	54	-	-	-	-	-	S		Neonatal Tachypnoea	Twitches
226	M	B	-	3.03	6	B	70	96	2	-	+	-	-	D96	No	RDS - I-C Haem.	Blood in C.S.F.
361	M	E	-	2.52	6	5	89	72	-	-	-	-	-	ND6	Yes	Neonatal Tachypnoea ) Toxoplasmosis )	Convulsions ) Hydrocephalus )
366	M	C	-	2.88	1	2	87	60	-	-	-	-	-	S		Neonatal Tachypnoea	Convulsions
34	M	C	PET	1.67	8	2½	64	9	-	-	-	-	-	D31	Yes	NT - Subarachnoid haemorrhage	
567	F	B	-	1.36	8	B	33	12	12	-	+	-	-	D12	Yes	RDS - Cerebral haemorrhage	

RESPIRATORY DISTRESS SYNDROME - MISCELLANEOUS CONDITIONS

Case No.	Maternity	Sex	Race	Diagnosis	Wt. (kg)	Apgar	Onset (hrs)	Mean RR	Duration (hrs)	Grunting (hrs)	Recession	Cyanosis	X-ray	ECG	pH	PCO2	BE	Outcome	P.N.	Diagnosis
170	PMH	M	B	IDM PET	4.08	7	B	94	35	6	-	-	+	-	7.288	43.5	-5.8	S		Normal X-ray ? HMD
164	PMH	F	B	Hydram- nios	2.89	2	B	35	10	-	-	+	-	-	-	-	-	D10	Yes	Pleural effusions + atelectasis
225	NSH	M	B	PET	4.33	9	1	77	25	12	+	+	-	-	-	-	-	D39	No	Ac. haemorrhage
228	StM	M	C	PET	1.81	1	2	60	5	-	-	+	-	-	-	-	-	D7	Yes	Pulmonary haemorrhage
265	GSH	F	C	-	1.70	2	1	65	27	-	+	+	+	-	7.07	50.0	-16.8	S		Abnormal X-ray ? HMD
327	StM	F	B	Forceps Fetal distress	2.21	1	B	33	4	2	-	+	-	-	-	-	-	D4		Diaphragmatic hernia
451	PMH	F	C	-	3.12	7	< 6	77	22	3	-	+	-	-	-	-	-	D22	Yes	Subcapsular haem.
409	PMH	M	C	-	2.74	6	†	75	120	3	+	+	-	-	-	-	-	S		Meningocele
498	PMH	F	C	-	2.75	8	B	98	168	-	-	+	+	-	7.188	55.4	-8.2	MND 28		? HMD + P.D.A.
583	GSH	F	B	IDM	1.78	5	1	76	50	-	+	+	+	-	7.23	55.0	-7.5	D72	Yes	Diaphragmatic hernia
631	PMH	F	C	CS	1.98	3	B	70	144	9	++	+	+	-	7.19	58.0	-9.3	S		Collapse R lung

INFANTS REFERRED FROM GREATER CAPE TOWN

Case No.	Sex	Race	Wt. (kg)	Onset (hrs)	Mean RR	Diastolic (hrs)	Grunting (hrs)	Respiration	Cyanosis	X-ray	ECG	pH	PCO <sub>2</sub>	BE	Outcome	P.M.	Diagnosis	Remarks
8	RCM	M	C	3.40	2	76	94	++	-	+	-	7.405	32.7	-5.2	S		Meconium aspiration	
25	RCM	M	C	2.18	4	70	31	+	-	+	-				S		NDA	
26	GSH	M	E	0.91	4	76	16	+	+	+	-				D20	No	? HMD	Abnormal radiograph
81	GSH	M	E	2.83	?	88	144	++	-	+	+	7.26	53.0	-5.0	S		CHMD	
82	RCM	M	C	1.36	?	80	21	+	+	+	-	7.20	48.0	-10.0	D21	Yes	CHMD	
83	RCM	M	E	2.24	4	-	96	++	-	+	-	7.16	60.0	-9.3	ND6	Yes	CHMD	Oes. atresia
84	GSH	M	E	2.72	B	48	IPPR	5	+	+	+	6.80	170	-19.0	D27	Yes	CHMD	Bilat. pneumothoraces Polycystic kidneys
86	GSH	M	E	2.06	B	65	22	++	-	+	+	7.35	45.0	-1.0	S		NDA	
87	RCM	M	E	1.61	B	50	18	+++	-	+	+	6.94	88.0	-16.5	D18	Yes	CHMD	
88	GSH	F	E	1.47	B	40	IPPR	2	+	+	+	7.33	25.5	-10.0	D3	No	CHMD	
89	RCM	M	C	1.44	B	64	41	42	+	+	-	7.26	53.0	-3.0	D47	No	CHMD	
90	GSH	M	C	1.76	B	76	28	27	+	+	+	7.166	64.0	-6.3	D29	No	CHMD	
91	GSH	M	E	3.63	24	71	22	38	-	+	+				D47	Yes	Aspiration syndrome	
92	GSH	F	C	2.86	12	55	30	++	+	+	+	7.20	33.0	-14	D42	No	CHMD	
93	GSH	M	C	1.75	1	70	48	++	+	+	+	7.30	38.0	-7.3	D9	Yes	NDA	
99	GSH	M	E	1.73	4	83	22	-	+	+	+	7.185	34.5	-14.5	D49	Yes	CHMD	Subarachnoid haem.
100	RCM	M	C	3.97	B	98	72	++	-	+	+	7.30	40.0	-6.5	S		NDA	
101	GSH	M	B	2.04	4	66	IPPR	++	-	+	+	6.93	50.0	-22.8	D25	Yes	CHMD	Subarachnoid Haem.
149	GSH	M	E	1.70	2	?	5	-	+	-	-				D5	Yes	CHMD	Subarachnoid Haem.
148	GSH	M	E	1.92	4	76	24	24	+	+	+	7.250	56.0	-4.5	ND	Yes	CHMD	IPPR 19 days
168	GSH	F	E	1.34	2	53	24	9	+	+	+	7.260	41.0	-8.6	ND5	No	CHMD	
234	GSH	M	E	3.85	B	67	36	8	-	+	+	6.935	22.8	-26	S		Anaemia	Remarkable response to BT
237	GSH	M	E	3.29	12	83	120	30	+	+	+	7.305	40.0	-6.1	S		NDA	Cerebral
240	GSH	M	C	2.35	6	76	55	++	+	+	+	7.130	56.0	13.0	D79	Yes	NDA	
272	GSH	M	E	3.40	6	64	5	-	+	+	+	7.384	34.6	-3.8	S		NT	
273	GSH	M	C	2.83	1	91	96	2	-	+	+	7.362	30.8	-7.2	S		Pneumothorax	
274	GSH	F	E	2.27	B	96	144	-	+	+	+	7.270	41.0	-7.8	S		CHMD	Lober pneumonia
312	GSH	M	C	1.64	4	93	96	-	-	+	-	7.375	34.7	-4.0	S		NT	
346	GSH	M	E	2.51	2	74	180	60	+++	+	+	7.181	48.0	-11.6	S		CHMD	
414	RCM	M	C	2.35	B	80	48	24	+	+	-	7.367	36.5	-3.8	S		NDA	Postmature
453	GSH	F	E	2.10	B	81	120	++	+	+	+	7.344	35.0	-6.0	S		CHMD	
463	RCM	F	C	1.98	B	72	96	21	++	+	-	7.152	39.0	-13.5	S		CHMD	
495	GSH	F	E	1.87	2	76	84	30	++	+	+	7.175	64.0	-6.8	S		CHMD	
511	RCM	F	E	2.97	4	80	96	30	++	+	-	7.298	41.6	-6.0	S		CHMD	
611	GSH	M	E	4.17	?	110	200	46	++	+	+	7.150	48.6	-11.2	S		Pneumothorax	Meconium aspiration

**ACID-BASE AND OXYGEN VALUES**

**IN**

**INFANTS WITH RDS**



Serial No.	Outcome	Age in hrs	pH	PCO <sub>2</sub> mmHg	BE mEq/L	BB mEq/L	Standard HCO <sub>3</sub> mEq/L	Actual HCO <sub>3</sub> mEq/L	PaO <sub>2</sub> mmHg	% Hb. saturation	% R-L shunt	% ambient oxygen	Treatment		
													NaHCO <sub>3</sub>	Tham	IPPR
101	D	15	6.928	50.0	-22.8	23.7	9.8	10.0		74.6	54	100			+
		16	7.048	37.0	-19.3	25.6	10.2	9.8		81.3	46	100			+
		17	6.940	55.8	-18.5	25.0	10.2	11.7		8.8	78	100		+	+
		19	6.800	90.0	-20.8	24.0	9.2	13.8						+	+
		24	6.905	71.5	-18.2	26.3	10.6	14.2						+	+
124	S	8	7.380	33.4	-4.0	47.0	21.0	19.0							
		16	7.300	35.5	-8.0	36.0	17.5	17.0						+	
		36	7.274	29.0	-12.2	32.4	14.6	13.0						+	
132	S	60	7.372	40.0	-1.5	46.4	22.5	23.0						+	
		6	7.248	51.0	-6.0	42.9	19.4	21.5							
		18	7.370	40.8	-1.6	44.0	23.6	22.8						+	
134	D	21	7.365	45.0	0	45.0	24.0	24.5							
		7	7.240	53.0	-5.8	42.5	19.6	21.8							
135	D	12	7.235	48.0	-7.5	40.0	18.2	19.6							
		8	7.400	35.0	-2.5	44.5	22.0	21.0							+
147	D	12	7.240	45.0	-8.4	40.2	17.7	18.5	48	81.5	64	100			+
		24	7.510	25.3	-1.6	44.2	22.5	18.5	355	100.0	26	100		+	+
		29	7.590	20.0	-0.8	46.0	23.2	18.5	320	100.0	27	100		+	+
		34	6.940	55.0	-20.5	25.0	9.7	11.4	32	38.0	65	100		+	+
		6	7.198	56.6	-7.2	40.2	18.5	21.3							
148	ND	7 1/2	7.247	46.2	-7.4	40.3	18.3	21.0	107	96.2	45	55			
		12	7.283	45.7	-3.5	43.5	21.5	24.2	39	63.0	71	100		+	
		18	7.375	36.2	-3.5	41.9	21.1	21.1	63	89.0	59	100		+	+
		24	7.322	36.7	-5.5	38.0	19.5	19.5	53	81.5	65	100		+	+
		27	7.178	33.4	-12.0	31.5	14.5	15.2	25	34.0	84	100		+	+
		30	6.979	53.0	-20.0	24.8	9.7	11.0	17	15.5	87	100			+
		31	7.081	31.0	-20.6	24.0	9.3	8.3	65	80.0	63	100			+
		32	7.104	49.0	-13.4	28.2	13.0	13.7	40	54.0	79	100			+
		33	7.274	36.5	-11.0	31.4	15.0	14.8	57	80.0	63	100			+
		36	7.334	32.0	-10.2	32.6	15.6	15.1	50	80.0	63	100			+
		40	7.074	49.0	-10.7	31.5	15.4	16.0	18	19.0	86	100			+
		46	7.059	45.5	-17.8	26.0	10.6	11.2	20	20.0	86	100			+
		50	7.621	18.5	-4.1	40.8	20.5	16.2	410	100.0	16	100			+
		56	7.497	27.0	-5.0	42.0	20.0	17.2	64	91.5	75	100			+
		8	7.250	56.0	-4.5	44.5	20.5	23.5	190	99.0	32	100			+
		13	7.310	48.0	-5.2	43.6	22.0	23.3	217	99.3	36	100			+
		19	7.308	54.0	-0.5	45.2	23.5	25.4	84	94.3	49	100			+
24	7.220	51.5	-6.6	39.0	18.7	20.5	162	98.6	29	100			+		
26	7.260	61.0	-1.6	46.0	22.6	25.5	50	76.0	70	100			+		
27 1/2	7.305	52.0	-1.5	46.1	22.7	25.2	30	47.0	81	100			+		
31	7.420	40.0	+1.4	48.4	25.1	25.1	46	81.0	54	100			+		
37	7.450	38.0	+2.4	52.0	25.9	25.3	51	86.0	66	100			+		
43	7.350	49.5	+0.2	48.7	24.2	26.7	38	69.0	61	100			+		
48	7.385	45.5	+1.8	47.8	25.4	26.6	60	88.8	59	100			+		
55	7.388	41.0	0	48.1	23.8	24.0	51	84.0	63	100			+		
61	7.390	47.0	+3.0	49.1	26.4	27.5	54	85.6	62	100			+		
65	7.400	47.0	+3.2	51.2	26.6	28.0	59	89.1	58	100			+		
71	7.400	46.0	+3.2	47.6	26.7	27.5	64	90.8	55	100			+		
80	7.388	46.5	+2.6	46.8	26.1	26.7	64	91.0	55	100			+		
117	7.360	49.0	+1.8	48.2	25.4	27.0								+	
165	7.164	95.0	+1.5	48.0	25.2	32.2								+	
167	7.280	68.0	+3.0	49.0	26.5	30.6								+	
174	7.400	49.0	+4.8	49.9	27.8	29.5								+	
		<u>Days</u>													
		8	7.380	57.0	+7.6	51.7	30.5	32.5							+
		9	7.260	92.0	+8.8	56.0	31.8	40.0							+
		10	7.320	67.0	+8.2	50.0	30.1	33.6							+
		11	7.310	63.0	+4.0	49.7	27.7	30.6							+
		11	7.090	106.0	-2.0	45.0	22.3	30.8							+
		12	7.190	74.6	-0.4	44.0	23.5	27.5							+
		14	7.300	55.6	+1.2	44.0	25.0	26.4							+





Serial No.	Outcome	Age in hrs.	pH	PCO <sub>2</sub> mmHg	BE mEq/L	BB mEq/L	Standard HCO <sub>3</sub> <sup>-</sup> mEq/L	Actual HCO <sub>3</sub> <sup>-</sup> mEq/L	PaO <sub>2</sub> mmHg	% Hb. saturation	% R - L shunt	% ambient oxygen	Treatment				
													NaHCO <sub>3</sub>	Tham	IPPR		
464	S	2½	7.151	56.1	-10.2	37.2	16.3	19.0									
		9	7.271	34.3	-9.6	35.1	16.4	15.3	56	86.2	6	21					
		21	7.402	33.5	-3.0	44.3	21.5	20.2	99	97.0	8	30					
		29	7.387	34.4	-3.8	41.0	21.0	20.0	86	95.6	9	30					
		47	7.356	29.0	-8.0	38.7	17.7	15.3	136	98.4	5	30					
		54	7.337	34.0	-6.8	41.1	18.7	17.8									
		72	7.331	34.8	-6.5	41.1	18.7	17.5									
465	D	7½	6.920	50.0	-21.5	23.4	8.8	10.0									
		9	7.115	99.0	+1.4	45.4	25.0	30.5									
		20	7.665	13.7	-3.6	41.8	21.0	15.0									
		22	7.432	26.6	-5.4	39.8	19.6	17.0									
		25	7.391	40.0	-0.4	46.0	23.4	23.5									
		31	7.425	33.0	-2.0	44.5	22.4	21.0									
479	D	44	7.283	45.5	-4.8	40.4	20.2	21.0									
		1	7.210	44.0	-8.0	35.5	17.5	17.2									
		4	7.146	80.0	-2.3	42.4	21.9	26.5									
480	S	8	7.243	53.0	-4.3	40.4	20.5	22.0									
		16	6.988	89.0	-11.0	33.8	15.5	20.0									
		14	7.220	46.0	-9.8	35.5	16.4	17.3									
		23	7.280	55.0	-1.0	43.5	23.0	24.8									
		36	7.393	49.4	+4.6	48.3	27.8	29.5									
		43	7.319	57.0	+0.3	51.0	24.1	28.0									
495	S	60	7.430	43.0	+3.9	46.9	27.2	27.5									
		72	7.409	41.0	+1.2	45.3	25.0	25.1									
		4	7.175	64.0	-6.8	41.0	18.8	22.7	192	98.8	22	75					
		11	7.305	36.5	-7.7	40.6	18.2	17.6	135	98.2	9	38					
		18	7.260	57.0	-3.0	45.0	21.6	24.8									
496	S	35	7.373	46.0	+1.2	47.0	25.0	25.8									
		60	7.332	46.5	-1.7	46.1	23.5	24.9									
		16	7.250	24.5	-15.2	31.2	13.1	10.4	135	98.0	19	55					
		20	7.310	33.4	-8.7	35.0	17.0	16.4	110	97.1	20	55					
497	S	36	7.385	39.5	+1.0	44.0	23.0	23.0									
		60	7.357	36.5	-4.5	40.0	20.0	19.8									
		3½	7.223	47.5	-7.6	37.1	18.0	18.7	124	97.0	48	100					
		8	7.273	36.0	-9.5	36.3	16.7	16.3	70	90.2	46	45					
		13	7.281	41.8	-6.8	39.6	18.7	19.0	82	94.0	40	55					
		23	7.215	53.0	-6.8	39.6	18.7	21.0	46	72.0	69	65					
		26	7.195	62.0	-5.3	41.0	19.8	23.7	50	76.0	69	100					
		35	7.245	48.4	-5.2	36.7	19.5	20.4	45	71.0	72	100					
		49	7.127	57.0	-11.5	35.5	15.4	18.0	52	72.0	71	100					
		53	7.425	41.5	+2.5	49.5	26.0	26.2	56	86.8	67	100					
		72	7.521	28.0	+1.3	49.4	25.0	22.5	108	98.2	41	100					
		78	7.453	30.0	-1.8	46.1	22.5	20.3	111	97.9	41	100					
		97	7.333	34.0	-7.0	40.0	18.6	17.5	161	99.0	34	100					
		103	7.416	36.0	-1.0	45.6	23.0	22.5	115	98.2	40	100					
		120	7.315	49.5	-1.8	46.1	18.6	24.4	112	97.4	42	100					
144	7.297	53.5	-0.4	44.2	23.5	25.2	85	94.6	35	45							
169	7.278	57.0	-0.4	44.2	23.5	26.0											
192	7.305	51.0	-1.0	43.7	23.0	24.4											
		<u>Days</u>															
		10	7.255	63.5	+1.4	44.9	24.4	27.2									
		11	7.265	76.6	+2.9	52.3	26.6	30.0									
		13	7.269	59.0	-1.0	45.5	23.0	25.6									
		15	7.306	55.5	0	47.4	24.0	26.5									
		<u>Hrs</u>															
511	S	24	7.298	41.6	-6.0	40.0	19.4	19.7									
		30	7.240	50.0	-7.0	41.5	19.6	20.5									
		48	7.370	42.0	-1.0	49.0	23.0	23.5									
517	D	6	7.160	60.0	-7.5	38.0	18.0	21.0									



Serial No.	Outcome	Age in hrs.	pH	PCO <sub>2</sub> mmHg	BE mEq/L	mEq/L	Standard HCO <sub>3</sub> mEq/L	Actual HCO <sub>3</sub> mEq/L	PaO <sub>2</sub> mmHg	% Hb saturation	R - L shunt		Treatment		
											%	%	NaHCO <sub>2</sub>	Tham	IPPR
93	S	7	7.300	38.0	-7.3	41.5	18.5	18.0		100.0	0	100			
		13	7.340	60.0	+3.2	53.2	26.5	32.6							
		24	7.320	46.0	-3.4	47.0	21.4	23.0							
		33	7.345	40.0	-3.5	46.2	21.3	21.3							
100	S	12	7.300	40.0	-6.5	40.5	18.9	19.0							
		14	7.300	40.0	-6.7	42.5	19.2	19.0							
		24	7.390	34.2	-3.6	43.4	21.1	20.0		95.5	?	?		+	
130	S	15	7.305	48.5	-2.6	43.9	21.8	23.3							
		20	7.315	46.5	-2.8	46.5	21.8	22.5							
		34	7.322	43.0	-3.6	43.3	20.0	21.3							
131	S	5	7.110	95.0	-7.5	43.6	18.5	29.0							
		10	7.120	65.0	-8.0	36.0	17.5	20.2							
		23	7.255	44.5	-7.1	38.3	18.3	19.0							
		27	7.190	52.0	-8.0	36.6	17.6	19.0		95.8	22	100			
		30	7.250	44.9	-7.2	39.5	18.4	19.4		96.0	21	100			
		34	7.290	36.5	-8.5	39.8	17.6	17.0							
		49	7.340	46.3	-1.2	46.2	23.0	24.6							
234	S	3	6.935	22.8	-26.0	18.6	6.6	5.0							
		4	7.165	27.5	-17.7	28.2	11.5	9.6							
		5	7.321	32.6	-8.2	37.9	17.5	16.2							
		10	7.460	36.0	+1.7	45.0	25.4	25.0							
237	S	27	7.305	40.0	-6.1	42.6	19.2	19.2	83	94.4	36	45			
		36	7.370	32.0	-5.5	43.5	19.8	18.0	113	97.8	22	38			
		49	7.395	41.0	+0.2	47.4	24.2	24.3	124	98.3	21	45			
240	D	13	7.130	56.0	-13.0	36.7	15.0	18.0	88	92.5	52	100			
		20	7.250	52.0	-5.3	42.4	19.8	22.0	116	97.4	47	100			+
		30	7.265	55.0	-4.0	45.7	21.0	24.0	87	94.7	35	45			+
		42	7.299	51.0	-3.0	47.6	21.6	24.2	121	97.8	27	55			+
		55	7.370	48.0	+1.0	52.0	24.6	26.8	101	97.0	26	55			+
		66	7.255	38.5	-9.8	38.3	16.7	16.5	235	99.2	31	100			
242	S	24	7.350	36.0	-5.0	44.0	20.2	19.7							
		7	7.300	48.0	-4.5	45.0	20.5	22.0							
		28	7.290	35.6	-9.1	43.4	17.7	16.3							
		75	7.350	40.4	-3.3	46.3	21.4	21.5							
414	S	18	7.367	36.5	-3.8	43.0	21.0	20.3							
494	S	12	7.305	31.3	-9.8	35.5	16.4	15.1							
		26	7.325	37.0	-6.2	41.9	19.2	18.7							+
<u>HMD - AUTOPSY</u>			<u>DIAGNOSIS</u>												
582	D	2	7.220	66.5	-3.4	45.0	21.3	25.8							
<u>RDS - UNDETERMINED</u>															
155	S	6	7.250	47.0	-7.4	41.2	18.5	20.0							
329	D	17	7.250	47.0	-7.3	41.1	18.0	19.0							
410	D	6	7.120	68.0	-9.4	38.2	17.0	21.4							
580	S	2	7.120	58.6	-10.8	35.3	15.8	18.4							
		7	7.210	61.0	-5.2	42.6	20.0	23.6							+
		26	7.380	44.5	+0.5	48.0	24.6	25.5							+
581	S	2	7.100	70.5	-10.9	37.5	16.0	21.1							
		7	7.180	75.0	-3.8	44.5	21.0	26.7							+
		27	7.345	52.0	+1.7	49.5	25.3	27.4							+
618	S	4	7.210	35.6	-13.5	36.2	14.6	13.8							
<u>PNEUMONIA</u>															
63	S	25	7.435	31.5	-2.0	46.0	22.4	21.2							
		41	7.475	29.5	-1.3	43.2	22.8	21.1							
		52	7.385	36.5	-2.7	43.8	21.8	21.2							
		77	7.338	27.5	-9.4	36.2	16.5	14.1							



**ACID-BASE VALUES**

**IN**

**NORMAL PREMATURE AND 'TERM' INFANTS**

YAW  
ON

SUMMARY OF ACID-BASE VALUES AT VARIOUS AGES IN HEALTHY

PREMATURE AND FULL-TERM INFANTS

	<u>Hours</u>	<u>PREMATURE</u>			<u>FULL-TERM</u>		
		<u>Mean</u>	<u>Standard deviation</u>	<u>Range</u>	<u>Mean</u>	<u>Standard deviation</u>	<u>Range</u>
pH	2	7.33	0.06	7.27 - 7.42	7.34	0.06	7.26 - 7.43
	4	7.35	0.04	7.28 - 7.42	7.38	0.04	7.33 - 7.46
	6	7.36	0.04	7.30 - 7.42	7.38	0.04	7.31 - 7.47
	12	7.38	0.03	7.33 - 7.44	7.40	0.03	7.33 - 7.46
	24	7.39	0.04	7.33 - 7.48	7.41	0.04	7.32 - 7.48
	48	7.37	0.05	7.29 - 7.46	7.42	0.05	7.31 - 7.50
	72	7.37	0.05	7.28 - 7.45	7.42	0.04	7.32 - 7.48
PCO <sub>2</sub> mmHg	2	42.8	6.8	31.7 - 52.0	41.4	8.8	24.5 - 60.0
	4	43.3	8.2	31.7 - 58.5	36.7	5.3	24.3 - 45.7
	6	40.9	9.6	29.5 - 60.5	36.4	3.6	27.6 - 42.0
	12	38.4	6.4	27.0 - 50.2	36.6	3.3	31.7 - 43.0
	24	35.8	4.0	27.6 - 43.0	34.9	4.0	28.5 - 43.0
	48	39.5	6.1	33.0 - 57.0	34.0	4.5	27.0 - 41.5
	72	36.8	5.2	29.0 - 45.0	35.5	5.4	25.0 - 46.0
Base excess mEq/L	2	-3.7	2.9	-8.5 + 2.1	-3.8	2.4	-8.7 + 0.9
	4	-2.3	2.6	-6.6 + 2.9	-2.5	1.6	-5.9 + 0.9
	6	-2.1	3.0	-8.6 + 4.2	-2.5	1.8	-5.8 + 2.2
	12	-2.3	1.8	-6.1 + 0.3	-1.4	1.8	-4.5 + 4.0
	24	-2.6	1.8	-7.4 0	-1.4	1.8	-4.3 + 3.7
	48	-2.7	1.2	-7.5 + 0.6	-1.2	1.7	-5.3 + 2.0
	72	-3.3	2.9	-9.6 - 0.5	-0.8	2.4	-4.8 + 3.1
Buffer base mEq/L	2	46.1	2.7	43.2 - 51.8	46.6	3.0	42.5 - 51.9
	4	47.8	3.0	44.0 - 53.2	47.5	1.8	45.0 - 51.2
	6	48.3	3.5	40.5 - 53.2	47.1	2.9	43.2 - 51.0
	12	46.7	2.7	41.1 - 50.3	47.6	2.6	44.4 - 53.0
	24	46.6	2.7	40.8 - 50.3	47.6	2.7	43.8 - 55.3
	48	46.2	2.8	41.8 - 51.0	47.8	3.2	39.6 - 51.5
	72	46.5	3.3	40.6 - 50.2	49.0	3.3	42.5 - 54.0
Standard HCO <sub>3</sub> mEq/L	2	21.2	1.8	17.6 - 25.6	21.1	1.8	17.7 - 24.6
	4	22.2	2.2	19.2 - 26.2	22.0	1.3	19.7 - 24.6
	6	22.5	1.4	17.6 - 26.0	21.9	1.6	19.7 - 25.7
	12	22.1	1.6	19.4 - 24.2	22.9	1.7	21.3 - 27.2
	24	21.9	1.6	18.4 - 24.0	22.8	1.6	20.5 - 26.8
	48	21.9	1.7	18.4 - 24.4	23.0	1.6	19.9 - 25.5
	72	21.4	2.0	17.1 - 23.5	23.3	2.1	20.0 - 26.0
Actual HCO <sub>3</sub> mEq/L	2	21.8	2.9	17.0 - 26.1	21.3	4.3	18.5 - 27.5
	4	22.9	3.7	17.0 - 30.5	21.4	1.4	18.0 - 23.4
	6	23.3	4.3	15.4 - 30.5	21.4	1.9	17.5 - 24.7
	12	21.7	2.6	17.2 - 26.0	22.1	2.0	19.5 - 27.4
	24	20.8	1.9	16.2 - 24.6	21.7	1.9	18.1 - 26.4
	48	21.6	1.6	17.6 - 24.6	21.3	2.0	19.4 - 26.0
	72	20.6	2.7	14.4 - 23.6	22.2	3.1	17.0 - 28.0

**ACID-BASE DETERMINATION**

**METHODS**

ACID-BASE DETERMINATION

Two methods of acid-base determination were employed in this survey. Apparatus for the Astrup micro-technique (Astrup et al., 1960) became available after the start of the survey and replaced the older technique of Van Slyke blood gas analysis which had been used in conjunction with a Metrohm pH meter.

The apparatus therefore consisted of:

Method 1: (a) The Van Slyke manometric apparatus for determination of whole blood total  $\text{CO}_2$  content using 0.2 ml of whole blood (Peters and Van Slyke, 1932).

(b) The Metrohm pH Meter E 300. Plasma total  $\text{CO}_2$  content corrected for pH and oxygen saturation was calculated with the Van Slyke and Sendroy (1928) line chart. The plasma bicarbonate,  $\text{PCO}_2$  and BE were read from the nomogram of Siggaard-Andersen (1964).

Method 2: (a) The Radiometer pH Meter 27.

(b) The Astrup micro-tonometer for equilibration by the Astrup method (Siggaard-Andersen, 1964).

Corrections were made for unsaturation and results were plotted on the nomogram provided to obtain  $\text{PCO}_2$ , actual bicarbonate and BE. Standard bicarbonate (Astrup, 1955) and BB (Singer and Hastings, 1948) were also obtained from the nomogram. The  $\text{CO}_2$  content of the gases used for equilibration were analysed with the Schölander (1947) micro-gas analyser (SE = 0.047%).

In order to determine the experimental error and assess the comparability of the two methods, a comparative study was carried out.

Blood samples of 3 ml were collected anaerobically after filling the dead space of a syringe with heparin. Determinations were carried out in duplicate and the results are shown on page xxix. Despite a wide range of observed values the standard error of all determinations was within acceptable limits. No significant difference was found between the two methods for any of the values, with the exception of the pH where the mean difference between the two methods was 0.009 (Malan, Evans and Keese, 1965).

Siggaard-Andersen (1964) has discussed in detail the theoretical and practical aspects of the Astrup micro-method (Method 2). This method has the advantage that arterialised capillary blood could be used in this survey. Gambino (1961) and Gandy et al. (1964) have demonstrated the validity of arterialised capillary blood samples. These authors stressed the importance of adequately warming the extremity and collecting spontaneously formed drops of blood and this has been done throughout this work. In newborn infants under 3 hours, or in the presence of impaired cardio-pulmonary function over 3 hours, the correlation between capillary and arterial blood was less good (Gandy et al., 1964).

Since the pH was measured at 38°C, correction was made routinely for the actual temperature (t) of the patient. The factor of Rosenthal (1948) was used:

$$\text{Blood } \text{pH}_{38} = \text{pH } t - 0.0147 (38 - t)$$

or,

$$\text{pH } t = \text{Blood } \text{pH}_{38} + 0.0147 (38 - t).$$

This factor is almost identical with that of Siggaard-Andersen (1964) and Adanson et al. (1964).

COMPARISON OF DIFFERENT METHODS OF DETERMINING ACID-BASE STATUS

Type	Oxygen		Total CO <sub>2</sub> blood	pH		HCO <sub>3</sub> <sup>-</sup> mEq/L		PCO <sub>2</sub> mmHg		Base excess mEq/L	
	Volume %	Van Slyke		Metrohms Radiometer	Van Slyke and Metrohm	Astrup method	Van Slyke and Metrohm	Astrup method	Van Slyke and Metrohm	Astrup method	Van Slyke and Metrohm
Cord	5.98	19.35	7.143	20.5	20.6	62.0	60.3	-9.0	-8.5		
Arterial	5.84	19.20	7.160	20.5	20.2	62.6	60.3	-9.8	-9.9		
Arterial	19.45	16.20	7.547	19.2	21.0	23.4	22.8	-1.5	-1.8		
Arterial	19.60	15.90	7.515	19.2	20.2	23.5	21.5	-1.4	-2.8		
Arterial	20.80	17.15	7.520	20.3	20.5	25.0	24.5	-0.5	-1.0		
Arterial	20.60	16.90	7.530	20.8	16.7	20.0	21.9	0.0	-5.0		
Arterial	16.40	12.70	7.482	14.6	16.7	21.6	22.1	-6.3	-5.2		
Arterial	16.7	13.10	7.465	15.3	17.25	21.2	23.8	-6.5	-5.8		
Arterial	16.60	13.25	7.475	15.0		21.7		-6.3			
Cord	16.40	13.40	7.470	15.3		21.7		-6.3			
Cord	11.47	20.40	7.105	22.0	19.2	73.0	81.0	-9.5	-5.4		
Venous	11.60	20.45	7.105	21.60	17.5	75.0	76.0	-10.0	-7.4		
Arterial	4.90	22.50	7.315	24.6	24.4	49.6	49.5	-1.0	-0.8		
Arterial	5.25	22.70	7.315	24.3		49.6		-1.2			
Arterial	22.70	19.00	7.500	22.0	22.4	28.9	28.8	+0.7	+1.8		
Arterial	22.60	17.95	7.510	22.7	21.4	29.8	27.6	+1.9	+0.9		
Arterial	19.10	18.90	7.465	22.2	20.4	30.7	28.7	-0.3	-0.8		
Arterial	19.70	18.20	7.465	22.7	20.0	32.3	28.5	+0.3	-1.4		
Arterial	22.50	16.37	7.380	19.0	20.3	33.5	35.0	-4.6	-3.4		
Arterial	23.00	16.30	7.377	18.6	20.5	33.4	36.0	-5.0	-3.4		
Arterial	17.75	19.05	7.380	22.0	20.2	38.5	35.6	-2.0	-3.6		
Venous	16.85	22.30	7.390	22.0	24.8	38.4	42.4	-2.0	+0.4		
Cord	11.95	21.50	7.394	25.0	24.8	43.0	43.0	+0.5	+0.3		
Arterial	12.30	20.40	7.375	25.2	24.5	44.2	41.6	+0.6	+0.3		
Arterial	7.65	20.40	7.245	22.2	24.2	53.0	53.5	-5.0	-3.6		
Arterial	7.75	20.24	7.275	22.4	15.4	55.0	20.2	-5.0	-7.2		
Arterial	16.05	13.75	7.499	14.9	15.7	20.0	20.5	-6.5	-6.7		
Arterial	16.20	13.60	7.493	15.6		20.7		-5.0			

Mean difference between duplicate determinations

Standard error	0.298	0.317	0.009	0.006
	0.005	0.008	0.003	0.001

$P \leq 0.3$

Mean difference between the two methods

Standard error	1.136	1.28	0.99
	1.420	1.53	1.14
	0.9	0.2	0.9

<sup>+</sup> P refers to the probability that the difference between the two means is due to chance  
<sup>\*</sup> P refers to the probability that the mean difference between the two methods is different from zero

**OXYGEN MEASUREMENTS**

## OXYGEN MEASUREMENTS

### Umbilical arterial catheterisation

Although there are alternative routes for collection of arterial blood in newborn infants (Thomsen, 1964), catheterisation of an umbilical artery is the method of choice in severely distressed infants.

The umbilical cord is cut quarter of an inch above the skin margin and the vessels identified. The tissue immediately adjacent to an umbilical artery is gripped with a fine-toothed forceps and a small metal probe gently introduced into the orifice of the cut artery which is usually in spasm. One only needs to dilate the orifice before a round-tipped catheter can be introduced and advanced until blood flows back. Attempts to pass the dilator further may rupture the vessel wall. The author tapes the catheter securely to the abdominal wall, while Stahlman (1964) advocates fixation of the catheter with a purse string suture to prevent accidental displacement and bleeding. After blood samples are taken, the catheter is filled with heparin/saline (10 u/cc) and left in situ. In this survey catheters were left for as long as 5 days without untoward effect. Most authors advocate shorter periods of time (Warley and Gairdner, 1962; Prod'homme et al. 1964 and Oype et al. 1965). Moss et al. (1965) were successful with umbilical arterial catheterisation in 100 out of 113 attempts. To prevent bleeding, withdrawal of the catheter should be prolonged over a few hours. Blanching of a leg (Smith, 1964) was seen in 2 infants in this study. Both recovered spontaneously on removal of the catheter. Other dangers are introduction of infection and thrombosis (Oype et al., 1965).

Gandy et al. (1964) advocated withdrawal of 1 ml of blood prior to taking the actual sample.

#### Measurement of oxygen content

Oxygen content was measured in the early part of the survey by means of the Van Slyke manometric apparatus, using 0.2 ml of whole blood (Peters and Van Slyke, 1932). The standard error of the measurement was 0.005 vols % (page xxix). Direct measurement of oxygen tension later became available.

#### Measurement of oxygen tension (PO<sub>2</sub>)

Oxygen tension was measured directly with a Clark type oxygen-electrode manufactured by Radiometer, Copenhagen. Severinghaus and Bradley (1958) have described the principle of the oxygen electrode and discussed the factors which affect the readings. As early as 1942 Berggren found this method for oxygen determination to be superior, both as regards accuracy and rapidity. Torres (1963) stated that the PO<sub>2</sub> electrode can be used with confidence in determining the blood oxygen tension but stressed that the readings should be done as soon after sampling as possible.

Two aqueous samples were used to calibrate the electrode:

- (a) Oxygen-free solution made from 0.01 M borax solution and sodium sulphite.
- (b) Solution of known oxygen tension. Distilled water equilibrated with room air at a constant temperature of 38°C in a water bath was used. The oxygen tension in room air was calculated from the following formula:

$$PO_2 = (\text{barometric pressure} - 47 \text{ mmHg}) \times 20.9\%$$

The unknown sample was then delivered and the  $PO_2$  read directly.

In order to determine the reliability and accuracy of the  $PO_2$  electrode, repeated estimations were done on the same aqueous or gas sample. Two oxygen mixtures were used:

1. Room air.  $PO_2 = 149$  mmHg
2. 30% oxygen and 70% nitrogen.  $PO_2 = 213$  mmHg

The results are shown below. All values are in mmHg.

Sample	Room air	Water equilibrated with room air	30% Oxygen	Water equilibrated with 30% oxygen
Number of determinations	10	10	10	10
Mean	149.5	149.75	210.2	198.9
S.D.	0.75	0.53	1.13	1.13
S.E. of mean	0.237	0.167	0.358	0.359

The electrode was thus extremely reliable and accurate in the range required for this survey. At higher levels the electrode gave slightly reduced readings for gas samples and much lower values for aqueous samples. Laughlin et al. (1964) also found the output of the electrode to be slightly lower for blood than for gas samples. Torres (1963), however, recorded good correlation between blood and gas mixtures. A 10% difference between duplicate measurements at levels over 200 mmHg was found by Fred'hem et al. (1964).

FORMULAE

FORMULAEOxygen capacity

Oxygen capacity in vols % = Haemoglobin in g % x 1.34

Warley and Gairdner, 1962  
Kirschbaum, 1964

Oxygen saturation

$$(a) \quad s = \frac{\text{Oxygen content}}{\text{Oxygen capacity}}$$

Where oxygen capacity was not calculated, the value of 20.8 vols% was adopted (Nelson et al., 1963).

(b) Calculated from the Oxyhaemoglobin Dissociation Curve

The line chart of Severinghaus (1958) was used to convert  $PO_2$  into saturation after correction of the  $PO_2$  for temperature and pH. Although Nelson et al. (1964) defined more accurately the oxyhaemoglobin dissociation curve in vivo for newborn infants, the chart of Severinghaus (1958) was much easier to use in practice. Similarly, the different correction factors of Hodley-Whyte and Laver (1964) for  $PO_2$  values over 120 mmHg were unimportant in this survey.

R - L Shunt

Three formulae were used to calculate R - L shunts depending on the method of oxygen determination and the level of  $PO_2$ .

(a) Standard equation 
$$\frac{O_2 \text{ capacity} - \text{arterial } O_2 \text{ content}}{O_2 \text{ capacity} - \text{mixed venous } O_2 \text{ content}}$$

(b)  $PaO_2$  130 mmHg (Fred'hem et al., 1964)

$$\frac{\dot{Q}_s}{\dot{Q}_T} = \frac{(PAO_2 - PaO_2) \times .00302}{(PAO_2 - PaO_2) \cdot 0.00302 + O_2 \text{ capacity} \times a-\bar{v} \text{ saturation difference}}$$

(c)  $PaO_2$  130 mmHg (Nelson et al., 1963)

$$\frac{\dot{Q}_s}{\dot{Q}_T} = \frac{\text{Capacity} (1 - Sa) + .00302 (PAO_2 - PaO_2)}{\text{Capacity} (1 - Sa) + .00302 (PAO_2 - PaO_2) + \text{capacity} \times \text{saturation difference}}$$

Unless measured, the saturation of mixed venous blood has to be assumed. Strang and MacLeish (1961) found an  $a-\bar{v}$  difference of 4 vols % applicable in RDS. Warley and Gairdner (1962) used a value of 5 vols %. Radolph et al. (1961) measured the  $a-\bar{v}$  differences during cardiac catheterisation and recorded 15% in well infants and 10-12% in those with IRDS. In this survey, an intermediate value of 3 vols % ( $\pm 15\%$ ) was assumed.

Alveolar Air equation

$$\text{Alveolar } PO_2 = \text{Inspired } PO_2 - \frac{PaCO_2}{R.Q.}$$

This simplified version was put forward by Campbell (1965) and is sufficiently accurate for most clinical purposes.

R.Q. = 0.8.

Calculation of Base to correct Metabolic Acidosis

$$0.6 \times BE \times \text{wt. in kg.} = \text{mEq}$$

$$\text{or } 0.6 \times BE \times \text{wt. in kg.} \times 2 = \text{ml } 4\% \text{ NaHCO}_3$$

In premature infants an estimated 60% of body weight is water that needs to be buffered. Because of the slow distribution of sodium bicarbonate in the body fluids (Kaplan et al., 1962) the amount should be given over 12 - 24 hours.

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BIBLIOGRAPHY

- Adamsens, K., Daniel, S.S., Gandy, G. and James, L.S. 1964  
*J. appl. Physiol.*, 19, 897.
- Ahvenainen, H.K. 1959 *J. Pediat.*, 55, 691.
- Amrus, C.M., Weintraub, D.H., Dunphy, D., Dowd, J.E., Pickren, J.W.,  
 Niswander, K.R. and Amrus, J.L. 1963 *Pediatrics*, 32, 10.
- Anderson, G.S., Green, C.A., Meligan, G.A., Newell, D.J. and  
 Russell, J.K. 1962 *Lancet*, 2, 585.
- Apgar, V., Meladay, D.A., James, L.S., Weisbrot, I.M. and Berrien, G.  
 1958 *J. Amer. med. Ass.*, 168, 1985.
- Arey, J.B. and Dent, J. 1953 *J. Pediat.*, 42, 1.
- Astrup, P. 1955 *Dan. med. Bull.*, 2, 136.
- Astrup, P., Jørgensen, K., Siggaard-Andersen, O. and Engel, K. 1960  
*Lancet*, 1, 1035.
- Auld, P.A.M., Rudolph, A.J., Avery, M.E., Cherry, R.B., Drorbaugh, J.E.,  
 Kay, J.L. and Smith, C.A. 1961 *Amer. J. Dis. Child.*, 101, 713.
- Avery, M.E. and Drolette, M. 1958 *Lancet*, 2, 960.
- Avery, M.E. and Oppenheimer, E.H. 1960 *J. Pediat.*, 57, 553.
- Avery, M.E. 1962 *Pediatrics*, 30, 324.
- Avery, M.E. The Lung and its Disorders in the Newborn Infant.  
 Philadelphia, W.B. Saunders Company, 1964.
- Bailey, N.T.J. Statistical Methods in Biology. London, The English  
 Universities Press Ltd. 1959.
- Baird, D. 1964 *J. Pediat.*, 65, 909.
- Barrie, H. 1960 *Brit. med. J.*, 1, 420.
- Barrie, H. 1962 *Lancet*, 2, 92.

- Bausan, W.A. and Nadelhaft, J. 1958 *Pediatrics*, 21, 813.
- Bausan, W.A. 1959 *Pediatrics*, 24, 194.
- Beard, A.G., Panos, T.C., Burroughs, J.C., Maranigan, B.V. and Ostalay, A.G. 1963 *J. Pediat.*, 63, 361.
- Behrle, F.C., Gibson, D.M. and Miller, H.C. 1951 *Pediatrics*, 7, 782.
- Benirschke, K. 1960 *Amer. J. Dis. Child.*, 99, 714.
- Benson, F. and Galander, O. 1959 *Acta Paediat.*, 48, Suppl. 118, 49.
- Berfenstam, R., Edlund, T. and Zettergren, L. 1958 *Acta Paediat.* 47, 82.
- Berggren, S.M. 1942 *Acta physiol. scand.*, 4, Suppl. 11.
- Bernstein, J. and Wang, J. 1961. *Amer. J. Dis. Child.*, 101, 390.
- Blanc, W.A. 1959 *Clin. Obstet. Gynec.*, 2, 705.
- Elystad, W., Landing, B.H. and Smith, C.A. 1951 *Pediatrics*, 8, 5.
- Elystad, W. 1956 (a) *Acta Paediat.*, 45, 103.
- Beda, D. and Muranyi, L. 1962 *Acta Paediat.*, 51, 490.
- Born, G.V.R., Daves, G.S., Mott, J.C. and Rennick, B.R. 1956 *J. Physiol.*, 132, 304.
- Boston, H.W., Geller, F., Cassady, G. and Smith, C.A. 1964 *J. Pediat.*, 65, 1043.
- Bound, J.P., Butler, N.R. and Sposter, W.G. 1956 *Brit. med. J.*, 2, 1191.
- Boutros, A.R. and Woodford, V.R. 1963 *Canad. Anaesth. Soc. J.*, 10, 428.
- Bower, B.D. and Cross, K.W. 1964 *Lancet*, 1, 274.
- Bonic, G. 1963 *Pediatrics*, 32, 1094.
- Branning, W.S. 1942 *J. clin. Invest.*, 21, 101.
- Briggs, J.M. and Hogg, G. 1958 *Pediatrics*, 22, 41.
- Bruns, P.D. and Shields, L.V. 1954 *Amer. J. Obstet. Gynec.*, 67, 1224.
- Bustow, K.C., Dr. P.H. and Klein, S.W. 1964 *Pediatrics*, 34, 163.
- Burnard, E.D. 1959 *Brit. med. J.*, 1, 134.

- Butler, N.R. and Bonham, D.G. Perinatal Mortality. London, Livingstone Ltd., 1963.
- Caffey, J. Pediatric X-Ray Diagnosis. 3rd ed. Chicago, The Year Book Publishers, 1956.
- Cedergren, B., Gyllensten, L. and Wernikell, J. 1959 Acta Paediat., 48, 477.
- Chapple, C.G. 1958 J. Amer. med. Ass. 166, 619.
- Chernick, V. and Avery, M.E. 1963 Pediatrics, 32, 816.
- Chernick, V., Heldrich, F. and Avery, M.E. 1964 J. Pediat., 64, 330.
- Chu, J., Clements, J.A., Gotten, E., Klaus, M.H., Sweet, A.Y., Thomas, M.A. and Tooley, W.H. 1965 Pediatrics, 35, 733.
- Chuang, K.A. 1962 Amer. J. Dis. Child., 103, 718.
- Claireaux, A.E. 1953 Lancet, 2, 749.
- Claireaux, A.E. in Modern Trends in Paediatrics (Second series). Helzel and Tizard ed. London, Butterworth, 1958.
- Clements, J.A. 1957 Proc. Soc. exp. Biol., 95, 170.
- Clifford, S.H. in Advances in Pediatrics, Levine, S.Z. ed. Chicago, Year Book Publishers, 1957.
- Cochran, W.D., Levison, H., Muirhead, D.M., Boston, R.W., Wang, C.S.C. and Smith, C.A. 1965 New Engl. J. Med., 272, 347.
- Cohen, M.M., Weintraub, D.H. and Lilienfeld, A.M. 1960 Pediatrics, 26, 42.
- Golgan, F.J., Eldrup-Jorgensen, S. and Lawrence, R.M. 1960 J. Amer. med. Ass., 173, 1557.
- Cook, C.D., Cherry, R.B., O'Brien, D., Karlberg, P. and Smith, C.A. 1955 J. clin. Invest., 34, 975.
- Cook, C.D., Sutherland, J.M., Segal, S., Cherry, R.B., Mead, J., McKelroy, M.B. and Smith, C.A. 1957 J. clin. Invest., 36, 440.
- Cook, C.D., Barrie, H. and Avery, M.E. in Advances in Pediatrics, Levine, S.Z., Chicago, Year Book Publishers, 1960.
- Cook, C.D., Drinker, P.A., Jacobson, H.N., Levison, H. and Strang, L.B. 1963 J. Physiol., 169, 10.

- Cook, G.D. and Cochran, W.D. 1964 *New Engl. J. Med.*, 270, 673.
- Cooke, W.D.D. 1960 *Med. J. Aust.*, 1, 847.
- Cort, R.L. 1962 *Acta Paediat.*, 51, 313.
- Cox, L.W. 1963 *Lancet*, 1, 841.
- Craig, J.M., Fenton, K. and Gitlin, D. 1958 *Pediatrics*, 22, 847.
- Craig, J.M. 1963 *Amer. J. Dis. Child.*, 106, 174.
- Cross, K.W. and Oppé, T.E. 1952 *J. Physiol.*, 116, 168.
- Crosse, V.M. 1957 *Ann. Paed. Fenn.* 5, 153.
- Gyvin, K.B. 1965 *Acta Paediat. Scand. Suppl.* 159, 65.
- Danks, D.M. and Stevens, L.H. 1964 *Lancet*, 2, 499.
- Davis, J.A. 1963 *Lancet*, 2, 1385.
- Daves, G.S., Jacobsen, H.N., Mott, J.C., Shelley, H.J. and Stafford, A. 1963 *J. Physiol.*, 169, 167.
- Daves, G.S., Hibbard, E. and Windle, W.F. 1964 *J. Pediat.*, 65, 801.
- Daves, G.S. 1965 *Abstr. Wld. Med.* 37, 73.
- Dawkins, M.J.R. in *Nutricia Symposium on The Adaptation of the Newborn Infant to extra-uterine Life* Leiden, Stenfert Kroese, 1964, p. 215.
- Day, R.L., Caliguiri, L., Kamenski, C. and Ehrlich, F. 1964 *Pediatrics*, 34, 171.
- De T-D and Anderson, G.W. 1953 *Obstet. gynec. Survey*, 8, 1.
- Deliveria-Papadopoulos, M. and Syver, P.R. 1964 *Arch. Dis. Childh.*, 39, 481.
- Deliveria-Papadopoulos, M., Levison, H. and Syver, P.R. 1964 *Arch. Dis. Childh.*, 40, 474.
- Bobbs, H.A., Franklin, R.R., Henley, W.S. and Desmond, M.M. 1961 *Circulation*, 24, 920.
- Donald, I. and Lord, J. 1953 *Lancet*, 1, 9.
- Donald, I. and Steiner, R.H. 1953 *Lancet*, 2, 846.
- Donald, I., Kerr, M.M. and Macdonald, I.R. 1958 *Scot. med. J.*, 3, 151.

- Downing, S.E., Talner, N.S. and Gardner, T.H. 1963 Amer. J. Physiol., 208, 237.
- Drillien, C.M. The Growth and Development of the prematurely born Infant. Edinburgh, Livingstone Ltd., 1964.
- Driscoll, S.G., Benirschke, K. and Curtis, G.W. 1960. Amer. J. Dis. Child., 100, 818.
- Driscoll, S.G. and Smith, G.A. 1962 Pediat. Clin. N. Amer., 9, 325.
- Dunn, P.M. 1965 Arch. Dis. Childh., 40, 62.
- Eliot, M.M. 1958 J. Amer. med. Ass., 167, 945.
- Ellis, K. and Madelhaft, J. 1957 Amer. J. Roentgenol., 78, 444.
- Emery, J.L. 1956 Lancet, 1, 405.
- Eason, Y., Giuntini, C., Lewis, M.L., Morris, T.O., Ferrer, M.I. and Harvey, R.M. 1964 J. clin. Invest., 43, 1146.
- Farber, S. and Sweet, L.K. 1931 Amer. J. Dis. Child., 42, 1372.
- Farquhar, J.W. 1962 Arch. Dis. Childh., 37, 321.
- Fearon, B., Smith, C., Delivoria-Papadopoulos, M., Levinson, H. and Swyer, P.R. 1964 Ann. Otol. (St.Louis) 73, 1082.
- Feinberg, S.B. and Goldberg, M.E. 1957 Radiology, 68, 185.
- Frailton, J.M.G. and Kitchen, W.H. 1962 Med. J. Aust., 2, 941.
- Gairdner, D. in Recent Advances in Paediatrics, 3rd ed. Gairdner, D. ed. London, Churchill, 1965.
- Gambino, S.R. 1961 Amer. J. clin. Path., 35, 175.
- Gandy, G., Grann, L., Cunningham, M., Adamsens, K.Jr. and James, L.S. 1964 Pediatrics, 34, 192.
- Gellis, S.S. and Hsia, D.Y. 1959 Amer. J. Dis. Child., 97, 1.
- Gitlin, D. and Craig, J.M. 1956 Pediatrics, 17, 64.
- Gomes, M.F. and Graven, S.N. 1964 Pediatrics, 34, 877.
- Graven, S.N. and Misenheimer, H.R. 1965 Amer. J. Dis. Child., 109, 489.
- Gregg, R.H. and Bernstein, J. 1961 Amer. J. Dis. Child., 102, 871.

- Gribetz, I., Frank, N.R. and Avery, M.E. 1959 *J. clin. Invest.*,  
38, 2168.
- Gruenwald, P. 1955 *Obstet. and Gynec.* 6, 471.
- Gruenwald, P., Nitowsky, H.M. and Siegel, I.A. 1963 *N.Y. St. J. Med.*,  
63, 277.
- Gruenwald, P. 1964 *Acta Paediat.*, 53, 470.
- Gruenwald, P. 1964 (a) *Pediatrics*, 34, 157.
- Gupta, J.M. 1965 *Lancet*, 1, 734.
- Haddad, H.M., Hsia, D.Y. and Gellis, S.S. 1956 *Pediatrics*, 17, 204.
- Hannan, L. 1939 *Ann. intern. Med.* 13, 923.
- Hanley, W.B., Braudo, M. and Swyer, P.R. 1963 *Canad. med. Ass. J.*,  
89, 375.
- Hardie, G., Heene, H. de V. and Kench, J.E. 1965 *Lancet*, 2, 876.
- Harris, L.E. and Steinberg, A.G. 1954 *Pediatrics* 14, 314.
- Harris, G.B.C. 1963 *Radiol. Clin. N. Amer.*, 1, 497.
- Heald, F. and Wilder, T.S. 1949 *J. Pediat.*, 34, 325.
- Hedley-Whyte, J. and Laver, M.B. 1964 *J. appl. Physiol.*, 19, 901.
- Heene, H. de V., Wittmann, W. and Malan, A.F. 1963 *S. Afr. med. J.*,  
37, 123.
- Heimer, C.B., Cutler, R. and Freedman, A.M. 1964 *Amer. J. Dis. Child.*,  
108, 122.
- Hobelth, M. 1965 *Acta Paediat. Scand. Suppl.* 159, 60.
- Hochheim, K. 1903. Quoted by De T-D and Anderson, G.W. 1953  
*Obstet. gynec. Surv.* 8, 1.
- Howie, V.M. and Wood, A.S. 1957 *J. Pediat.*, 50, 6.
- Hutchison, J.H., Kerr, M.M., McPhail, M.F.M., Douglas, T.A., Smith, G.,  
Norman, J.N. and Bates, E.H. 1962 *Lancet*, 2, 465.
- Hutchison, J.H., Kerr, M.M., Douglas, T.A., Inall, J.A. and Crosbie, J.C.  
1964 *Pediatrics*, 33, 956.
- Inall, J.A., Bluhm, M.M., Kerr, M.M., Douglas, T.A., Hope, G.S. and  
Hutchison, J.H. 1963 *Arch. Dis. Childh.*, 40, 480.

- Irving, F.C. in Perinatal Mortality. Butler, N.R. and Bonham, D.G. ed., London, Livingstone Ltd., 1963.
- Jaco, N.T. 1963 *Pediatrics*, 32, 922.
- James, L.S. and Howe, R.D. 1957 *J. Pediat.*, 51, 5.
- James, L.S. 1959 *Pediatrics*, 24, 1069.
- James, L.S. and Adansons, K. Jr., 1964 *New Engl. J. Med.*, 271, 1352.
- Johnson, W.C. and Meyer, J.R. 1925 *Amer. J. Obstet. Gynec.* 9, 151.
- Jelly, H., Molyneux, P. and Howell, D.J. 1962 *J. Pediat.*, 60, 889.
- Kaiser, I.H. 1964 *Amer. J. Obstet. Gynec.*, 90, 638.
- Kaplan, S.A. 1962 *Amer. J. Dis. Child.*, 103, 1.
- Kaplan, S.A., Fox, R.P. and Clark, L.C. 1962 *Amer. J. Dis. Child.*, 103, 4.
- Karlberg, P., Geck, C.D., O'Brien, D., Cherry, R.B. and Smith, C.A. 1954. *Acta Paediat.*, 43, Suppl. 100, 397.
- Karlberg, P. and Gelander, O. in Recent Advances in Paediatrics. 3rd ed. Gairdner, D. ed., London, Churchill, 1963.
- Keitel, H.G. 1959 *Amer. J. Dis. Child.* 97, 583.
- Keith, J.D., Rose, V., Braudo, N. and Rowe, R.D. 1961 *J. Pediat.*, 59, 167.
- Kerpel-Frenius, H., Varga, F. and Bata, G. 1964 *Arch. Dis. Childh.*, 39, 473.
- Kirschbaum, T.H. 1964 *Amer. J. Obstet. Gynec.*, 88, 823.
- Kottler, R.E., Malan, A.F. and Heese, H. de V. 1964 *S. Afr. J. Radiol.*, 2, 36.
- Kovalcik, V. 1963 *J. Physiol.*, 169, 185.
- Landing, B.H. 1957 *Pediatrics*, 19, 217.
- Latham, E.F., Nesbitt, R.E.L. and Anderson, G.W. 1955 *Bull. Johns Hopk. Hosp.*, 96, 173.
- Laughlin, D.E., McDonald, J.S. and Bedell, G.N. 1964 *J. Lab. clin. Med.*, 64, 330.
- Leape, L.L. and Longino, L.A. 1964 *Pediatrics*, 34, 246.

- Levine, O.R. and Klumenthal, S. 1961 Amer. J. Dis. Child., 102, 467.
- Levison, H., Boston, R.W., Muirhead, D.M., Wang, C.S.C., Weiss, J.B. and Smith, C.A. 1964 Amer. J. Obstet. Gynec., 88, 795.
- Lieberman, J. 1963 Amer. J. Med., 35, 443.
- Lubchenco, L.O. 1959 Pediatrics, 24, 996.
- McKay, R.J. Jr. and Smith, C.A. in Textbook of Pediatrics, Nelson, W.E. ed. Philadelphia, W.B. Saunders Co., 1959, p. 323.
- McNicol, M.W. and Campbell, E.J.H. 1965 Lancet, 1, 336.
- Malan, A.F., Evans, A. and Heese, H. de V. 1965 S. Afr. med. J., 39, 575.
- Martin, J.K. 1963 Canad. med. Ass. J., 89, 995.
- Maxwell, G.M., Rowe, G.G., Afonso, S., Crompton, C.W. and Castillo, G.A. 1959 Clin. Res. 7, 387.
- Meschan, I., Marvin, H.N., Gordon, V.H. and Regnier, G. 1953. Radiology, 60, 383.
- Miller, H.C. and Hamilton, T.R. 1949 Pediatrics 3, 735.
- Miller, H.C. and Jennison, M.H. 1950 Pediatrics, 5, 7.
- Miller, H.C. 1957 Pediat. Clin. N. Amer. 4, 17.
- Miller, H.C. 1957 (a) Pediatrics 20, 817.
- Miller, H.C. and Smull, N.W. 1957 Pediatrics, 19, 224.
- Miller, H.C., Behrle, F.C., Smull, N.W. and Elm, R.D. 1957 Pediatrics, 19, 387.
- Miller, H.C., Behrle, F.C. and Smull, N.W. 1958 Pediatrics, 22, 665.
- Miller, H.C., Behrle, F.C. and Smull, N.W. 1959 Pediatrics 23, 676.
- Miller, H.C. 1962 J. Pediat., 61, 2.
- Miller, H.C. 1962 (a) J. Pediat., 61, 9.
- Miller, H.C. 1963 Pediatrics, 31, 573.
- Mitchell, R.G. 1964 Arch. Dis. Childh., 39, 73.
- Moore, C.E., Kay, J.L., Desmond, M.M. and Dutton, R.V. 1960 J. Pediat., 57, 824.

- Moss, A.J., Duffie, E.R. and Emmanouilides, G.C. 1963 *Pediatrics*, 32, 175.
- Moss, A.J., Duffie, E.R. and Fagan, L.M. 1963 (a) *J. Amer. med. Ass.*, 184, 48.
- Moss, A.J., Emmanouilides, G.C., Adams, F.H. and Chuang, K. 1964 *Pediatrics*, 33, 937.
- Mott, J.C. 1961 *Brit. med. Bull.*, 17, 144.
- Nahas, G.G. 1962 *Pharmacol. Rev.*, 14, 447.
- Neligan, G.A. and Smith, C.A. 1960 *Pediatrics*, 26, 735.
- Nelson, N.M., Prod'hom, L.S., Lipsitz, P.J., Cherry, R.B. and Smith, C.A. 1961 *Amer. J. Dis. Child.*, 102, 517.
- Nelson, N.M., Prod'hom, L.S., Cherry, R.B., Lipsitz, P.J. and Smith, C.A. 1962 *Pediatrics* 30, 975.
- Nelson, N.M., Prod'hom, L.S., Cherry, R.B., Lipsitz, P.J. and Smith, C.A. 1963 *J. appl. Physiol.*, 18, 534.
- Nelson, N.M., Prod'hom, L.S., Cherry, R.B. and Smith, C.A. 1964 *J. clin. Invest.*, 43, 606.
- Neustein, H.B. and van Breemen, V.L. 1956 *Amer. J. Path.*, 32, 613.
- Nicolopoulos, D.A. and Smith, C.A. 1961 *Pediatrics*, 28, 206.
- Nixon, W.C.W. in Perinatal Mortality, Butler, N.R. and Bonham, D.G. ed. London, Livingstone Ltd., 1963.
- Opie, L.H., Kadas, T. and Govers, W. 1963 *Lancet*, 2, 551.
- Oppy, T.E., Priestley, B.L. and Redstone, D. 1963 *Pediat. Clin. N. Amer.*, 12, 723.
- Oski, F.A., Allen, D.M. and Diamond, L.K. 1963 *Pediatrics*, 31, 297.
- Östalay, A.G. and Beard, A.G. 1963 *J. Pediat.*, 63, 530.
- Pattle, R.E. 1955 *Nature*, 175, 1125.
- Pattle, R.E., Claireaux, A.E., Davies, P.A. and Cameron, A.H. 1962 *Lancet*, 2, 469.
- Payne, W.W. and Acharya, P.T. 1963 *Arch. Dis. Childh.*, 40, 436.
- Perry, R.E., Hodgman, J. and Cass, A.B. 1963 *J. Pediat.*, 62, 838.

Peters, J. and Van Slyke, D.D. Quantitative Clinical Chemistry,  
Vol. II Methods, Baltimore, Williams and Wilkins Co., 1932.

Peterson, H.G. Jr. and Pendleton, M.E. 1955 Amer. J. Roentgenol.,  
74, 800.

Phillips, K.G., Armstrong, J.G. and Delta, B.G. 1959 Canad. med. Ass. J.  
80, 800.

Pineus, J.B., Gittleman, I.F., Saito, M. and Sobel, A.E. 1956 Pediatrics,  
18, 39.

Potter, E.L. in Advances in Pediatrics, Levine, S.S. ed. Chicago,  
The Year Book Publishers, 1953.

Prod'hom, L.S. in Naticia Symposium on The Adaptation of the Newborn  
Infant to extra-uterine life. Leiden, Stenfort Krees, 1964.

Prod'hom, L.S., Levison, H., Cherry, R.B., Drorbaugh, J.E., Hubbell, J.P.  
and Smith, C.A. 1964 Pediatrics, 33, 682.

Prod'hom, L.S., Levison, H., Cherry, R.B. and Smith, C.A. 1965  
Pediatrics 35, 662.

Prosser, R. 1964 Arch. Dis. Childh., 39, 236.

Reardon, H.S., Field, S., Vega, L., Carrington, E., Arey, J. and  
Baumann, M.L. 1957 Amer. J. Dis. Childh., 94, 558.

Reynolds, E.O.R., Jacobson, H.M., Motoyama, H.K., Kikkawa, Y.,  
Craig, J.M., Orsalesi, M.M. and Cook, C.D. 1965 Pediatrics, 35, 382.

Robertson, B. 1963 Acta Paediat. 52, 569.

Robertson, B., Tunell, R. and Rudhe, U. 1964 Acta Paediat., 53, 433.

Robillard, E., Alarie, Y., Dagenais-Peruse, P., Baril, H. and Guilbeault, A.  
1964 Canad. med. Ass. J., 90, 55.

Roe, B.B. and Stephens, H.B. 1956 J. thorac. Surg., 32, 279.

Rogers, W.S., Gables, C. and Gruenwald, P. 1956 Amer. J. Obstet. Gynec.  
71, 9.

Rosahn, P.D. and Sheanakul, C. 1961 Amer. J. Dis. Childh., 102, 236.

Rosenthal, T.B. 1948 J. biol. Chem., 173, 25.

Rowe, G.G., McKenna, D.H., Jaramillo, C.V. and Grumpton, C.W. 1964  
Amer. J. med. Sci., 248, 424.

Rudolph, A.J. and Smith, C.A. 1960 J. Pediat., 57, 905.

- Rudolph, A.M., Drorbaugh, J.E., Auld, P.A.M., Rudolph, A.J., Nadas, A.S.  
Smith, G.A. and Hubbell, J.P. 1961 *Pediatrics*, 27, 551.
- Sahga, G.A., Neville, W.K. and Del Guercio, L.R.M. 1961  
*Surgery*, 50, 547.
- Sara, G. 1965 *Med. J. Aust.*, 1, 99.
- Schaffer, A.J., Markowitz, M. and Perlman, A. 1955 *J. Amer. med. Ass.*,  
159, 663.
- Schaffer, A.J. *Diseases of the Newborn*, Philadelphia, W.B. Saunders Co. 1960
- Scholander, P.F. 1947 *J. biol. Chem.*, 167, 235.
- Schultze, G. 1958 *Radiology*, 70, 230.
- Scott, J.M. 1965 *Arch. Dis. Child.*, 40, 426.
- Severinghaus, J.W. 1958 *J. appl. Physiol.*, 12, 485.
- Severinghaus, J.W. and Bradley, A.F. 1958 *J. appl. Physiol.*, 13, 515.
- Shallard, M.A. and Williams, A.L. 1965 *Med. J. Aust.*, 1, 540.
- Shelley, H.J. 1964 *Brit. med. J.*, 1, 273.
- Shepard, F., Gray, J. and Stahlman, M. 1964. *J. Pediat.*, 65, 1078.
- Siggaard-Andersen, O. *The Acid-base Status of the Blood* 2nd ed.  
Copenhagen, Munksgaard, 1964.
- Silver, H.K. and Nyhan, W.L. 1954 *Pediatrics*, 14, 666.
- Silverman, W.A. and Andersen, D.H. 1956 *Pediatrics*, 17, 1.
- Silverman, W.A. and Elans, W.A. 1957 *Pediatrics*, 20, 477.
- Silverman, W.A. and Silverman, R.H. 1958 *Lancet*, 2, 588
- Singer, R.B. and Hastings, A.B. 1948 *Medicine*, 27, 223.
- Sivanesan, S. 1961 *J. Pediat.*, 59, 600.
- Smith, G.A., Fedkin, S., Young, W., Minkowski, A. and Gushman, N. 1949.  
*Pediatrics*, 3, 34.
- Smith, G.A. *The Physiology of the Newborn Infant*. 3rd ed. Oxford,  
Blackwell Scientific Publications, 1959.
- Smith, G.A. in *Nutricia Symposium on The Adaptation of the Newborn  
Infant to extra-uterine life*. Leiden, Stenfort Kroeese, 1964.

- Smith, G.A. 1965 *Pediatrics*, 36, 257.
- Snyder, F.F. 1961 *Obstet. and Gynec.*, 18, 677.
- Stahlman, M., Young, W. and Payne, G. 1962 *Amer. J. Dis. Child.*, 104, 526.
- Stahlman, M.T., Young, W.C. and Payne, G. 1962 (a) *Sth. med. J.*, 55, 1320.
- Stahlman, M., Young, W.C., Payne, G.A. and Gray, J. 1963. *J. Pediat.*, 63, 862.
- Stahlman, M., Le Quire, V.S., Young, W.C., Merrill, R.E., Birmingham, R.T., Payne, G.A. and Gray, J. 1964 *Amer. J. Dis. Child.*, 108, 373.
- Stahlman, M.T. 1964 *Pediat. Clin. N. Amer.*, 11, 363.
- Steiner, R.E. 1954 *Brit. J. Radiol.*, 27, 491.
- Stern, L. and Lind, J. 1960 *Ann. Rev. Med.*, 11, 113.
- Stern, L. in Boston, R.W., Geller, F., Cassidy, G. and Smith, G.A. 1964 *J. Pediat.*, 65, 1043.
- Strang, L.B., Andersen, G.S. and Platt, J.W. 1957 *Lancet*, 1, 934.
- Strang, L.B. and MacLeish, M.H. 1961 *Pediatrics*, 28, 17.
- Strang, L.B. 1963 *Brit. med. Bull.*, 19, 45.
- Sutherland, J.M., Oppé, T.E., Lacey, J.F. and Smith, G.A. 1959 *Amer. J. Dis. Child.*, 98, 24.
- Sutin, G.J., Horner, R., Heese, H. de V. and Malan, A.F. 1963 *Arch. Dis. Childh.*, 40, 402.
- Swyer, P.R. 1960 *Canad. med. Ass. J.*, 82, 347.
- Thomas, D.V., Fletcher, G., Sunshine, P., Schafer, I.A. and Klaus, M.H. 1963. *J. Amer. med. Ass.*, 193, 183.
- Thomsen, A. 1964 *Acta Paediat.*, 53, 237.
- Tizard, J.P.M. in Rudolph, A.J. and Smith, G.A. 1960. *J. Pediat.*, 57, 905.
- Tizard, J.P.M. 1962 *Proc. roy. Soc. Med.*, 55, 772.
- Tizard, J.P.M. in Nutricia Symposium on The Adaptation of the Newborn Infant to extra-uterine Life Leiden, Stenfert Kroese, 1964.
- Tizard, J.P.M. 1964 (a) Personal communication

- Teoley, W., Gardner, R., Thung, N. and Finley, T. 1961  
Fed. Proc., 20, 428.
- Torres, G.E. 1963 J. appl. Physiol., 18, 1008.
- Treelstra, J.A., Jenxis, J.H.P., Visser, H.K.A. and Van der Vlugt, J.J.  
in Nutricia Symposium on The Adaptation of the Newborn Infant to  
extra-uterine Life Leiden, Stenfert Kroese, 1964.
- Tunell, R., Breberger, U. and Okman, L. 1965 Acta Paediat. Scand.,  
54, 199.
- Usher, R.H. 1959 Pediatrics, 24, 562.
- Usher, R.H. 1961 N.Y. St. J. Med., 61, 1678.
- Usher, R.H. 1961 (a) Pediat. Clin. N. Amer., 8, 525.
- Usher, R.H. 1962 Postgrad. Med., 31, 44.
- Usher, R. 1963 Pediatrics, 32, 966.
- Usher, R.H., McLean, F. and Maughan, G.B. 1964 Amer. J. Obstet. Gynec.  
88, 806.
- Van Slyke, D.D. and Sendroy, J. 1928 J. biol. Chem., 79, 781.
- Vines, R. 1963 Med. J. Aust., 1, 201.
- Wallgren, G., Barr, M. and Rudhe, U. 1964 Acta Paediat., 53, 1.
- Wang, G.S.C., Levison, H., Muirhead, D.M., Boston, R.W. and Smith, C.A.  
1963 J. Pediat., 63, 732.
- Warley, M.A. and Gairdner, D. 1962 Arch. Dis. Childh., 37, 455.
- Webb, J.K.G., John, T.J., Jadhav, M., Graham, M.D. and Walter, A. 1962  
J. Indian Pediat. Soc., 1, 193.
- West, J.B., Dollery, C.T. and Heard, B.E. 1964 Lancet, 2, 181.
- Younesai, M.K. 1962 Pediatrics, 29, 332.
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