A REVIEW OF THE RESPIRATORY DISTRESS SYNDROME IN CAPE TOWN

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The greatest loss of infant life occurs around the time of birth[1] and the mortality for first-day deaths has shown less improvement than for any other time during the first year.[2] '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.'[3] About two-thirds of all deaths in the newborn are associated with respiratory failure.[4-6] 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. Early and intensive care is essential if any reduction in mortality and morbidity is to be achieved. Paediatricians, and obstetricians also, should therefore be aware of the predisposing factors and be able to recognize respiratory distress in newborn infants.

The present report is based on observations on 217 infants suffering from the respiratory distress syndrome (RDS). The term RDS is used to describe a clinical picture of respiratory difficulty, irrespective of cause. A positive diagnosis of RDS is made on the presence of two or more of the following criteria:

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 and the classification of RDS in this unit have previously been discussed.[7] It is hoped that this review will provide useful information to those entrusted with the care of newborn infants.

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MATERIAL AND METHODS

The study covered a period of 12 months during which 217 infants with RDS were seen in the 5 maternity hospitals associated with the University of Cape Town Medical School. The total number of live births in the period under review was 10,412, of whom 1,306 (12·5%) were premature by weight (i.e. <2·5 kg.). The infants were representative of the population in Cape Town which is comprised of 3 different ethnic groups: White, Cape Coloured and Bantu.

Clinical examinations and observations were carried out by one of us (A.F.M.) with the assistance of the nursing and medical staff. Once the diagnosis of RDS had been made, appropriate investigations were carried out where possible to elucidate the pathology.[5,9] These included serial chest radiograms; acid-base and blood-gas analysis; lumbar puncture and electrocardiogram where indicated; and autopsy examination when permission could be obtained. The final diagnosis of the pulmonary pathology was made in 108 infants on radiographic and/or autopsy studies. The correlation between radiographic and histological diagnosis was higher than 90%. In the other 50% of distressed infants, chest radiography was not available because of lack of facilities in the maternity hospitals, nor were autopsies performed to determine the cause of RDS. Infants who developed respiratory distress for the first time after 24 hours are not included in this report. There were several cases of pneumonia, septicaemia and haemorrhagic disease which fell into this category.

General treatment consisted of nursing these infants in incubators with high temperature and humidity. Sufficient oxygen

TABLE I. SUMMARY OF 217 INFANTS WITH RESPIRATORY DISTRESS SYNDROME

Diagnosis	No.	% Total births		%		%		Wt. (kg.)	Apgar at 1 min.	Onset signs (hrs.)	Resp. rate	RR> 60 or signs (hrs.)	Grunting %	Grunting (hrs.)	Recession %	Cyanosis %	Mortality %	Average death (hrs.)
		Prem.	Term	M	F	Prem.	Term	Average										
Clinical hyaline membrane disease	54	3·5	0·1	65	35	78	22	1·97	5·1	1·0	67	58	83	16	80	93	55	36
Neonatal disseminated atelectasis	10	0·3	0·06	60	40	40	60	2·67	4·9	3·0	69	29	70	11	70	70	10	38
Pneumonia	13	0·5	0·08	69	31	54	46	2·53	4·6	1·2	60	37	85	17	38	69	69	34
Pneumothorax	5	0	0·05	80	20	0	100	3·19	5·8	0·5	72	70	60	3	80	80	0	—
Massive aspiration	5	0·3	0·03	60	40	40	60	2·42	3·5	1·8	47	28	100	20	100	100	100	32
Congenital heart disease	4	0·1	0·03	50	50	25	75	2·62	4·0	1·0	73	74	0	—	25	75	75	200
Cerebral	6	0·2	0·04	67	33	33	67	2·84	3·0	0·3	52	47	84	9	33	84	50	39
Miscellaneous	11	0·4	0·06	36	64	45	55	2·67	4·6	0·8	69	56	55	7	38	69	64	26
RDS undetermined	109	6·3	0·1	57	43	87	13	1·73	4·6	1·2	56	39	89	11	40	66	61	19
Total	217	12·8	1·65	60	40	69	31	2·10	4·7	1·2	58	37	69	14	50	68	50	35

was given to relieve cyanosis or maintain a PaO_2 of 100 mm.Hg. In the more severe cases intravenous fluid (dextrose and/or fructose) was administered via a scalp vein with the addition of sodium bicarbonate to correct metabolic acidosis. Antibiotics were only given when an umbilical arterial catheter was left *in situ* and when infection was suspected from the history or radiography.

RESULTS

Clinical Findings

A summary of the clinical details of the 217 infants with RDS is given in Table I. The over-all incidence of RDS is 2·08%, with no significant difference between the races. The incidence is much higher in premature than in 'term' infants. Males are more frequently affected than females ($P < 01$). The only exceptions to this are the congenital heart disease and miscellaneous groups. Apgar scores 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 respiratory rate (RR) was calculated from the onset of signs, until death or 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 RDS is 50% and accounts for 64% of early neonatal deaths. The largest category of all is the undetermined group.

Acid-Base Values

The average acid-base values in RDS are shown in Table II. These figures represent determinations on the initial examination. It was impossible to standardize the time and circumstances of acid-base determinations. The acid-base values will vary with age, degree of anoxia and preceding treatment, if any. The vast majority of readings were done in the first 12 hours of life. Normal values for premature and 'full term' infants are available for comparison.[10]

SPECIFIC DISORDERS OF RESPIRATION

It is proposed to discuss various causes of RDS separately, quoting the findings and figures from this study. Pertinent references to the literature will be indicated but not discussed.

Clinical Hyaline Membrane Disease

Hyaline membrane disease (HMD) is the most frequent cause of respiratory distress in newborn infants and accounts for 66% of deaths from pulmonary pathology.[2,5,11-14] A confident diagnosis can be made during life on the characteristic chest film illustrated in Fig. 1.[15] The term 'clinical hyaline membrane disease' (CHMD) is pre-

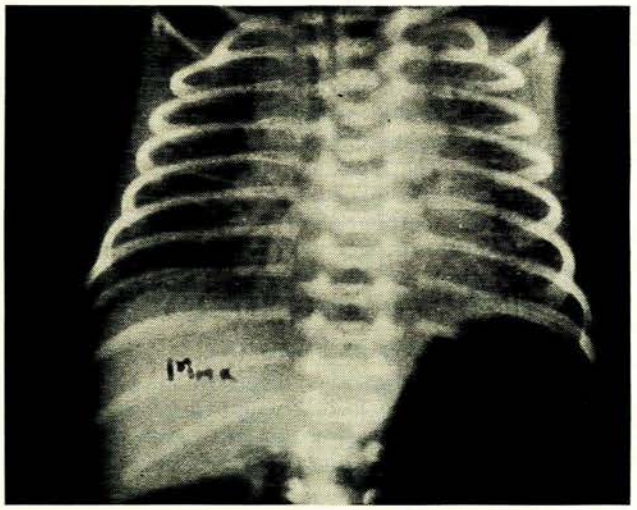

Fig. 1. See text.

TABLE II. RDS—AVERAGE INITIAL ACID-BASE VALUES

Diagnosis	No. of cases	pH	PCO_2 mm. Hg	Base excess mEq./l.	Buffer base mEq./l.	Standard HCO_3^- mEq./l.	Actual HCO_3^- mEq./l.
Clinical hyaline membrane disease	32	7·184	55·2	−8·5	38·5	17·5	19·9
Neonatal disseminated atelectasis	7	7·245	55·2	−6·2	41·7	19·3	21·9
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
RDS—undetermined	7	7·210	53·5	−7·7	40·6	18·2	20·2

ferred for a diagnosis during life. CHMD occurs only in infants born before term, with a higher incidence in males, infants of diabetic mothers and after delivery by caesarean section.[16] The clinical picture is one of tachypnoea, grunting, cyanosis, marked sternal and costal recession and peripheral oedema. The striking feature on auscultation is the diminished air entry, which is a most useful aid in clinical differentiation from other causes of RDS. A slow RR in the face of severe illness signifies a poor prognosis.[17-19] Apnoeic attacks are frequent and usually herald a fatal termination. The peak age of death is 30 hours, with very few deaths after 48 hours. Once an infant has attained 72 hours the prognosis is excellent, with 97% survival. In this study there was no statistical difference in the outcome between males and females. At autopsy the lungs are firm, purple-red and liver-like. On histological examination one finds profound alveolar atelectasis. The alveolar ducts are dilated and contain eosinophilic membranes in 71% of cases. A deficiency of surfactant (surface tension lowering agent) seems to be responsible for the condition. The underlying pathogenesis still needs further elucidation but the most acceptable theory at present is that there is some pulmonary vascular derangement in the affected infants. Pneumothorax occurred in 16% of infants, while intracranial haemorrhage was present in 22·5% of autopsies.

Arterial blood-gas analysis reveals profound hypoxaemia, variable hypercapnia and secondary metabolic acidosis. The biochemical values in CHMD have been submitted for publication.[20] The assessment of severity would appear to correlate best with the ambient oxygen requirements.[20] *Early* metabolic treatment with oxygen and sodium bicarbonate[21-24] will make the difference between survival and death in moderate severe illness. Severely affected infants succumb in spite of conventional therapy. A small number of the latter survive with assisted mechanical ventilation. The high mortality in this report reflects the lack of adequate management of these infants in the various maternity hospitals. The mortality rate for CHMD in the neonatal respiratory unit, Groote Schuur Hospital, during the same period was 40%.[21,22,25] CHMD remains the major problem in present-day neonatal paediatrics.

Neonatal Disseminated Atelectasis (NDA)

A radiographic appearance suggestive of an aspiration syndrome (Fig. 2) is called neonatal disseminated atelectasis.[26] In the initial stages these infants closely resemble those with mild to moderate CHMD, but recovery is more rapid. Most striking in these infants is the good air entry. The incidence of oedema, crepitations and apnoeic attacks are also lower.[20] Gestational maturity and birthweight are greater than for CHMD, while the low Apgar scores at one minute favour depression with possible aspiration of material. Only one infant required more than 40% ambient oxygen to relieve cyanosis, and metabolic acidosis was often corrected spontaneously. One infant labelled NDA on a single chest film died and autopsy showed that hyaline membranes were, in fact, present. The value of serial chest films in differential diagnosis should again be emphasized.[8] No cases of pneumothorax were seen despite the generalized emphysema in NDA.

Whether this condition is a separate entity or a variant of CHMD in more mature infants, is uncertain. Prod'hom *et al.*[27] described similar radiographic features in their type II HMD cases, all of whom survived. Others[21,23] have also noted that not all moderate HMD infants had significant radiological changes. The role of aspiration of clear fluid in the causation of respiratory distress is undetermined.[28] The practical value of this differentiation lies in the very good prognosis associated with the radiographic features of NDA.

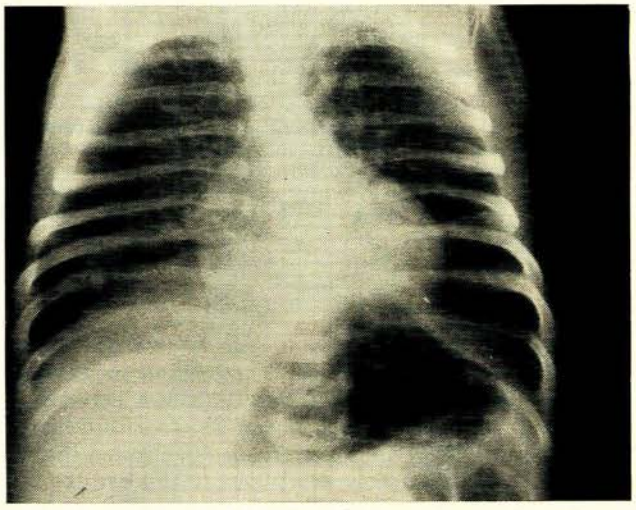

Fig. 2. See text.

Pneumonia

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 although it should be the easiest to eliminate.

Congenital pneumonia was diagnosed in 13 newborn infants in this study—5 during life and 8 at autopsy. An example of the radiographic appearance is shown in Fig. 3. The incidence of pneumonia in deaths from RDS was 13·8% and compares well with other reports.[11,13,14] Pneu-

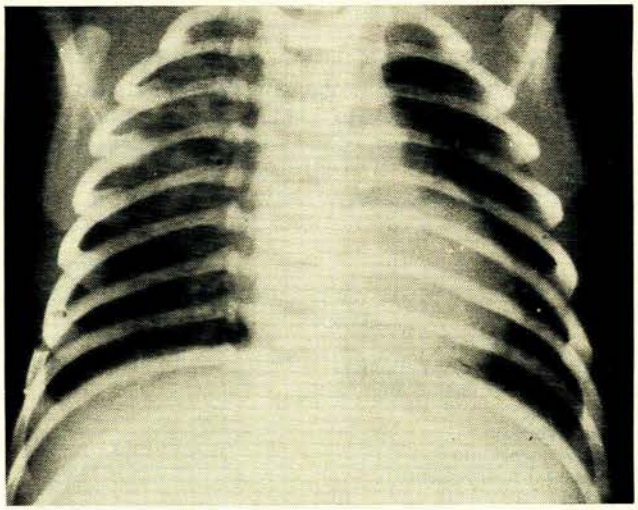

Fig. 3. See text.

monia is more common in males and in premature infants.[12,29] Signs of respiratory distress appear soon after birth and are probably indicative of ante- or intrapartum infection.[30] Grunting is present in 85% of cases and is the most consistent sign.[17,31] The other signs are tachypnoea and cyanosis (69%), but recession is not a prominent sign.[5,31] Focal crepitations[18] were present in 2 cases only. One acid-base determination was done on an acyanotic infant and showed a respiratory alkalosis.[32]

The most important associated obstetrical features are maternal pyrexia and prolonged rupture of the membranes.[33] It seems reasonable to investigate and observe infants born after rupture of membranes for more than 24 hours. Confirmation of a clinical diagnosis can be found in radiology or evidence of infection in the amnion, placenta or nose of the infant.[5,12,29] Antibiotic treatment should be prompt and vigorous and be effective against both Gram-negative and Gram-positive organisms. Bacteria isolated at autopsy from 2 patients were streptococcus and klebsiella respectively. Ampicillin and cloxallin together are used in this unit.

Pneumothorax

Recognition of pneumothorax in the newborn is very important as prompt treatment can be lifesaving in cases of tension. The detection of pneumothorax will depend on a high index of suspicion plus a knowledge of the predisposing factors and physical findings.[34] Radiographic confirmation is imperative (Fig. 4).

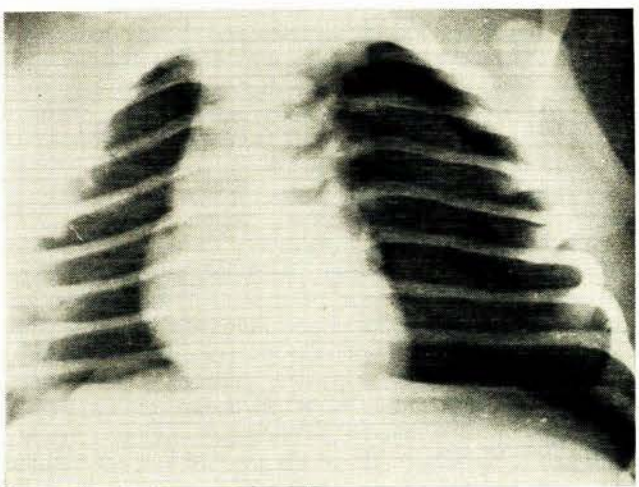

Fig. 4. See text.

The incidence of symptomatic spontaneous pneumothorax in this study was 0·05%. None of the infants was premature by weight. There is a strong male preponderance and in most instances the onset of distress occurs shortly after birth, if not in the delivery room itself. Aspiration of meconium and mucus is a predisposing cause due to unequal expansion of the lung during the first few breaths.[35] After rupture of alveoli, the air may tract to either the mediastinal or visceral pleura.

A prominent chest bulge on the side of the pneumothorax is the most characteristic finding. Associated with decreased air entry on the same side, tachypnoea and cyanosis, it is virtually diagnostic. Unusual irritability and restlessness is often present. Except for those with tension pneumothorax or meconium aspiration, the infants show little disturbance of their acid-base balance. High concentrations of ambient oxygen will facilitate the absorption of extrapulmonary air.[35] 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 recognized early and treated properly.

Massive Aspiration

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. Massive aspiration refers to those infants in whom it is felt that aspiration of amniotic fluid and its particulate matter (meconium in two and squames in three) was responsible for respiratory distress and death.

In affected infants the birthweight is usually over 2·5 kg.[23] and the majority show features of 'postmaturity' such as wrinkled and peeling skin and meconium staining.[25,36] The average respiratory rate was 55/min.[23,25] with grunting in all cases.[18] Although recession is present, the severity is mild.[18,25,37] Cyanosis, on the other hand, is a severe problem.[23] Crepitations may or may not be heard on auscultation.[25,28,37] Radiology will confirm the presence of any pulmonary abnormality. There is usually a hyperexpanded 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 hyper-aeration produce a honeycomb appearance (Fig. 5).

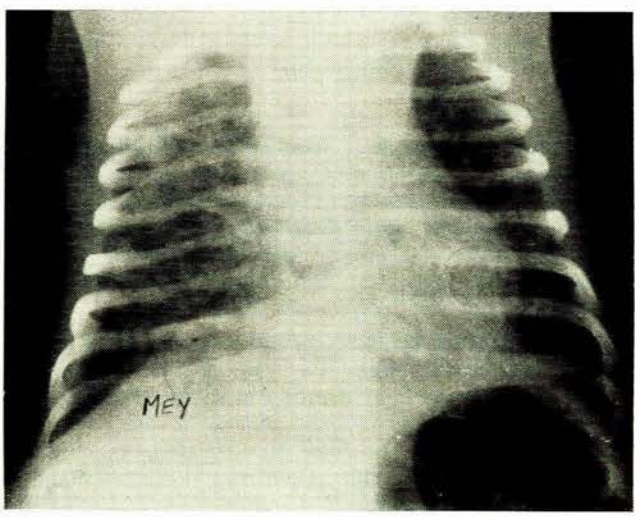

Fig. 5. See text.

A combined metabolic and respiratory acidosis is present.[23,38] The mortality in severe cases is high and pneumothorax a frequent complication.[36-38] Cor pulmonale is said to be common.[23] 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.[28] Treatment should be directed towards correcting anoxia and acidosis and treating cardiac failure.

Congenital Heart Disease

Congenital heart disease is an infrequent cause of RDS in the first 24 hours of life. The distress is characterized by tachypnoea and cyanosis with minimal recession and absent grunting.[25] The cyanosis is disproportionately severe for the degree of distress and retraction.[25,28] The chest radiogram may be abnormal. Fig. 6 illustrates how the

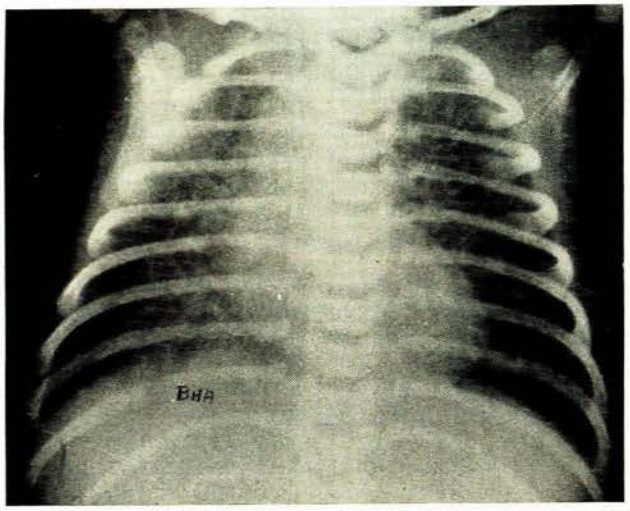

Fig. 6. See text.

fine mottling produced by severe pulmonary congestion may simulate primary pulmonary disease.[5] Auscultation of the heart is of limited value in differential diagnosis as murmurs may only become apparent later. An abnormal electrocardiogram is a helpful guide. The mortality here corresponds to the published figure of 75%.[25]

Cerebral Infants

Disturbance of cerebral function is often reflected in disturbance of respiration. Cerebral damage in the newborn may be due to intracranial haemorrhage or anoxia, sustained before or during delivery. Only severe intracranial lesions with cerebral depression cause RDS as defined in this unit. The majority of 'cerebral' infants have tachypnoea with respiratory alkalosis.[38]

The diagnosis of cerebral disturbance was made on the presence of clinical signs such as irritability, twitches, convulsions, apnoea and a full fontanelle. Primary pulmonary pathology was thought unlikely in the absence of marked grunting and recession. Radiographic examination shows normal lungs. Confirmation of a diagnosis of intracranial haemorrhage should be sought by spinal puncture. Males outnumber females especially in cases of intracranial haemorrhage,[39] while premature infants are at greater risk of intraventricular haemorrhage.[39,40] There is a high incidence of instrumental and breech delivery. Asphyxia and trauma are probably both causative factors. Treatment is that of the underlying pathology.

Miscellaneous Conditions

In 11 infants RDS was due to miscellaneous conditions as shown in Table III.

TABLE III. RDS—MISCELLANEOUS CONDITIONS

Condition	*Cases*	*Deaths*
Suspected HMD	3	1
Acute haemorrhage	2	2
Diaphragmatic hernia	2	2
Pulmonary haemorrhage	1	1
Pleural effusion	1	1
Unilateral atelectasis	1	0
Meningomyelocoele	1	0

Suspected Hyaline Membrane Disease

On 3 infants the final diagnosis was not established despite radiographic examination and an autopsy in one of them. Two recovered—one with a normal chest film and the other an abnormal film which could not be defined further. The third infant had characteristic clinical and radiological features of CHMD. A combined metabolic and respiratory acidosis was present. In order to relieve cyanosis, oxygen was administered until death occurred at 28 days. The pulmonary histological changes were thought to be due to HMD with secondary changes caused by the oxygen therapy.[41]

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 is similar to the pulmonary causes of RDS.[23,38] Pallor and falling haemoglobin and the lack of immaturity should aid the differential diagnosis. The mortality is high but completely reversible with early blood transfusion and sodium bicarbonate to control acidosis. It is, therefore, extremely important to recognize this condition.

Diaphragmatic Hernia

This was the cause of respiratory distress in 2 female premature infants. One never established adequate respiration and died at 4 hours. In the other, the bowel was reduced and the hernia closed surgically but she died postoperatively. The associated pulmonary hypoplasia[42,43] is a major obstacle in successful recovery after surgical repair. Great care should be taken in the resuscitation of these infants as traumatic pneumothorax results readily. Although a diaphragmatic hernia may be suspected clinically when a scaphoid abdomen and bowel sounds in the chest are present, radiology will show the true state of affairs.

Pulmonary Haemorrhage

Pulmonary haemorrhage not associated with other pathology was found in one infant only at autopsy. In other studies,[13,25,44,45] however, it was a fairly common pathological finding. It would appear that the diagnosis cannot be made during life. Very little is known about this condition and the aetiology is obscure.[28]

Pleural Effusions

Pleural effusions with pulmonary collapse were found at autopsy in one infant. Severe distress and cyanosis with

a RR of 35/min. had been present from birth. An additional feature was generalized oedema and death ensued at 10 hours. The pleural fluid was yellow in colour and contained a few cells. Perry *et al.*,[46] in 1963, found only 13 reported cases of pleural effusion, but stressed its importance because of the dramatic relief afforded by prompt thoracocentesis. It is agreed[28,37,46] that these are early cases of chylothorax and that the fluid only becomes chylous after milk feeds. The pathogenesis is unknown.

Unilateral Atelectasis

Unilateral atelectasis occurred in a premature infant delivered by caesarean section. Treatment was conservative 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.

Mild respiratory distress was present in an infant who also had a meningomyelocoele.

RDS—Undetermined

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 lower birthweights. The clinical picture and ccurse was similar to CHMD and, like others,[25] we feel that the majority probably fell into the HMD category. The acid-base values were also similar to CHMD. Some with birthweights below 1·0 kg. may have been due to pulmonary immaturity or primary atelectasis.[25]

SUMMARY

The clinical, radiological and pathological findings as well as initial acid-base values in 217 infants suffering from the respiratory distress syndrome of the newborn in Cape Town, are presented. The incidence is higher in premature and male infants but no significant difference is found between the races. In the light of this study the individual causes of the respiratory distress syndrome are discussed with brief reference to the literature.

We wish to thank the matrons and staff of the maternity hospitals for their interest and assistance; the paediatric registrars for clinical help; and the Department of Pathology, University of Cape Town, for autopsy studies. Clinical facilities were made available by Dr. J. G. Burger, Medical Superintendent of Groote Schuur Hospital, Mowbray Maternity and Peninsula Maternity Hospitals; Dr. E. Barrow, Medical Superintendent of St. Monica's Maternity Home and Dr. R. Nurok, Medical Superintendent of New Somerset Hospital. We are indebted to the Council for Scientific and Industrial Research for financial support and the Staff Research Fund, University of Cape Town and the Teaching Hospitals Board for equipment used. Dr. R. E. Kottler reviewed the chest films with us. Finally, we would like to express our gratitude to Prof. F. J. Ford for his encouragement of this project and his constructive criticisms of the findings and to Mrs. O. M. Cartwright for her help in the preparation of this manuscript.

REFERENCES

1. Eliot, M. M. (1958): J. Amer. Med. Assoc., **167**, 945.
2. Arey, J. M. and Dent, J. (1953): J. Pediat., **42**, 1.
3. Smith, C. A. (1964): In *Nutricia Symposium on The Adaptation of the Newborn Infant to Extra-Uterine Life*. Leiden: Stenfert Kroese.
4. Briggs, J. N. and Hogg, G. (1958): Pediatrics, **22**, 41.
5. Driscoll, S. G. and Smith, C. A. (1962): Pediat. Clin. N. Amer., **9**, 325.
6. Fearon, B., Smith, C., Delivoria-Papadopoulos, M., Levison, H. and Swyer, P. R. (1964): Ann. Otol. (St. Louis), **73**, 1082.
7. Malan, A. F. (1966): S. Afr. Med. J., **40**, 660.
8. Harris, G. B. C. (1963): Radiol. Clin. N. Amer., **1**, 497.
9. Dawes, G. S. (1965): Abstr. Wld Med., **37**, 73.
10. Malan, A. F., Evans, A. and Heese, H. de V. (1965): Arch. Dis. Childh., **40**, 645.
11. Bound, J. P., Butler, N. R. and Spector, W. G. (1956): Brit. Med. J., **2**, 1191.
12. Benirschke, K. (1960): Amer. J. Dis. Child., **99**, 714.
13. Sivanesan, S. (1961): J. Pediat., **59**, 600.
14. Butler, N. R. and Bonham, D. G. (1963): *Perinatal Mortality*. London: E. & S. Livingstone.
15. Donald, I. and Steiner, R. E. (1953): Lancet, **2**, 846.
16. Malan, A. F., Evans, A. and Heese, H. de V. (1966): S. Afr. J. Obstet. Gynaec., **4**, 13.
17. James, L. S. (1959): Pediatrics, **24**, 1069.
18. Usher, R. H. (1961): N.Y. St. J. Med., **61**, 1677.
19. Stahlman, M., Young, W. C., Payne, G. A. and Gray, J. (1963): J. Pediat., **63**, 862.
20. Heese, H. de V. and Malan, A. F. (1966): To be published.
21. Hutchison, J. H., Kerr, M. M., Douglas, T. A., Inall, J. A. and Crosbie, J. C. (1964): Pediatrics, **33**, 956.
22. Usher, R. (1963): *Ibid.*, **32**, 966.
23. Stahlman, M. T. (1964): Pediat. Clin. N. Amer., **11**, 363.
24. Boston, R. W., Geller, F., Cassady, G. and Smith, C. A. (1964): J. Pediat., **65**, 1043.
25. Hanley, W. B., Braudo, M. and Swyer, P. R. (1963): Canad. Med. Assoc. J., **89**, 375.
26. Kottler, R. E., Malan, A. F. and Heese, H. de V. (1964): S. Afr. J. Radiol., **2**, 36.
27. Prod'hom, L. S., Levison, H., Cherry, R. B. and Smith, C. A. (1965): Pediatrics, **35**, 662.
28. Avery, M. E. (1964): *The Lung and its Disorders in the Newborn Infant*. Philadelphia: W. B. Saunders.
29. Blanc, W. A. (1959): Clin. Obstet. Gynec., **2**, 705.
30. Bernstein, J. and Wang, J. (1961): Amer. J. Dis. Child., **101**, 350.
31. Schaffer, A. J., Markowitz, M. and Perlman, A. (1955): J. Amer. Med. Assoc., **159**, 663.
32. Boda, D. and Muranyi, L. (1962): Acta paediat. uppsala, **51**, 490.
33. Anderson, G. S., Green, C. A., Neligan, G. A., Newell, D. J. and Russel, J. K. (1962): Lancet, **2**, 585.
34. Malan, A. F. and Heese, H. de V. (1966): Acta paediat. scand., **55**, 224.
35. Chernick, V. and Avery, M. E. (1963): Pediatrics, **32**, 816.
36. Peterson, H. G. jnr. and Pendleton, M. E. (1955): Amer. J. Roentgenol., **74**, 800.
37. Schaffer, A. J. (1960): *Diseases of the Newborn*. Philadelphia: W. B. Saunders.
38. Usher, R. H. (1962): Postgrad. Med. J., **31**, 44.
39. Tizard, J. P. M. (1964): In *Nutricia Symposium on The Adaptation of the Newborn Infant to Extra-Uterine Life*. Leiden: Stenfert Kroese.
40. Donald, I., Kerr, M. M. and Macdonald, I. R. (1958): Scot. Med. J., **3**, 151.
41. Bruns, P. D. and Shields, L. V. (1954): Amer. J. Obstet. Gynec., **67**, 1224.
42. Roe, B. B. and Stephens, H. B. (1956): J. Thorac. Surg., **32**, 279.
43. Sabga, G. A., Neville, W. E. and Del Guercio, L. R. M. (1961): Surgery, **50**, 547.
44. Claireaux, A. E. *in* Holzel and Tizard, eds. (1958): *Modern Trends in Paediatrics* (2nd series). London: Butterworth.
45. Ahvenainen, E. K. (1959): J. Pediat., **55**, 691.
46. Perry, R. E., Hodgman, J. and Cass, A. B. (1963): *Ibid.*, **62**, 838.