THE RESPIRATORY DISTRESS SYNDROME OF THE NEWBORN.

Studies of blood gases and acid/base balance with the object of formulating principles of treatment.

by

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PREFACE

The work described in this thesis was carried out in the Department of Medicine, Cambridge University, by the courtesy of Professor J. S. Mitchell, Regius Professor of Physic. All the patients were under the care of Dr. D. M. T. Gairdner who supervised my research and to whom I am greatly indebted for constant help and advice.

CONTENTS

Introduction

Respiratory failure accounts for a large, if not the largest, percentage of deaths during the first 48 hours of life. During the last ten years a great deal of research has been devoted to this early respiratory failure. The syndrome has been known by different names at different times; hyaline membrane disease (because pulmonary hyaline membrane is a frequent autopsy finding), congestive pulmonary failure, vernix membrane disease, pulmonary syndrome, and more recently the respiratory distress syndrome. A vast literature on the subject has accumulated. Many new and interesting facts have come to light and although many new theories have been put forth to explain the syndrome, the cause is still unknown.

Although the cause of the respiratory distress syndrome is unknown, the clinical picture is a recognizable one, that of respiratory failure with certain characteristic features, rib and sternal recession, an expiratory moan and poor air entry. Physiologically, examination of arterial blood reveals varying degrees of oxygen lack

(O_2-unsaturation), CO_2 retention (raised P_{CO_2}) and acidosis (low pH). The aim of treatment must thus be to correct, as far as this may be possible, these consequences of respiratory failure, in order to give the baby optimal conditions for survival during what is, in a proportion of cases at least, a self-limited illness.

The aim of this study

In this study we have sought,

(1) to define the physiological disturbances found in the respiratory failure of the respiratory distress syndrome,

(2) to establish the principles which should govern the correction of these disturbances.

The main approach has been to make a detailed study of a relatively small number of cases, observing them from the earliest stages of the illness, until recovery or death, with serial measurements of four variables - the oxygen saturation, CO_2 tension, pH and bicarbonate of arterial blood.

Before describing our own results, we give a summary of what is already known about the subject under the following headings:

Respiratory Distress Syndrome

1. Definition.
2. Clinical findings.
3. Blood gas findings and acid/base status.
4. Other biochemical findings.
5. Pulmonary function tests.
6. E.C.G.
7. Radiology.

8. Differential diagnosis.
9. Mortality.
10. Pathology; hyaline membrane - historical review and composition of the membrane.
11. Aetiology of the respiratory distress syndrome.

1. Definition. A form of respiratory failure affecting newborn infants especially prematures, babies of diabetic mothers, and babies of mothers who have had antepartum haemorrhage. The condition is characterized by rapid respirations, rib and sternal recession on inspiration, a respiratory moan on expiration and poor air entry.

2. Clinical findings. Early workers believed that there was an initial symptom free period after birth, lasting anything from a few minutes to a few hours. This free period was then followed by the unmistakable picture described in the definition. Some observers feel that this latent period does not occur (James, 1959; Cantor et al., 1958). They insist that some evidence of respiratory difficulty can always be detected immediately after birth.

On auscultation, besides the diminished air entry, fine crackling rales are often heard.

In the early stages cyanosis is usually relieved by raising the ambient oxygen concentration.

Oedema is usually present at birth and becomes more pronounced as the condition becomes worse (Usher, 1959; Sutherland et al., 1959). Smull's data (1958) confirms that infants with respiratory distress have a larger percentage of body water.

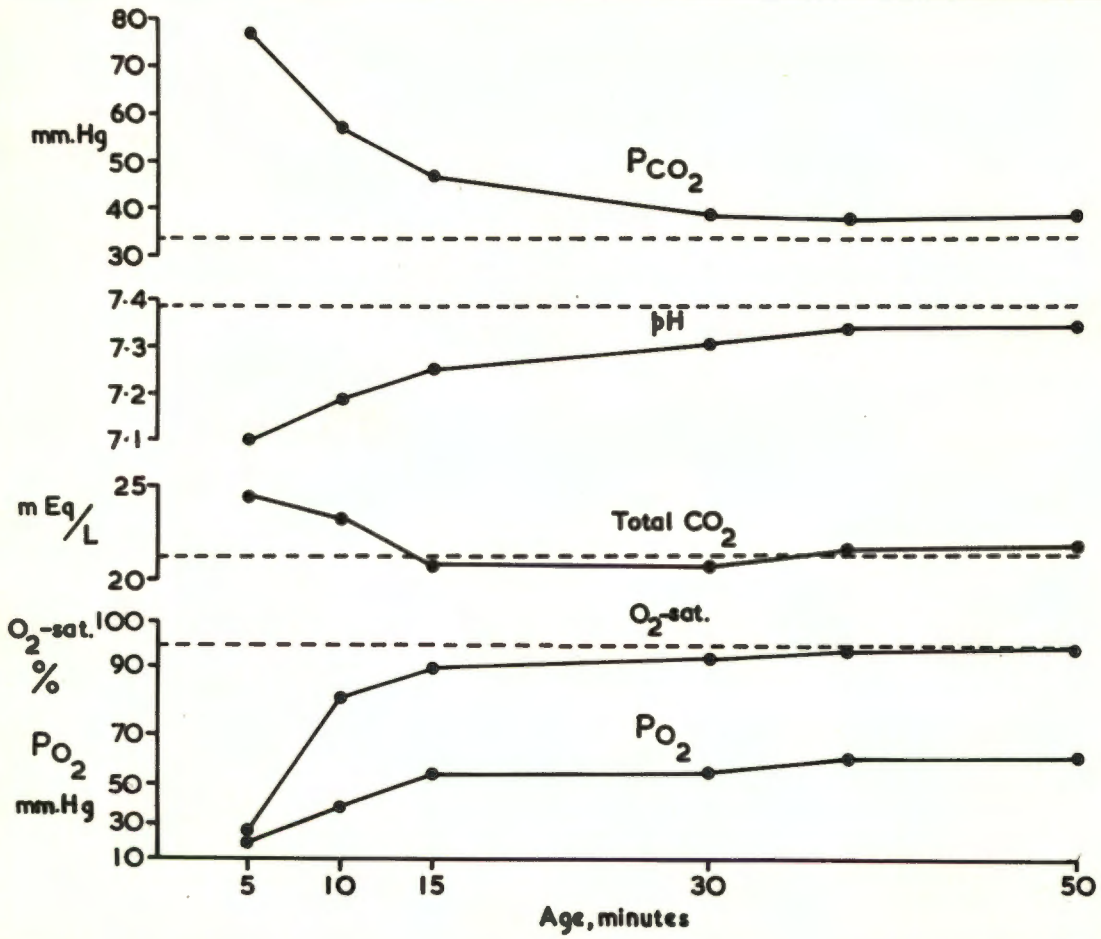


Fig. 1

Blood gas studies, average of 30 normal infants, in the first hour of life (T. K. Oliver et al., Pediatrics 1960, 50, 346).

Note pure respiratory acidosis recovering in first 10 minutes, also the low mean P_{O_2} despite normal O_2-saturation.

Karlberg (1960) has shown that the body temperature of babies with respiratory distress tends to be subnormal.

Flaccidity and unresponsiveness become evident terminally. If death does occur, it is usually between 12 and 48 hours. If the infant survives 72 hours, spontaneous recovery is the rule and there is no evidence of residual pulmonary damage.

3. Blood gas findings and acid/base status. Blood gas studies have been made on normal and distressed newborn infants (Reardon et al., 1950, 1960; Blystad, 1956; James, 1959). Reardon et al. thought that a respiratory and metabolic acidosis was present at birth in normal infants. The respiratory acidosis was corrected by the fourth hour of life. The metabolic acidosis is partially corrected in the first 24 hours by the elevation of the bicarbonate and buffer anions.

Recently, Oliver et al. (1961) have published results for the first hour of life (Fig. I illustrates this). These results differ from Reardon et al. They have shown that in normal infants delivered by vertex presentation the acid/base changes are essentially those of a pure respiratory acidosis. In depressed babies and babies born by caesarean section, a metabolic acidosis is superimposed. In normal infants the recovery from the acidosis is prompt, occurring in the first ten minutes of life. In section babies it took 20-40 minutes. They also found that although normal full term babies had a oxy-haemoglobin saturation of about 95% they nonetheless had moderate hypoxaemia as indicated by the mean P_{O_2} (arterial oxygen tension) of 61.7 mm. Hg, compared with a value of 100 mm. Hg in adults.

In the respiratory distress syndrome the blood gas findings and the acid/base status depend on the stage of the illness. The blood oxygen saturation is usually low and falls as the condition becomes worse. The P_{CO_2} is raised and the bicarbonate is lowered i.e. a combined respiratory and metabolic acidosis.

4. Other biochemical findings. Usher (1959) has emphasized that hyperkalaemia is a feature of the neonatal respiratory distress syndrome. This fits in well with the observations of Scribner et al. (1955), Simmons and Avedon (1959), and Giebisch et al. (1955) that a fall in pH results in a shift of potassium from the cells to the extra cellular space and a consequent rise in serum concentrations. This is true whether the reduction in pH is metabolic or respiratory in origin. When pH is controlled profound changes in P_{CO_2} or CO_2 content do not cause a potassium shift (Simmons and Avedon, 1959).

Nicolopoulos and Smith (1961) have shown that not only is there hyperkalaemia but there is also excessive excretion of sodium and nitrogen during the first 48 hours post-natally in infants with respiratory distress. The same phenomena may, however, occur to a lesser extent in premature infants or infants of diabetic mothers without distress and may occur to an even greater extent in extreme prematurity alone.

5. Pulmonary function tests. Cook and co-workers (1955, 1957) and Karlberg and co-workers (1954) have done pulmonary function tests on normal and distressed infants. They showed that in distressed babies

functional dead space was increased, and tended to be compensated by an increased minute volume. Compliance is markedly decreased. There is therefore increased energy expenditure for each breath. At least four times more energy may be used per breath in a severely distressed infant.

Stahlman (quoted by James, 1959) has shown that infants with respiratory distress revealed a somewhat lower diffusion capacity than had been found in normal infants.

6. Electrocardiographic changes. Usher (1959) described a series of E.C.G. changes in infants with respiratory distress. He attributed these changes to the hyperkalaemia found in the infants. Keith et al. (1961) did serial E.C.G. studies in babies with respiratory distress. They were of the opinion that the changes found suggested left ventricular overloading due to a patent ductus arteriosus.

7. Radiological findings. Donald and Steiner (1953) have described the radiological findings they consider typical. At first there is fine miliary mottling (ground glass appearance) more or less uniformly distributed throughout the lung fields. This picture appears within a few hours and is probably due to alveolar collapse. Caffey (1945) described a similar picture and claimed that it was a physiological phenomenon in prematures representing small areas of atelectasis. It called for no treatment and resolved within a few days or weeks. He ascribed this picture to structural immaturity of the alveolar buds. Donald and Steiner hold that these are not physiological. They are found in "hyaline membrane disease" proved at autopsy.

Ifthe clinical course is downhill the fine mottling becomes coarse and tends to coalesce. Ultimately the shadows become confluent until definite lobar and lobular consolidation and collapse are recognisable. If on the other hand the condition improves, the initial mottling slowly resolves and the lung fields become clear.

8. Differential diagnosis is usually not difficult. Sometimes disorders of the central nervous or gastro-intestinal systems may confuse the picture. The smallest or most profoundly depressed infants may be too feeble to have either retractions, a grunt or a rapid respiratory rate. Congenital heart disease in failure, neonatal pneumonia or infection, though rare compared with frequency of the respiratory distress syndrome, may present a similar appearance.

9. Mortality. Because the criteria for clinical diagnosis vary in different institutions, it is difficult to give accurate figures for the mortality rate. According to Bauman (1958) there is roughly a 60% mortality. Half of these showed hyaline membrane at autopsy. When death occurs, it is usually in the first 48 hours and only rarely after 72 hours.

In the series reported by Briggs and Hogg (1958) the patients without hyaline membrane died earlier than those having associated membranes. In Bauman's series those without membrane died later.

10. Pathology. Potter (1962) describes this as follows. The lungs in hyaline membrane disease are the size of well-expanded lungs but have the consistency of liver. They are a uniform dark, red purple

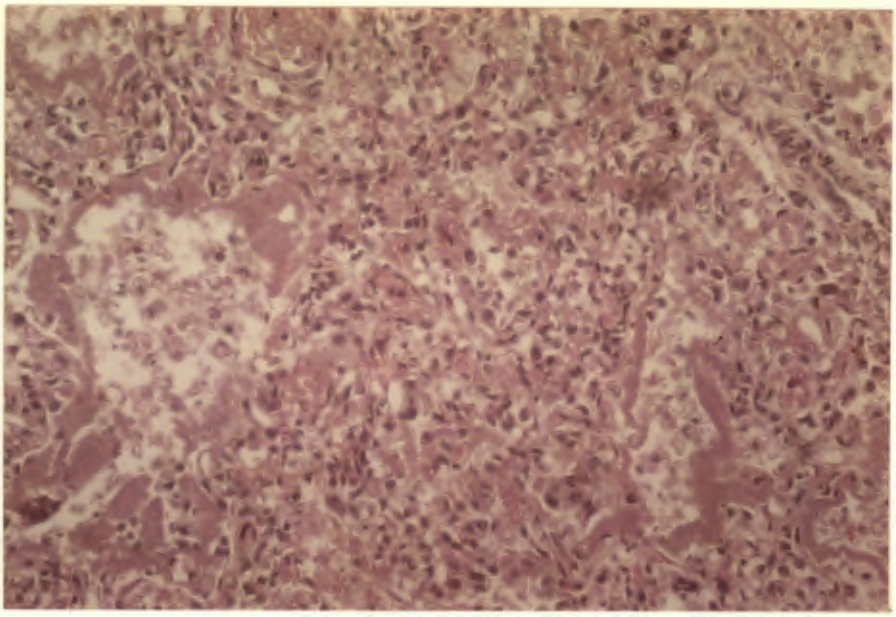


Fig. 2

Lung in the respiratory distress syndrome.

Low power H. and E. stain showing marked atelectasis. The air where present is in the alveolar ducts. The alveoli are filled with debris and macrophages and lined with thick hyaline membrane.

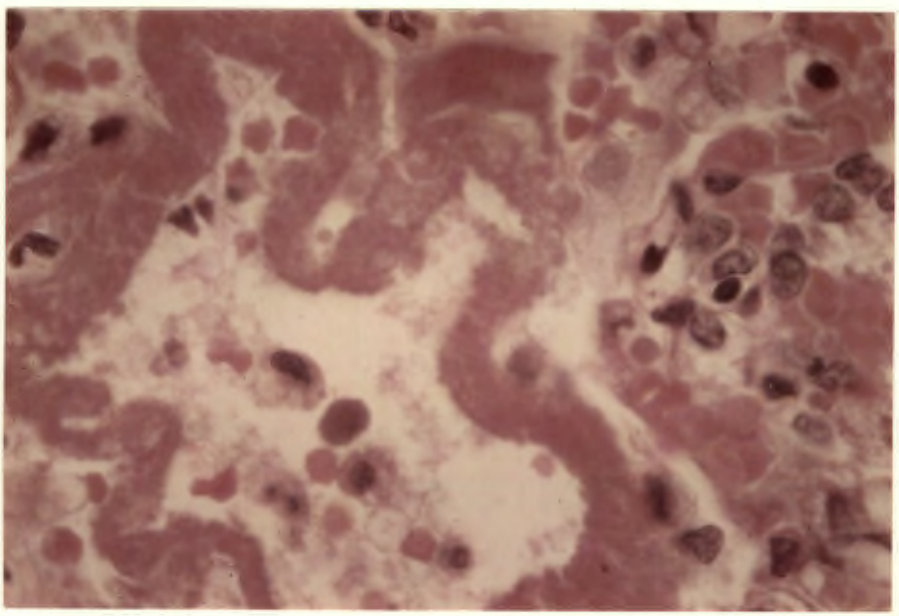


Fig. 3

Lung in the respiratory distress syndrome.

High power view showing thick hyaline membrane lining alveolar duct.

in colour and sink in water. Histologically there is widespread reabsorption of air and the walls of many alveolar ducts and most alveoli are collapsed giving a solid appearance to the lung parenchyma between the few alveoli that remain open. If an attempt is made to expand such lungs with air after removal from the body, the proximal spaces become greatly over-distended and the distal ones even more collapsed. An intense capillary engorgement is present and is responsible for the colour and increase in weight. The inner surfaces of the alveolar ducts that remain open are covered by an irregular layer of homogeneous eosinophilic material. This hyaline membrane must form a mechanical barrier to normal respiratory exchange by blocking off some portions of pulmonary tissue and by coating the remainder in such a way that the capillaries are deprived of contact with the oxygen containing atmosphere (Figs. 2 and 3). As stated in the previous section, hyaline membrane is present in about 50% of cases of the respiratory distress syndrome coming to autopsy. Atelectasis is a very constant finding.

Infants dying after 24-48 hours are likely to have haemorrhage, pneumonia or other signs of infection superimposed (MacGregor, 1946; Potter, 1953; Gruenwald, 1958).

The hyaline membranes have exerted an almost hypnotic influence, as James has said (1959), in the thinking of those investigating neonatal respiratory failure. Therefore, a brief historical survey of the work and views on hyaline membrane is justified at this juncture.

An attempt will also be made to show how the emphasis has shifted from the obsession with hyaline membrane to a more comprehensive interpretation of the clinical and pathological findings.

Hyaline Membrane

(i) Historical review. In 1903 Hochheim first described pulmonary hyaline membranes in the newborn. He reported two cases and expressed the opinion that the membranes were due to aspiration of amniotic fluid. Johnson, in 1923, describing pulmonary hyaline membranes suggested that they were part of a neonatal pneumonia.

Farber and Sweet (1931) and Farber and Wilson (1932) put forward the hypothesis that the membranes were due to the "peripheralization by respiratory activity of aspirated amniotic fluid contents, especially vernix, in the distal passages of the lungs". For about ten years this was the accepted view. The only contrary opinion was that of Rosenthal (1935). He thought that the membranes were derived from degenerated respiratory epithelial cells.

In 1951 Blystad and co-workers investigating the aspiration of amniotic contents theory concluded that the membranes were formed from the accumulation and concentration of the protein present in amniotic fluid.

Tregillus (1951) tried to show histologically that bronchial epithelial injury played a part in the pathogenesis of pulmonary hyaline membrane.

Miller and co-workers (1951) produced pulmonary oedema by bilateral vagotomy in their experimental animals. This was followed by hyaline

membrane. They concluded that the membranes formed from the protein in the oedema fluid were similar to those in the newborn infant.

Arey (1952) at the 5th M and R Paediatric Research Conference held the opinion that vascular damage, probably due to uterine anoxia could lead to transudation with formation of membranes from plasma protein. Gruenwald at the same conference pointed out that too much attention was focussed on the membranes, and called them "eosinophilic herrings". He maintained that the atelectasis was the most important factor causing respiratory difficulty, the membranes being secondary, and originating possibly from the oedema fluid frequently seen in the lungs.

Tran Dinh De and Anderson (1954) produced both hyaline membranes and atelectasis in newborn guinea pigs by oxygen poisoning alone and by oxygen poisoning plus bilateral vagotomy. Bruns and Shields also published the results of their experimental work in 1954, which showed that a high concentration of oxygen (over 70%) given continuously for prolonged periods to guinea pigs was injurious to the pulmonary epithelium and produced hyaline membranes.

From now onwards, although hyaline membranes still remained very much in the centre of the stage, clinicians and research workers were beginning to think in terms of a recognizable clinical syndrome which had as part of its pathology, hyaline membranes.

Donald and Lord (1953) and Donald and Steiner (1953) by clinical and radiological studies confirmed the progressive atelectasis in

infants with respiratory distress. Petersen and Pendleton (1955) and Feinberg and Goldberg (1957) also described a specific radiological picture found in these babies with respiratory distress.

Silverman and Anderson (1956) devised a scheme for scoring retraction and so helping to evaluate the severity of the distress. The Apgar (1958) scoring system aims at assessing the condition of the infant one minute after the infant is born. This examination is useful as a baseline, if distress develops later.

Rogers and Gruenwald (1956) showed that prematurity and antepartum haemorrhage predisposed to the respiratory distress syndrome. Cohen and co-workers (1960) confirmed these findings. Silverman and Silverman (1958) and Avery and Drolette (1958) indicated that prematurity of any degree was a predisposing factor. Caesarean section was also implicated. It was, however, shown by Strang and co-workers (1957) and Hess (1958) that the increased risk was due to the factors necessitating the section.

(ii) Composition of the membrane. By 1954 there was still no agreement as to the composition of the membrane. Most workers believed that the membrane originated from plasma protein. Laufe and Stevenson (1954) suggested that membranes were formed from a combination of exudate and amniotic fluid - the amniotic fluid acting as a thromboplastic agent. Lynch and Mellor (1956) and Duran-Jorda (1956) deduced from histological studies that the membranes were probably derived from blood substances. In 1956 Gitlin and Craig by fluorescent antibody techniques showed that fibrin was the main constituent of hyaline membrane.

Recent workers have again revived the ideas of Rosenthal and Tregillus on the origin of pulmonary hyaline membrane from degenerating epithelial cells. Kloos and Wulf (1957) examining the staining reactions of hyaline membranes showed the presence of an acid mucopolysaccharide derived, in their opinion, from the basement membrane of the pulmonary capillaries. More recently Carone and Spector (1960) produced hyaline membranes in rats by introducing acid polysaccharides endotracheally after producing pulmonary oedema with alphanaphthyl thiourea. They suggested that in humans the membranes may form from the interaction of plasma protein with aspirated mucus or other source of polysaccharide. Buckingham and Sommers (1960) also showed that the membranes contained nucleoprotein.

Van Breeman, Neustein and Bruns (1957) using the electron microscope have shown that fibrin is the chief constituent of the membrane and incorporated within the fibrin there is cellular debris including nuclei and cytoplasmic constituents.

Summing up, we see that although much has been learnt about the composition of the membrane, we still do not know the cause. The membrane has been produced in experimental animals by a variety of methods. Pulmonary oedema seems to be a prerequisite for membrane formation. Capers (1961) has described hyaline membrane as an autopsy finding in adults in several different diseases. It would appear that hyaline membrane is an end result rather than a cause - the "final common path" of a variety of conditions of which the respiratory distress syndrome is but one.

The aetiology of the respiratory distress syndrome. Any hypothesis concerning the cause of the respiratory distress syndrome will have to offer an explanation of:

1. Atelectasis - because most of the disordered pulmonary function can be explained on the basis of atelectasis.
2. Formation of the membrane.

1. Atelectasis. Some workers have considered the hyaline membrane to be a primary cause of the atelectasis. Once the membranes are present they will prevent the artificial expansion of the excised lung (Behrle et al., 1951; Craig et al., 1958). But only half of the cases of the respiratory distress syndrome have membrane, although all show atelectasis. It appears therefore that the membranes are not the primary cause of the collapse but once formed may perpetuate and aggravate it.

Other factors favouring collapse.

(a) The elasticity of the lung itself. The elastic force is maximal when the lung is distended and minimal at the end of expiration. Complete collapse from this cause is unlikely.

(b) Surface tension of the alveolar lining. Clements and coworkers (1958, 1959) measured the surface tension of lung lining material, presumably a mucoprotein. They observed that surface tension depended on area and showed that the low surface tension accompanying a decrease in surface area would favour the stability of the alveoli at the end of expiration and would help to prevent atelectasis.

Pattle (1958) studying the stability of bubbles expressed from the lungs of foetal guinea pigs, noted that they were less stable than those from the lungs of adult guinea pigs. Avery and Mead (1959) found that extracts and washings of the lungs of infants under 1200 gm. lacked the low surface tension of similar material from more mature subjects. The same absence of a surface tension lowering factor was found in infants dying from the respiratory distress syndrome. It appears, therefore, that the surface behaviour of lung extracts is related to maturation. Clements and co-workers (1958) postulate that the absence of an alveolar lining substance causing a low surface tension would predispose to atelectasis. Gruenwald (1960) found this low surface tension substance absent in some still born infants and uniformly present in babies weighing 3000 gm. or more, and also in babies that survived 48 hours or more including those with respiratory distress. Gruenwald (1953, 1955, 1958) also found that the inflation of lungs of stillborn prematures required more pressure than was necessary in more mature lungs. This is probably due to the absence of the factor which normally reduces surface tension. The lack of this factor may well prove to be the most important cause of atelectasis in the respiratory distress syndrome.

2. Formation of the membrane. Gitlin and Craig (1956) have shown that the membranes contain a large amount of fibrin. Most of the fibrin must come from the intravascular space. Transudation can only take place if there is either (i) an increased pressure difference

between the pulmonary capillaries and the alveolar spaces or (ii) increased capillary permeability.

(i) Heart failure if present would account for increased pulmonary capillary pressure. Lendrum (1955) and Shanklin (1959) have suggested that the respiratory distress syndrome is associated with heart failure. They base their opinions on finding evidence of congestion in the lung fields, pulmonary oedema and the fact that hyaline membranes contain exudative plasma constituents. Baar (1956) has demonstrated oedema fluid in the lungs of babies with respiratory distress. Burnard (1959) showed enlargement of the heart in distressed babies. This disappeared as the baby improved. He also reported that following asphyxia many babies have an increased heart weight. Stahlman (1959) claims to have had some success with digitalis in the treatment of the respiratory distress syndrome.

Dawes and co-workers (1955) showed that in newborn lambs the ductus arteriosus remained patent for many hours and even days after birth, allowing a major left to right shunt. James (1959) and Prec and Cassels (1955) have shown that in newborn infants the ductus also remains open for several hours after birth and that there is usually a left to right shunt.

Rudolph and colleagues (1961) have shown by cardiac catheterization studies that there is a large left to right shunt through the ductus in infants with respiratory distress. It is possible that the large patent ductus increases the load on the left heart in the respiratory distress syndrome.

In spite of these observations, there is evidence which suggests that increased intravascular pressure due to cardiac failure is not primary in the pathogenesis of the respiratory distress syndrome. Firstly there is the lack of association with congenital heart disease (Blystad et al., 1951; Driscoll et al., 1960) especially the forms of congenital heart disease that might be expected to produce maximum pulmonary venous pressure. Secondly Rudolph et al. (1961) found only a slight increase (15 mm. Hg) in left atrial pressure. This pressure is insufficient to explain transudation. They also reported that the pressures in the right atrium, right ventricle and pulmonary arteries showed no increase in the distressed group. The pulmonary artery pressure was lower than normal in most of these cases. The evidence thus suggests that there is insufficient back pressure from the left ventricle to implicate it as the primary cause of the pulmonary findings in the respiratory distress syndrome.

(ii) Increased capillary permeability. Peripheral oedema is more marked in distressed than in normal babies of the same weight (Usher, 1959; Sutherland et al., 1959). Usher (1959) also found that the oedema fluid in babies with respiratory distress had a high protein content, which would suggest increased capillary permeability. Other evidence suggesting capillary damage includes the increased amount of cerebro-spinal fluid (Potter, 1943) in distressed infants, and the increased incidence of cerebral and pulmonary haemorrhage in infants of diabetic mothers and premature infants (Driscoll et al., 1960 and Ziegler, 1957).

3. Other important recent findings. Lieberman and Kellogg (1960) and Lieberman (1961) have shown that the lung tissues of babies dying from the respiratory distress syndrome had a diminished fibrinolytic activity. There was a deficiency of fibrinolytic activators and a low level of profibrinolysin in the plasma. This prevents the dissolution of intra-alveolar fibrin resulting in its retention and subsequent formation of hyaline membranes.

Rudolph and Smith (1960), Usher (1959), and Nelligan (1960) have all reported a low systemic blood pressure in the respiratory distress syndrome. There is as yet no evidence that the lower blood pressure plays a direct part in the causation of the illness.

Strang and MacLeish (1961) investigating infants with severe respiratory distress by analysis of gases in arterial and venous blood during the breathing of pure oxygen, concluded that the infants suffered from a reduced alveolar ventilation and from a right to left physiological shunt.

Black et al. (1959, 1960), because they found eosinophilic infiltration of the thymus and immaturity of the lymphoid tissues in infants who had hyaline membranes, postulated the possibility of adrenal insufficiency in the respiratory distress syndrome.

To put forward a hypothesis to include all these varied findings is at the moment impossible. There are still too many missing pieces in the pattern. We shall, however, endeavour to discuss our results in the light of some of these findings.

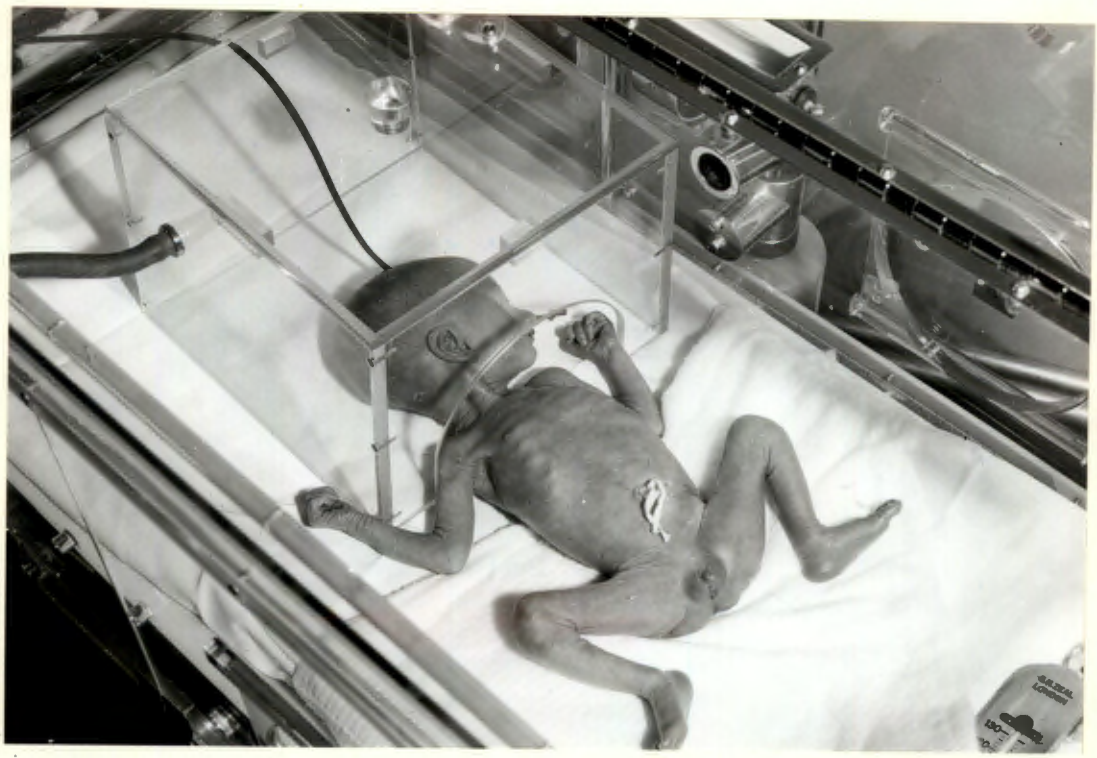


Fig. 4

Baby in incubator with small perspex box covering head. This allows high O_2 levels at low flow rates.

PRESENT INVESTIGATION

Material and Methods

The infants studied were those who, because of the presence of respiratory symptoms during the first few hours of life, were considered likely to develop the respiratory distress syndrome. These symptoms were rapid or laboured breathing, apnoeic spells, indrawing of ribs or sternum, or expiratory moan. A majority of the infants were premature, but some of the most severe cases of the respiratory distress syndrome were born at term. In all 24 cases were studied.

The infants were nursed in an incubator, the temperature of which was adjusted to maintain the baby's rectal temperature near to 37°C. As it was desired to observe the effect of widely different concentrations of inspired O_2, and at times to use high concentrations, it was sometimes convenient to enclose the baby's head in a small "perspex" hood which easily fitted within the incubator (Fig. 4). High O_2 levels could thereby be maintained with low flow rates of O_2 to the hood. This O_2 supply could be independently warmed and humidified. Ambient O_2 levels were measured with a Beckmann D2 analyser.

Arterial samples from an iliac artery were obtained by means of a plastic catheter (O.D. 2mm.) inserted into an umbilical artery. With experience it was found possible to introduce the catheter in almost every infant, including those of less than 1 kg. After taking a blood sample the catheter was filled with heparin saline (50 units/ml.) which prevented clotting for a period of up to 8 hours. The end of the

catheter was then closed, and the cord stump and surrounding skin powdered with chlorhexidine and covered with a sterile dressing. The catheter has been left *in situ* for up to $2\frac{1}{2}$ days. After this time femoral artery puncture has been used when required.

Blood samples of about 1.5 ml. were taken under sterile and anaerobic conditions with a syringe, the dead space of which had been filled with heparin saline. A metal washer incorporated in the syringe provided a means of stirring. The syringe was capped and kept on ice until analysis, which was done within one hour. O_2-content was measured in duplicate or triplicate with the Roughton-Scholander syringe technique (Roughton and Scholander, 1943). O_2-capacity was either measured in the same way, after equilibrating the sample for 10 minutes with air, or more usually by measuring the Hb concentration in a photoelectric colorimeter which was regularly checked against an iron standard and the cyan-methaemoglobin method. For the ratio (O_2 combining power in vols.%)÷(Hb in g%) thirteen samplings of foetal blood gave a mean value of 1.33 (range 1.31-1.36); ten samplings of adult blood gave a mean value of 1.35 (range 1.33-1.38). We therefore took 1.34 vols. as the combining power of 1g. Hb. Percentage saturation was expressed simply as 100 x (O_2-content of sample)÷(O_2-content of sample equilibrated with air).

pH was measured with the Astrup apparatus (Astrup, Jørgensen, Andersen and Engel, 1960), correcting for temperature by adding 0.014 for each °C. the body temperature was below 37° (Rosenthal, 1948).

By using this apparatus to measure the change in pH after the sample has been equilibrated with 4% and 8% CO_2 in O_2, the P_{CO_2} and the standard bicarbonate concentration can be derived by means of a nomogram. Throughout this thesis plasma bicarbonate concentration implies standard bicarbonate (HCO_3^- measured at a standard P_{CO_2} of 40 mm. Hg and a body temperature of 37°C.), which we have chosen as the most appropriate measure of metabolic acidosis or alkalosis.

Measurement of Shunt

If the O_2-capacity of blood equilibrated with air at room temperature and a P_{O_2} of 150 mm. Hg is C_{O_2}, then its O_2-content when equilibrated with a gas at some higher P_{O_2} and any given temperature will be given by,

$$O_2\text{-content} = \frac{100}{f} \quad (C_{O_2} - 0.71) + 100. \frac{\alpha}{760} \times P_{O_2} \quad \ldots\ldots\ldots (1)$$

where 0.71 is the amount of physically dissolved O_2 in vols.% at a P_{O_2} of 150 mm. and an average room temperature of 18°C.; and α is the solubility coefficient of O_2 in ml. O_2/ml. blood at 760 mm. Hg. A value for α at different temperatures is available (Dittmer and Grebe, 1958), extrapolating if necessary for temperatures below 20°C.

The factor 100/f relates to the fact that the maximum O_2-carrying potential of Hb is not completely taken up when, as O_2-capacity is ordinarily measured, blood is equilibrated with air, since at a P_{O_2} of 150 mm. adult Hb is known to be significantly less than 100% saturated (Nahas, Morgan and Wood, 1952). Further, some Hb present

in normal blood as carboxy- and met-Hb may be converted to HbO_2 when blood is equilibrated with gas of high P_{O_2}. These and other factors affecting measurements of O_2-capacity have been discussed in detail by Roughton, Darling and Root (1944).

In order to derive a value for f appropriate to the conditions of this study, samples of foetal and adult blood were equilibrated in a tonometer with a series of gas mixtures containing from 60 to 100% O_2. The P_{O_2} of the gas was calculated, the O_2-capacity and -content of the samples were measured and the values inserted in equation (1), enabling f to be calculated. Results are shown in Table I.

Gas	Temp. C.	PO_2 mm. Hg	Adult or foetal blood	O_2-capacity	O_2-content	$\frac{100}{f}$
100% O_2	37	713	A	22.80	24.85	100/97.6
96% O_2, 4% CO_2	37	685	F	18.14	20.09	100/97.1
96% O_2, 4% CO_2	37	695	F	20.27	22.14	100/97.9
92% O_2, 8% CO_2	37	665	F	20.27	22.06	100/97.9
60% O_2, 40% N_2	19	452	F	20.27	21.89	100/98.8
					Mean	100/97.9

Table I

Calculation of factor f (equation 1) for blood equilibrated with gases of varying O_2-tension.

The results are satisfactorily consistent, the value for f ranging between 97.1 and 98.8 with a mean of 97.9. This figure implies that the O_2-capacity as measured represented only 97.9% of the full capacity

for O_2 carriage by Hb as attained under conditions of high O_2-tension. Of the residual 2.1% of unsaturation, 1.2% would be accounted for if the amount of unsaturation of adult Hb at P_{O_2} 150 mm. (Nahas et al., 1956) obtains also for foetal Hb. This would leave 0.9% of unsaturation to be accounted for by the other factors mentioned. In applying equation (1) we have throughout taken f to have the value 97.9.

Alveolar P_{O_2} was calculated from the "alveolar air equation",

$$\text{alveolar } P_{O_2} = F_{O_2}(P_B - P_W) - P_{CO_2}\left(F_{O_2} + \frac{1 - F_{O_2}}{R}\right) \quad \ldots\ldots\ldots (2)$$

where F_{O_2} is the fraction of O_2 in the inspired gas; P_B the barometric pressure in mm. Hg and P_W the water vapour pressure at body temperature; and R the Respiratory Quotient, taken to be 0.8. P_{CO_2} in this equation is strictly <u>alveolar</u> P_{CO_2}, which under most conditions differs negligibly from <u>arterial</u> P_{CO_2}. Large R - L shunts (over 70%) do cause arterial P_{CO_2} appreciably to exceed alveolar values (Strang and MacLeish, 1961) although the effect on alveolar P_{O_2} as calculated by equation (1) is unimportant under the conditions of this study, and no correction for it was therefore made.

Any admixture of unoxygenated blood with the blood coming from pulmonary capillaries causes a depression of O_2-content of systemic arterial blood, and measurement of this depression enables the percentage of the heart output which is so shunted to be calculated, according to the "shunt equation",

$$\% \text{ shunt} = 100 \times \frac{(O_2\text{-content of blood from pulmonary capillaries}) - (O_2\text{-content of arterial blood})}{(O_2\text{-content of blood from pulmonary capillaries}) - (O_2\text{-content of mixed venous blood})} \quad \ldots (3)$$

With high inspired O_2-concentrations it can be assumed that blood leaving the pulmonary capillaries is fully saturated with O_2 (see below), so that under these conditions alveolar P_{O_2} being known (equation 2), the O_2-content of pulmonary capillary blood can be calculated (equation 1). The O_2-content of arterial blood is measured directly. The O_2-content of mixed venous blood, however, cannot be measured in the neonate, because the possibility of shunting through the foramen ovale and ductus arteriosus would necessitate blood being sampled from the pulmonary artery distal to the ductus. It is generally assumed that there is a difference of about 5 vols.% between the O_2-contents of arterial and mixed venous blood. Strang and MacLeish (1961) concluded that in their series of newborn infants with respiratory distress an arterio-venous difference of 4 vols.% was applicable. Fortunately the value is not critical, since the denominator in equation (3) tends to be large compared with the numerator. We have throughout assumed a value of 5 vols.% for the arterio-venous difference in O_2-content. If now we put Δ for the difference between the O_2-content of pulmonary capillary and arterial blood, equation (3) can be written simply as,

$$\% \text{ shunt} = \frac{100\,\Delta}{\Delta + 5} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

It should be noted that the percentage shunt can be calculated equally well whether the subject inspires 100% O_2 (as is usual in

estimating shunts), or any other known high concentration of O_2. To be valid for this purpose the inspired O_2-concentration must be sufficiently high to satisfy two requirements. (1) Hb must be virtually 100% saturated. For example, if 40% O_2 is inspired the alveolar P_{O_2} will be 250 mm. Hg and (adult) Hb will be 99.65% saturated. If 50% O_2 is inspired alveolar P_{O_2} will be 315 mm. and Hb will be 99.9% saturated. (2) Blood leaving pulmonary capillaries must be fully oxygenated. There are both theoretical and clinical grounds for the view that arterial unsaturation due to pulmonary defect, whether one of diffusion, distribution or ventilation, is highly sensitive to small rises in inspired O_2-concentration (Shephard, 1956; Perkins, 1958; Campbell, 1960). Because of this fact, a failure under resting conditions to achieve normal saturation with levels of inspired O_2 of about 40%, implies the presence of some degree of R-L-shunt. (A pulmonary defect so gross that blood flows through some parts of lung without appreciable gas exchange, acts as a shunt).

In order to test the validity of our methods and of the various assumptions made in calculating shunts, we have in ten instances compared the shunt calculated for an infant inspiring (1) 100% O_2, and (2) from 40 to 80% O_2. Results are set out in Table 2, and show that there is fair agreement in most instances between shunt values when calculated at two levels of inspired O_2.

We conclude that it is practicable to calculate the size of shunt for any infant in whom O_2-capacity and -content are known, when O_2 at

not less than 40-50% is breathed. Shunts in distressed infants are often large, making a moderate degree of error acceptable.

Case	Age hours	Respiratory symptoms	1. Inspiring 100% O_2 %	2. Inspiring <100% O_2 %
14	$2\frac{1}{2}$	+++	32	35 (with 80% O_2)
13	$2\frac{1}{2}$	+	10	3 (with 56% O_2)
15	4	++	21	25 (with 50% O_2)
15	16	++	26	34 (with 70% O_2)
16	$4\frac{1}{2}$	+++	20	33 (with 46% O_2)
17	5	+	24	25 (with 68% O_2)
11	8	++	15	13 (with 60% O_2)
11	28	++	18	18 (with 50% O_2)
9	11	+	9	16 (with 48% O_2)
8	11	+	13	15 (with 40% O_2)

Table 2

Shunt calculated at two levels of inspired oxygen.

Premature Infants without Respiratory Distress

Amongst the infants studied were some who during the first few hours of life had tachypnoea, brief apnoeic spells or expiratory moan. These symptoms were at no time accompanied by laboured breathing or rib recession, and they disappeared during the course of 24 to 36 hours. Ten such infants were studied, all were premature, nine weighing less than 1.9 kg. The arterial P_{CO_2} in this group was normal

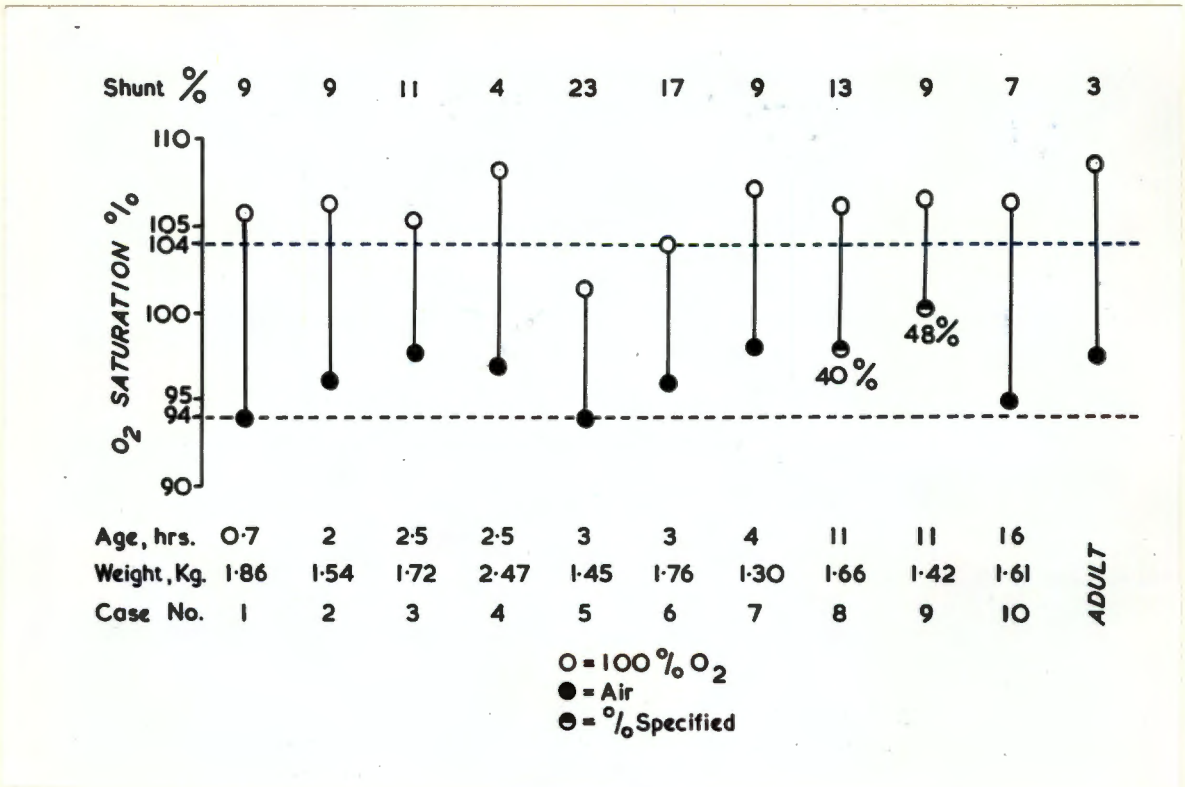


Fig. 5

Arterial saturation of 10 premature infants, aged 0.7-16 hours, breathing air (or 40-48% oxygen) and breathing 100% oxygen, with R-L shunt values.
Normal adult shown for comparison.

or low, ranging from 24 to 44 mm. Hg at the time of the measurements, which were made some time during the first 16 hours of life. Although, therefore, these infants were studied because initially they presented as possible early cases of the respiratory distress syndrome, their subsequent course gave no evidence of pulmonary disorder. Findings in this group (Fig. 5) thus provide a baseline by which to judge the findings in infants with respiratory distress.

Arterial O_2-saturation measured in 8 cases while breathing air was 94% or more, and in the remaining 2 cases while breathing 40-45% O_2 was 98% or more.

Pure O_2 was then administered by means of a face mask with a flow rate of 5 L/min. A steady state was considered to have been reached after 10 minutes, Strang and MacLeish (1961) having shown that in normal newborns under these conditions one minute suffices to wash out nitrogen from the lungs. Arterial O_2-saturation while breathing pure oxygen was from 104% to 108% (Fig. 5). From these data R-L shunts were calculated. In the majority of this group of "normal" prematures the shunt values lay between 7 and 11% (7 out of 10 cases), with a range from 4 to 23% and a mean of 10.6%. For comparison similar data for an adult are shown, with a shunt value of 3%.

The following case is typical of this group:

Case 1. (Fig. 6) The mother, a primipara aged 40 years, went into spontaneous labour when 34 weeks present. The delivery was an easy assisted breech. The baby, weighing 1.86 kg., was limp and breathing was not

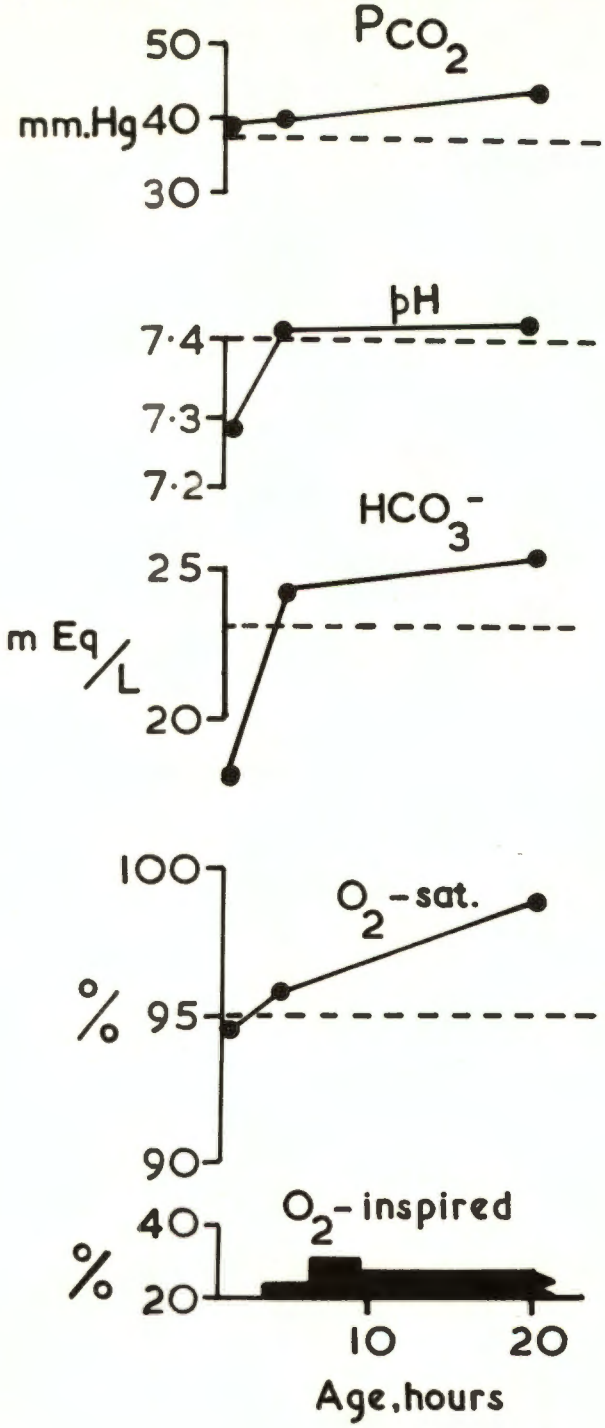


Fig. 6

Case 1. A typical case of a "normal" premature, weight 1.86 kg. Changes in arterial P_{CO_2}, pH, bicarbonate, and O_2-saturation during first 20 hours after birth.
Dotted lines indicate average normal values - arterial P_{CO_2} 37 mm. Hg, pH 7.4, standard bicarbonate 23 mEq./L., O_2-saturation 95%.

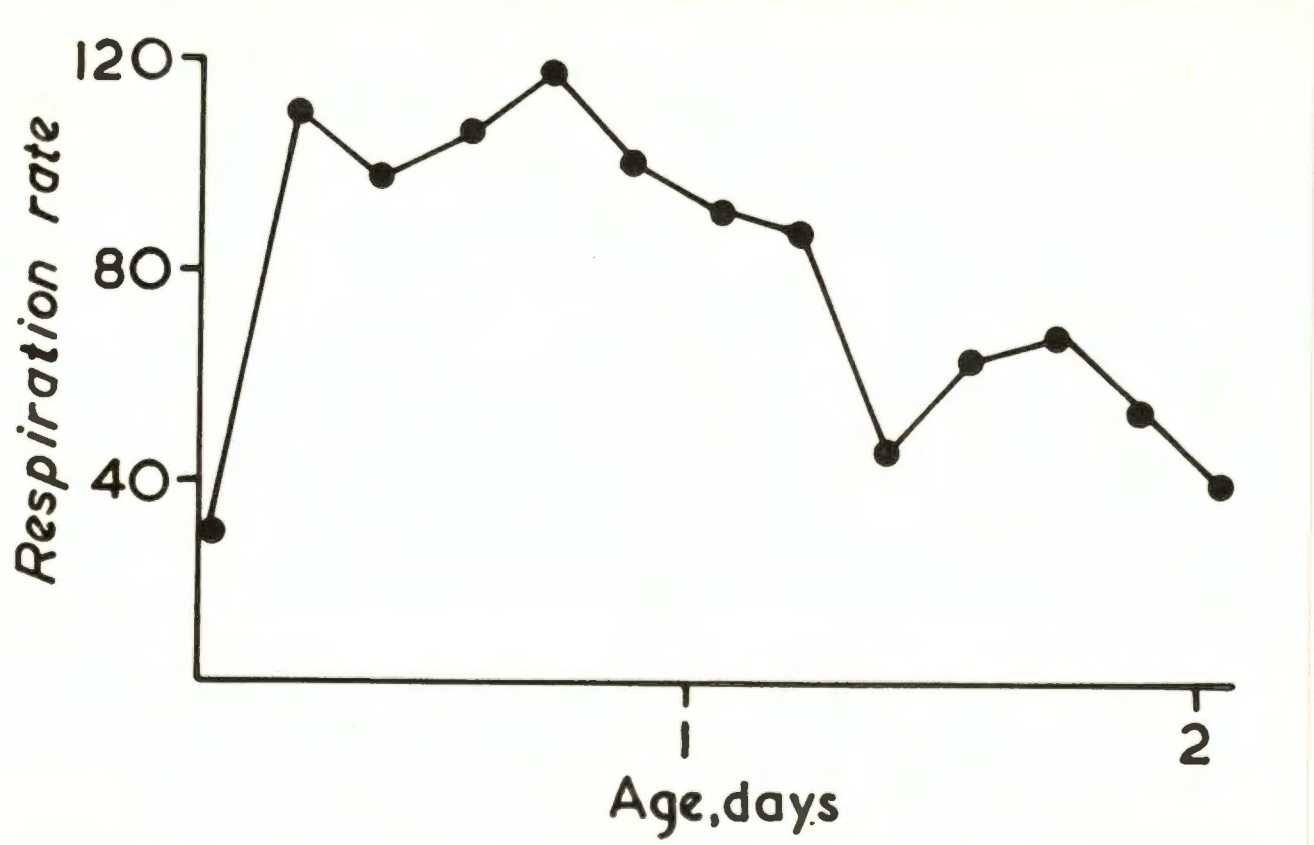


Fig. 7

(Case 1). Respiratory rate during first 2 days of life showing development of marked tachypnoea after birth, as seen in some prematures in the absence of respiratory distress.

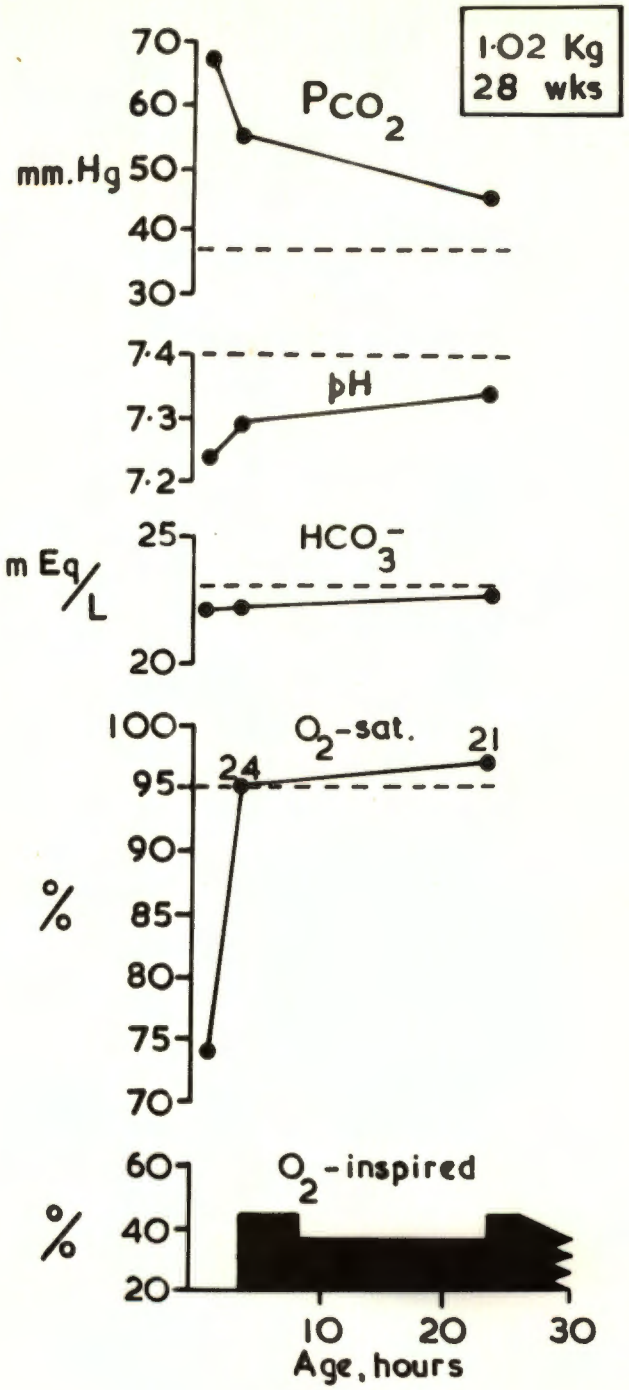


Fig. 8

(Case 23). Premature infant of very low birth weight, 1.02 kg. Some delay in attainment of normal respiratory function, as compared with less immature infant, compare Case 1.

established until positive pressure O_2 has been given for a short while. Thereafter, he required very little extra oxygen to maintain a good saturation. The P_{CO_2}, pH and bicarbonate were normal. The only abnormal feature was tachypnoea, the respiration rate rising to 118 per minute at 4 hours (Fig. 7). Except for a mild apnoeic attack on day 2, respiration was entirely normal at the end of 48 hours.

The following case illustrates the immediate post-natal course of an infant on the borderline of viability.

Case 23. (Fig. 8) A male infant born at 28 weeks weighing 1.02 kg. He was cyanosed at birth and required positive pressure oxygen for a few minutes. He then maintained a good O_2-saturation on about 40% O_2. Initially he had a respiratory acidosis, with a P_{CO_2} level of 67 mm. Hg. This steadily improved (Fig. 8) and was almost fully corrected at 30 hours.

Thus although this infant exhibited some delay in achieving normal respiratory function, he did not show distress.

Infants with Respiratory Failure

Amongst the infants with respiratory failure were some who exhibited the typical clinical pattern of the respiratory distress syndrome, as already defined. Four examples of this group have been selected for full description here, in order to illustrate varying degrees of severity.

A rather different pattern of respiratory failure was presented by some other infants, all of very low birth weight, in whom apnoeic attacks were the predominant feature. Whether or not these infants are to be regarded as suffering from an essentially different condition, is a matter we shall return to later. Three examples of this group are described here, one with survival and two ending fatally.

Typical cases of the Respiratory Distress Syndrome

The following are described:

1. Moderately severe case (Case 11).
2. Severe case (Case 12).
3. Very severe cases (Cases 13 and 22).

In any case of respiratory failure much information as to the type of respiratory disorder present can be derived from a knowledge of (1) the arterial O_2-saturation in relation to the concentration O_2 breathed, (2) the arterial P_{CO_2}. Such information in turn provides some theoretical basis for planning treatment. In each case the course of the illness is traced in terms of O_2-saturation, percentage R-L shunt (except in case 19), pH, P_{CO_2}, and HCO_3^-.

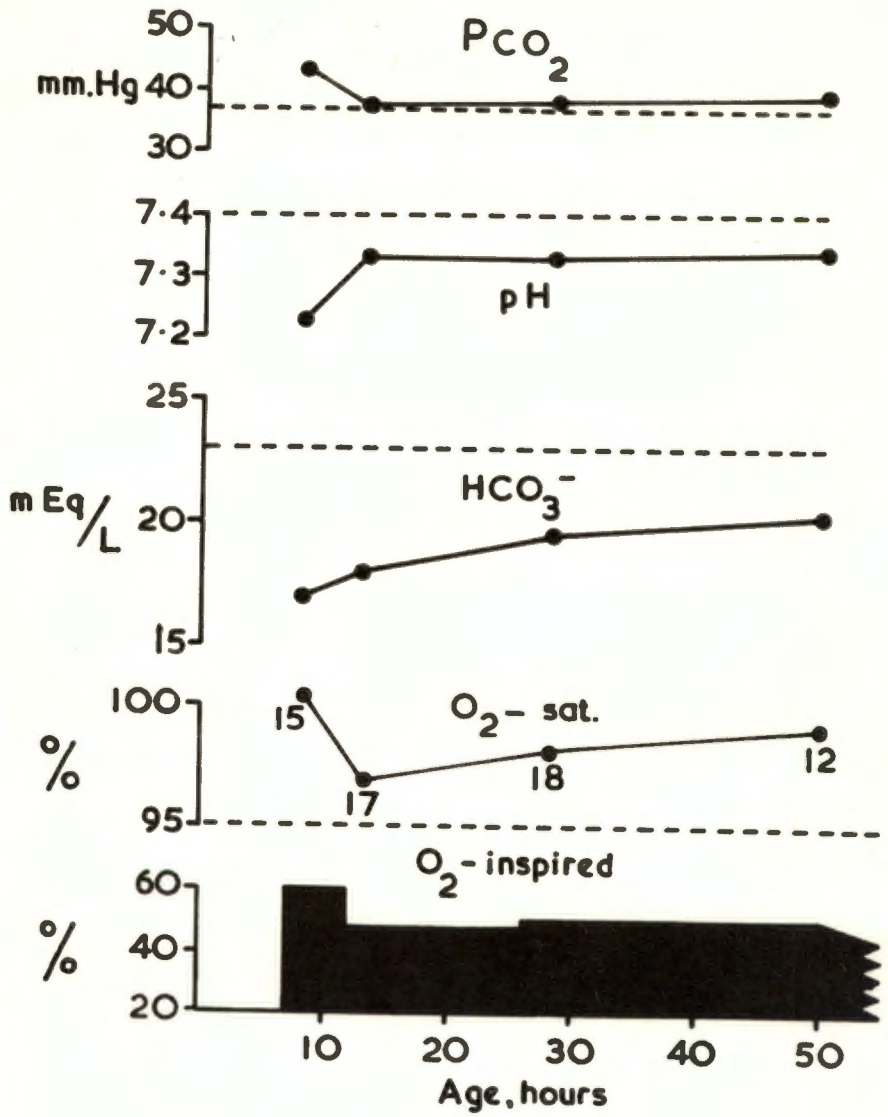


Fig. 9

(Case 11). Moderately severe respiratory distress syndrome. The figures below the O_2-saturation graph give the % R-L-shunt.

1. Moderately severe

Case 11. (Fig. 9) A full-term baby of 2.62 kg. born normally at home. He breathed without delay but over the next hour became increasingly cyanosed. At 2 hours he collapsed and stopped breathing, but was revived by mouth-to-mouth breathing. He reached hospital after six hours when respiration was slow and gasping, and cyanosis severe. Oxygen was given, at first with intermittent positive pressure by mask, then into an incubator. The colour rapidly returned to normal, and breathing became regular but rapid (78-100/min.) with expiratory moan and rib recession. Air entry was very poor, particularly over the L-lung. A radiograph showed an enlarged heart, and ground glass opacity of the lungs, more marked on the left (Figs. 10 and 11). Clinically therefore, he now presented the typical picture of the respiratory distress syndrome.

His colour remained normal while breathing O_2 at about 40%, but every time the O_2-concentration was reduced to that of air, respiratory distress increased seriously and marked cyanosis reappeared. The breathing remained distressed for 48 hours, after which his O_2-dependence lessened, although a week elapsed before extra O_2 could be entirely omitted.

Reference to Fig. 9 shows that initially at 8 hours there was a moderate metabolic acidosis (HCO_3^- 17 mEq/l) reflecting the 6 hour period of hypoxia prior to reaching hospital; plasma bicarbonate tended to correct itself over the next 40 hours. The P_{CO_2} was

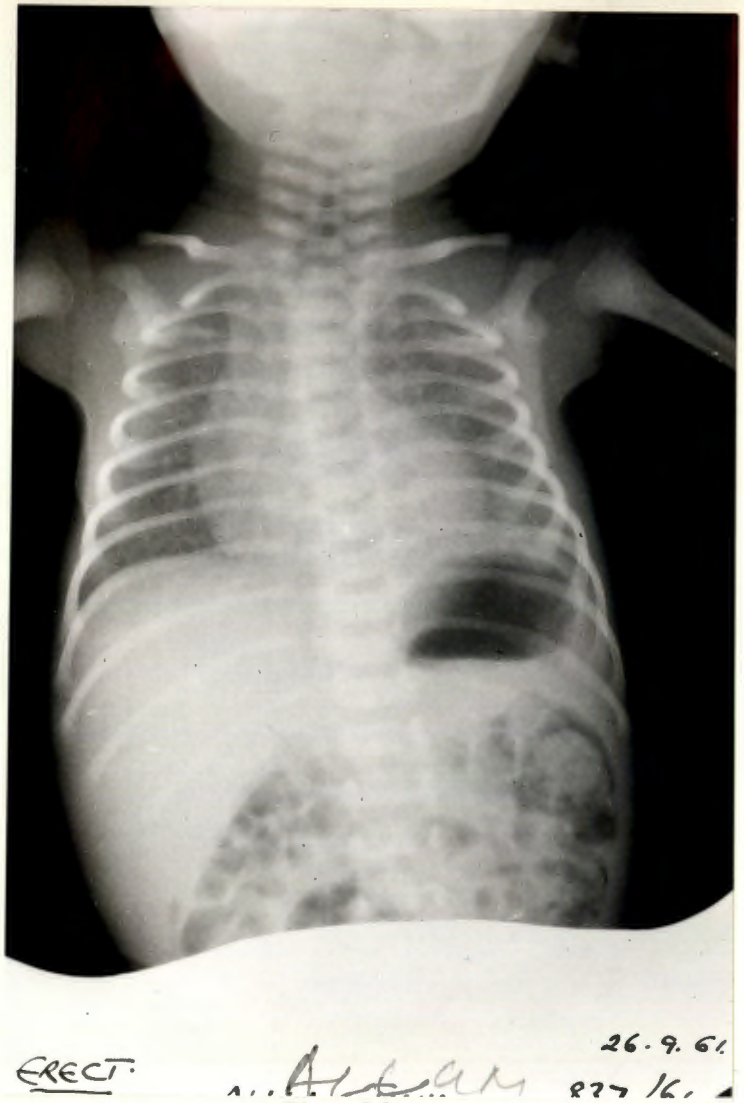


Fig. 10

(Case 11). Aged 48 hours.
Radiograph showing ground glass appearance of the lungs and enlargement of heart.

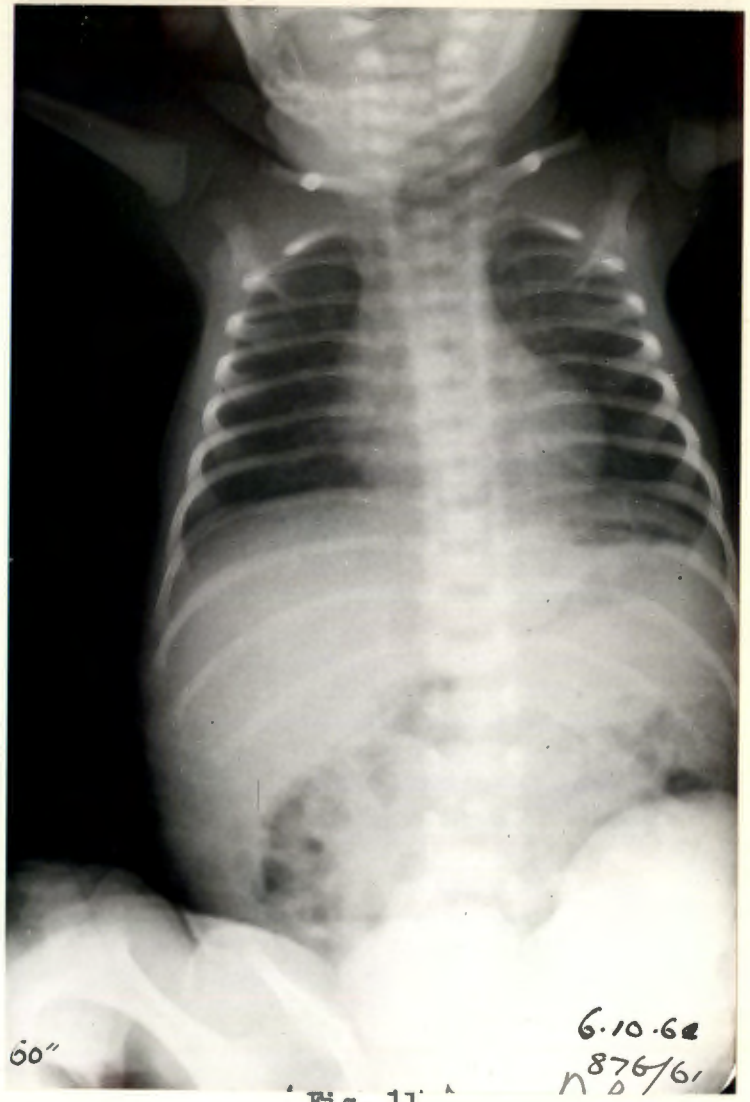


Fig. 11

(Case 11). Aged 9 days.
Radiograph showing clear lung fields and heart size within normal limits.

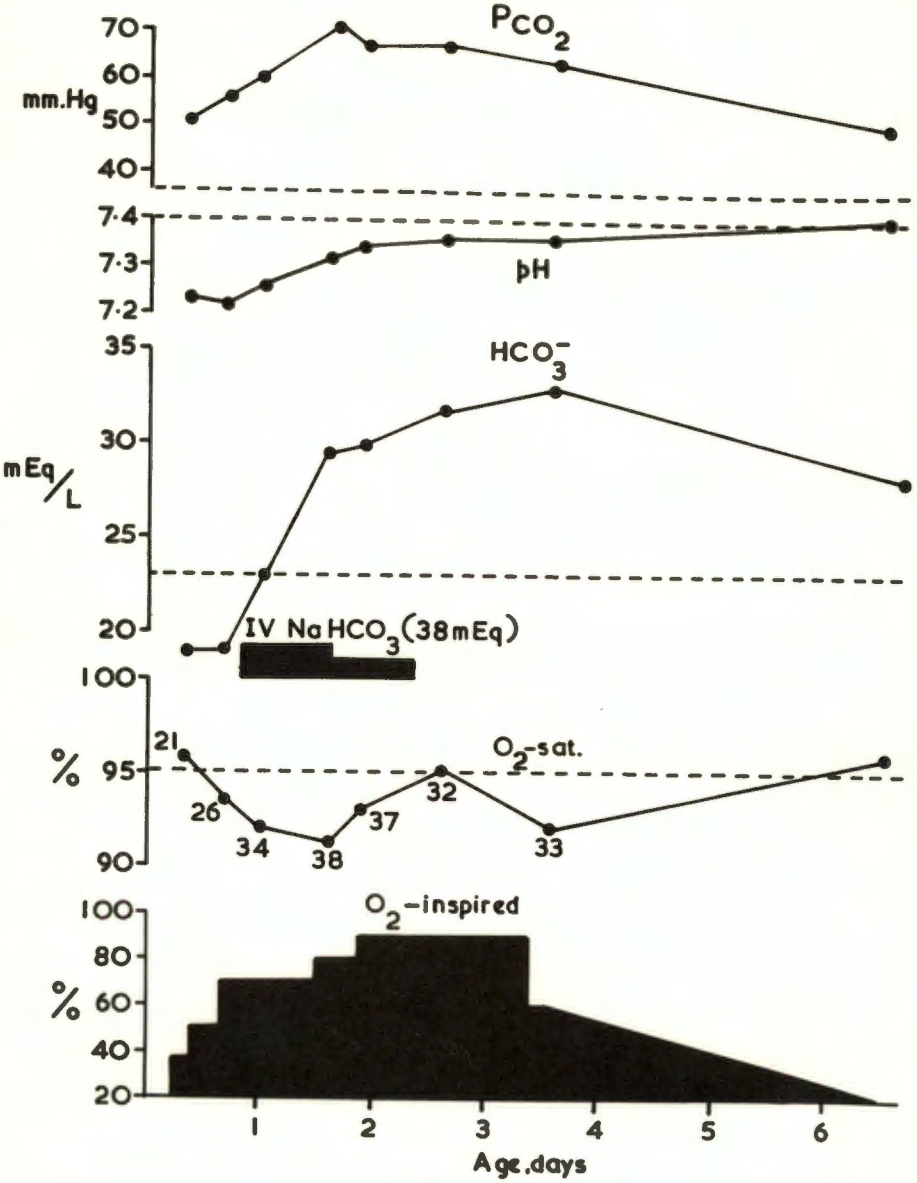


Fig. 12

(Case 12). Severe respiratory distress syndrome.
(see legend to Fig. 6).
The figures below the O_2-saturation graph give the % R-L-shunt.

virtually normal throughout. The oxygen saturation, measured in an ambient O_2-concentration of 48-60%, was always in the high normal range between 97% and 100.3%. The R-L shunts varied between 12 and 18%, values which are not outside the range for "normal" prematures (Fig. 5).

Summary: Respiratory distress syndrome of moderate severity, characterized by an O_2-responsive hypoxia; a small R-L shunt (less than 20%) and the absence of hypercapnia.

2. Severe

Case 12. (Fig. 12) A baby of 2.86 kg. delivered by caesarean section, after labour had begun at 36 weeks and become complicated by transverse lie. He breathed without delay but within ½ hour had developed rapid laboured breathing with moaning and recession. By 4 hours cyanosis was marked but was at this stage relieved by 35% oxygen. Air entry was poor over both lungs, with generalized fine rales. A radiograph (on Day 2) showed ground-glass opacity of both lungs.

Respiratory distress became steadily worse over the next 48 hours O_2-saturation falling from 96% to 91.5% despite the ambient O_2 being gradually raised to 90% (Fig. 3). R-L shunt values were constant at 32-38% during this phase. At the same time the P_{CO_2} rose steadily to a maximum of 70 mm. Hg. With a view to compensating the acidosis, mainly respiratory, $NaHCO_3$ was given by intravenous drip, 65 ml./kg./day of a solution of $NaHCO_3$ 100 mEq/L in 10% glucose, reducing the strength of the $NaHCO_3$ successively after 20 hours. The plasma bicarbonate

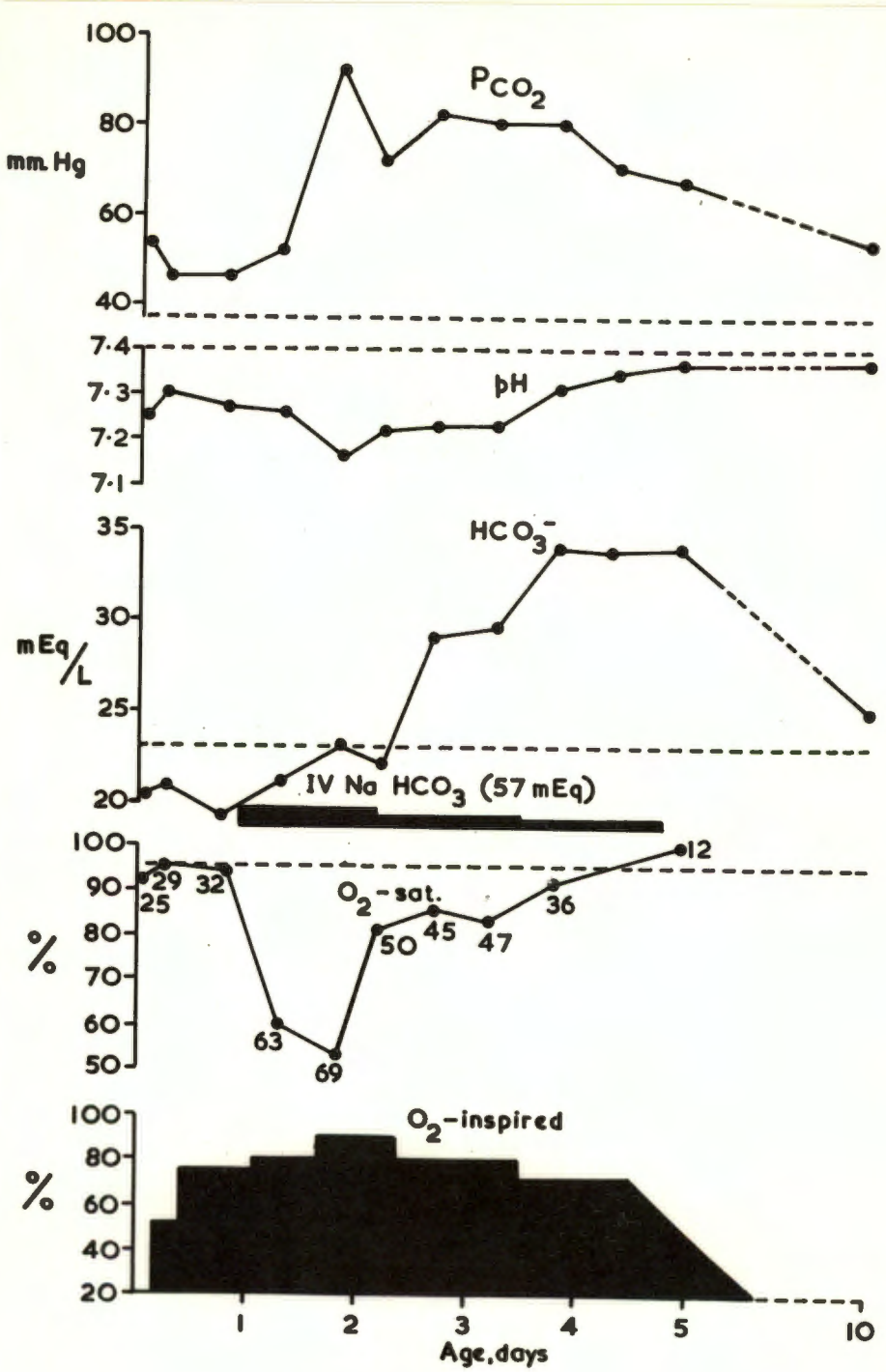


Fig. 13

(Case 13). Very severe respiratory distress syndrome. (see legends to Figs 6).

+ 12

thereby rose from 19 to 33 mEq/L and the pH from 7.2 to 7.4. Improvement began on Day 4 and by Day 7 the baby was able to maintain normal O_2-saturation in air.

Summary: Respiratory distress syndrome of severe degree with recovery, characterized by moderate R-L shunt (about 35%); an O_2-saturation which could be maintained at 90-95% by giving O_2 up to 90%; and considerable hypercapnia.

3. Very severe case

Case 13. (Fig. 13) Born at 37 weeks gestation by elective caesarean section for maternal diabetes, weight 2.84 kg. He breathed without delay, but by 40 minutes when investigations were begun, breathing had become slightly laboured, with some recession and moaning. By 6 hours respiratory distress was already severe and cyanosis could only be prevented by raising the ambient oxygen to 50% (Fig. 13). By Day 2 respiratory distress was extreme, and cyanosis was now present even in 90% oxygen, arterial saturation falling to a low level of 53%, at which stage P_{CO_2} had risen to 92 mm. Hg. Intravenous $NaHCO_3$ was given under the same scheme as for case 12 in order to correct the acidosis, mainly respiratory (lowest pH 7.18). Throughout the first four days he remained desperately ill, but by day 5 he was able to tolerate successive lowering of the ambient concentration, respiration gradually returning to normal by about Day 10.

Summary: Respiratory distress syndrome of extreme severity with recovery in the infant of a diabetic mother, characterized by a

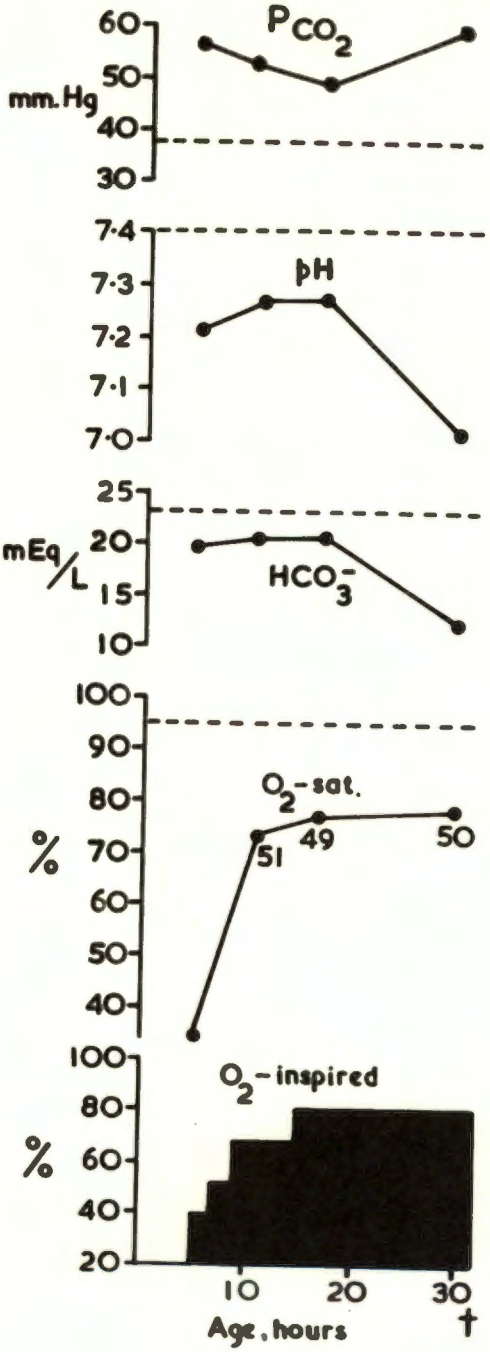


Fig. 14

(Case 22). Very severe respiratory distress syndrome.

large R-L shunt (about 70%); 0_2-saturation below 60% even in 90% 0_2; severe hypercapnia.

Case 22. (Fig. 14) An 18 year old primipara gave birth to twins, unattended, in a caravan. This is twin 2. He weighed 1.52 kg. Because of difficult breathing from birth, he was admitted to hospital four hours later. He was cyanosed and had marked rib and sternal recession. The air entry was poor. Respirations about 90/min. were irregular.

The colour improved on 40% oxygen but as time went on he needed more oxygen to prevent cyanosis. Even on 80% oxygen the arterial saturation never rose above 80%.

For the first 20 hours, the bicarbonate remained at 20 mEq/L. The P_{CO_2} dropped from 58 to 48 mm. Hg and the pH went up 0.7 units. A series of apnoeic attacks then followed with rapid deterioration of the infant's condition (cf. Fig. 14). He died when he was 32 hours old.

Histology of lungs showed poorly aerated premature lungs with hyaline membrane in alveoli and alveolar ducts. (Figs. 15 and 16).

Summary: Very severe respiratory distress syndrome with large R-L shunt. Condition appeared to improve at first on high concentrations of oxygen. A series of apnoeic attacks was then followed by rapid deterioration.

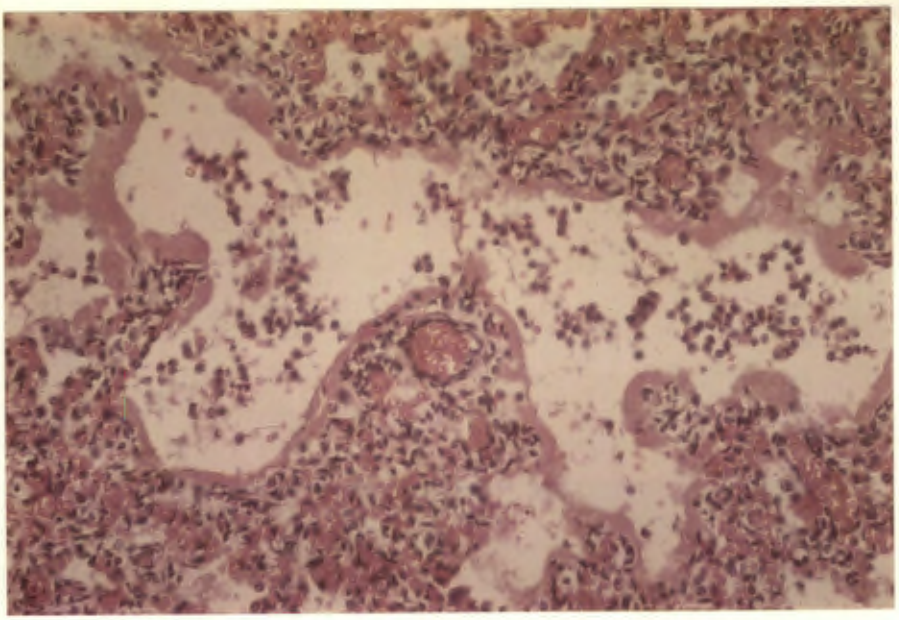


Fig. 15

(Case 22). Very poorly aerated lungs with hyaline membrane in alveoli and alveolar ducts (H. and E. stain).

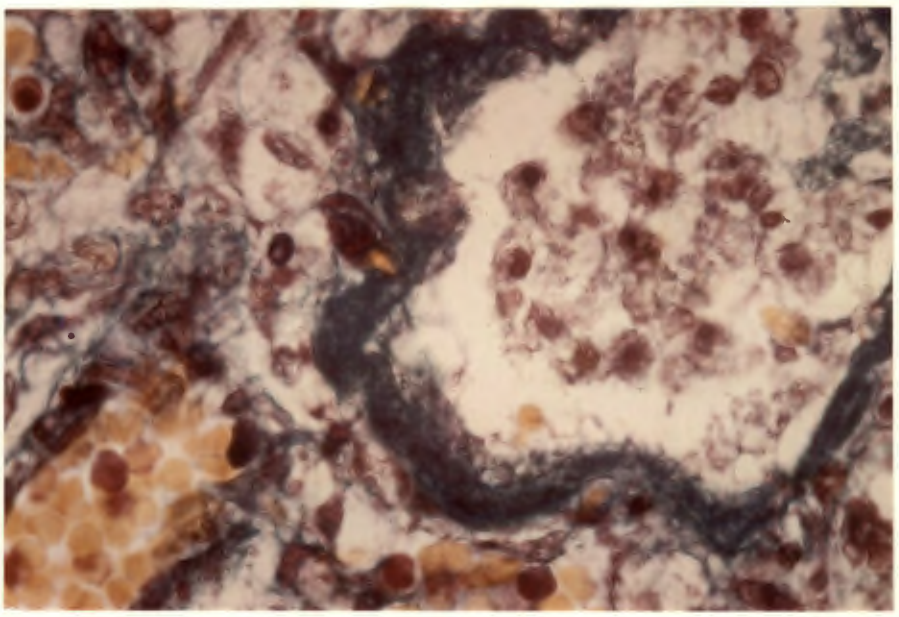


Fig. 16

(Case 22). High power, picro-mallory stain showing hyaline membrane in blue.

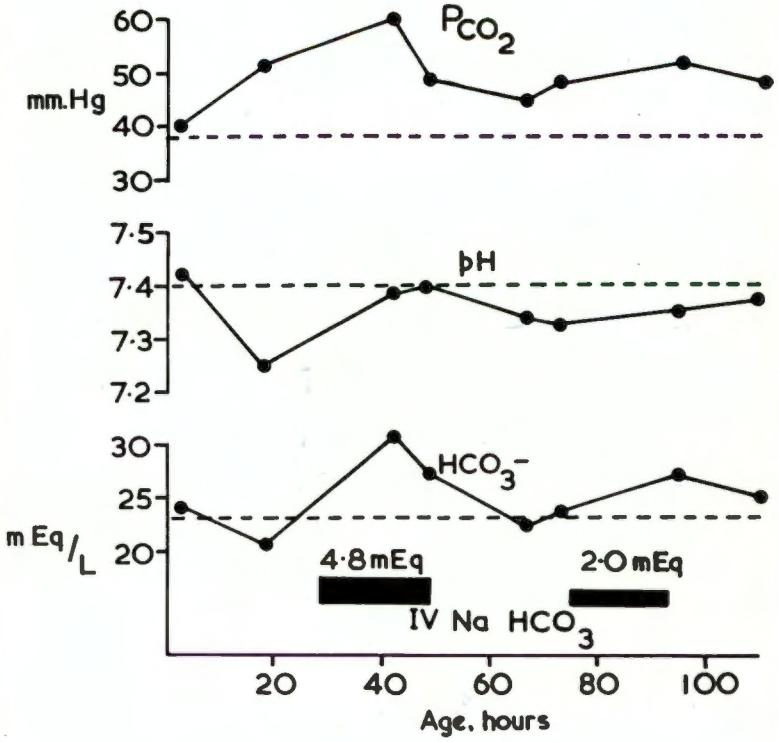


Fig. 17

(Case 19). Weight 1.22 kg.
Moderately severe respiratory failure with apnoeic spells right from the outset.

(The O_2-saturation was not estimated in this case).

Cases of Respiratory Failure with Apnoeic Attacks as the Predominant Feature

The following cases are described:

1. Moderately severe case (Case 19).
2. Very severe cases (Cases 20 and 21).

1. Moderately severe

Case 19. (Fig. 17) The mother had an incompetent cervix, and a Shirodkar stitch was inserted at 26 weeks. Two weeks later she went into labour spontaneously. She had a temperature of 101°F. and a foul-smelling vaginal discharge.

The baby who weighed 1.22 kg. was apnoeic for almost 10 minutes after birth. She responded to sucking out of the air passages and positive pressure oxygen by mask. 2½ hours later the colour was good in 40% oxygen. There was moderate rib and sternal recession. Air entry was fair on the left side and poor on the right. Breathing was regular at 68/min. when she was not having apnoeic spells.

Because the mother was infected we thought it inadvisable to pass a catheter into the baby's umbilical artery. All the tests were done on arterialized blood collected from a heel prick, and the oxygen saturation was not measured.

3½ hours after birth the pH was 7.42, P_{CO_2} 42 mm. Hg and the bicarbonate 24.5 mEq/L - all within normal limits.

On Day 2 the apnoeic attacks were a little more frequent. In between attacks about 40% oxygen was needed to maintain a good colour.

The P_{CO_2} went up to 51 mm. Hg, the pH dropped to 7.25. The bicarbonate was 20.5 mEq/L. Because of the respiratory acidosis, intravenous glucose/bicarbonate infusion was given (65 ml./kg./day of a solution of $NaHCO_3$ 100 mEq/L in 10% glucose). After 12 hours the pH had risen to 7.39 and the bicarbonate to 30.5 mEq/L., but the P_{CO_2} had now risen to 60 mm. Hg. The apnoeic spells were fairly frequent and rib recession was still present. The infusion was stopped after 20 hours.

On Day 3 because the pH was slowly falling the infusion was restarted and continued for 18 hours.

On Day 5 the baby was very much improved. The P_{CO_2} was 48 mm. Hg and the bicarbonate and pH were normal. The baby still had the occasional apnoeic attack and required extra oxygen (30-40%) for about ten more days.

Summary: During the first 5 days apnoeic attacks were prominent. In between attacks there was marked oxygen dependence, requiring 30-40% oxygen to maintain a good colour. The moderate hypercapnia may have been due more to the repeated apnoeic attacks than to any pulmonary lesion.

2. Very severe cases

Case 20. (Fig. 18) The mother, a primipara, had a small haemorrhage a day before the baby was born at 27 weeks gestation. The delivery was spontaneous vertex. The baby weighed 0.94 kg. He was apnoeic for 5 minutes after birth and was revived with positive pressure oxygen

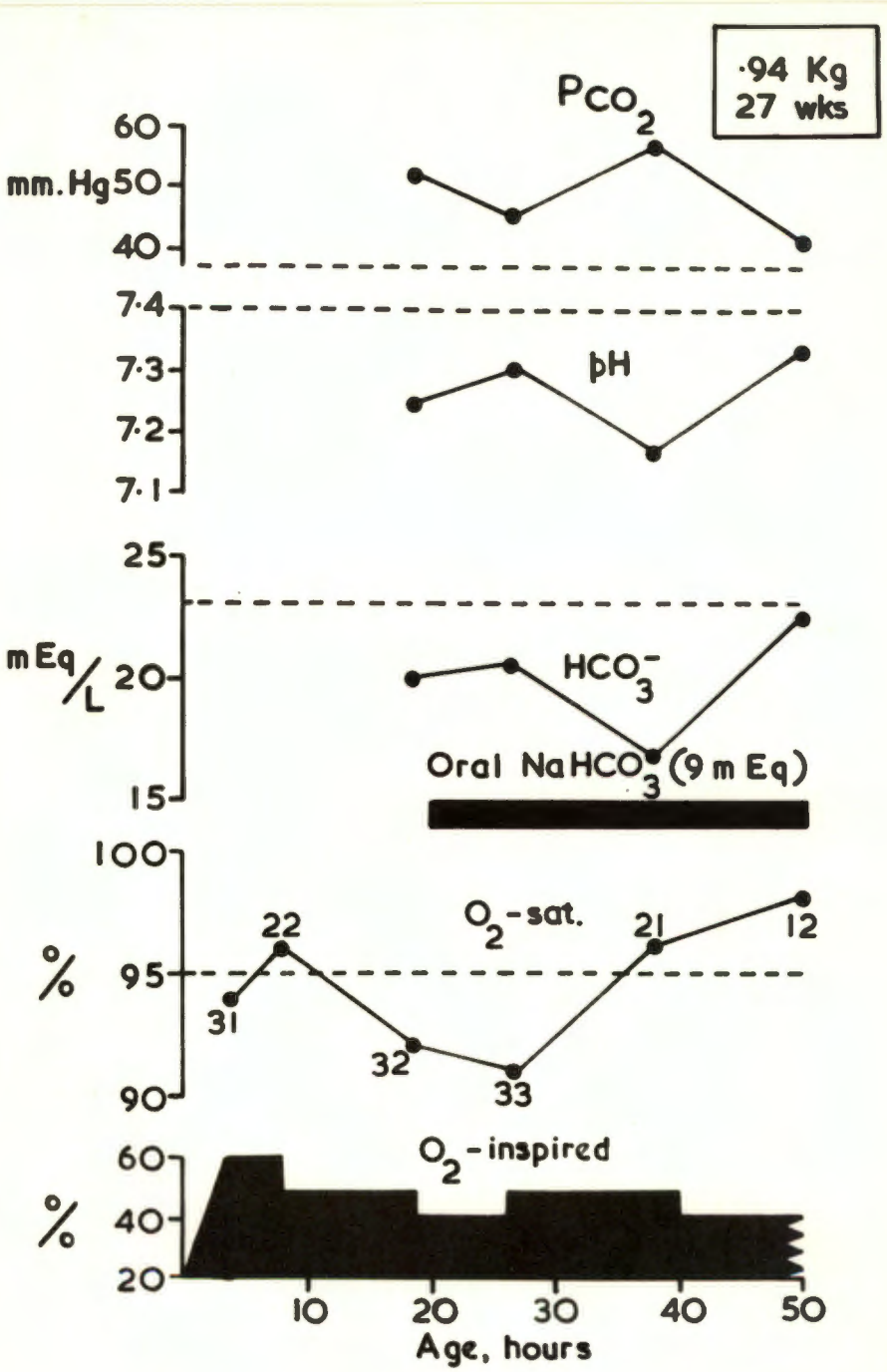


Fig. 18

(Case 20). Weight 0.94 kg. Respiratory failure in a previable baby with severe apnoeic attacks. Note marked improvement in respiratory function by 50 hours. (Subsequent to this, however, the apnoeic attacks became worse by the 4th day, and led to death on the 5th day). (See legends to Figs 6 + 12)

by mask. Two hours later he was a good colour in 40% oxygen. There was moderate rib recession and the air entry was poor. By 4 hours the ambient oxygen had to be increased to 60% to attain an arterial saturation of 96%. Apnoeic attacks were also evident at this stage. At about 18 hours, because of a respiratory acidosis, glucose bicarbonate tube feeds were started (15 mEq bicarbonate/100 ml. in 10% glucose) at the rate of 2 ml./hour increasing to 4 ml./hour. At 40 hours a metabolic acidosis was also present.

By 50 hours the blood gases were nearly normal. With an ambient O_2 concentration of 40%, the O -saturation was 97%. The P_{CO_2} was 42 mm. Hg, the pH 7.35 and the bicarbonate 22.5 mEq/L. The baby still had apnoeic attacks but the breathing in between these was fairly normal. At this stage the baby, although previable by period of gestation appeared capable of survival. However, by Day 4 the apnoeic spells had become very frequent and protracted. There was rapid deterioration in the baby's condition. He died on Day 5.

Histology of the lung showed collapsed lung in which bronchioles and alveolar ducts were distended with air. There was no evidence of hyaline membrane.

Summary: A very small premature infant with respiratory failure characterized by repeated apnoeic attacks; hypoxia responding to 40-60% oxygen; R-L shunt varying from 12-33%; hypercapnia of moderate degree.

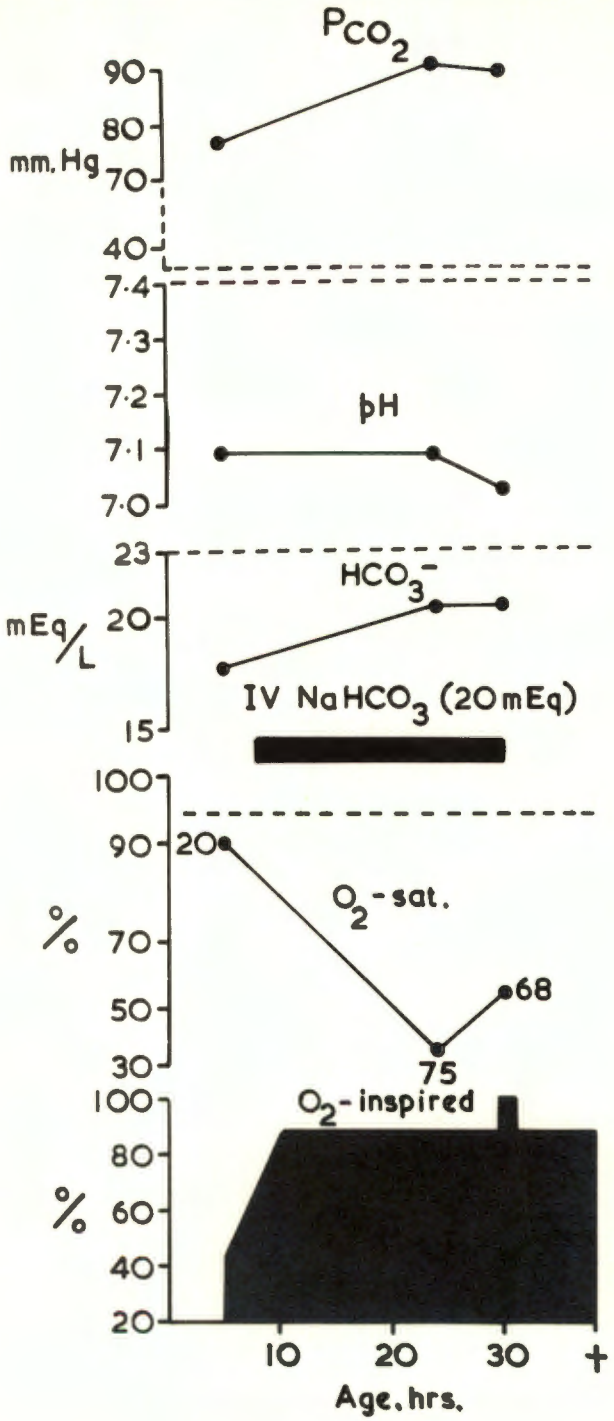


Fig. 19

(Case 21). Weight 2.08 kg. Very severe respiratory failure with repeated apnoeic attacks.

Case 21. (Fig. 19) A premature male infant born on district, spontaneous vertex delivery, weight 2.08 kg. Had difficulty with breathing right from birth. Revived by mouth to mouth breathing. Breathed unassisted after 40 minutes.

At 4 hours old his colour was good on 40% O_2. Rib and sternal recession was marked. Air entry was poor and there was an expiratory moan. The respiratory rate varied from 40-60/min.

At 9 hours, because of a respiratory acidosis (P_{CO_2} 77.5 mm.Hg) and a moderate metabolic acidosis (S. Bicarbonate 17.75 mEq/L) and pH 7.09, glucose bicarbonate infusion was started under the same scheme as case 12.

By 24 hours the O_2 saturation had dropped to 34%, although the baby was breathing almost pure oxygen (cf. Fig. 19). The bicarbonate rose to 20 mEq/L but the pH remained at 7.1. The respiratory rate ranged from 60-100/min. Air entry was very poor and rib recession was marked. At this stage apnoeic attacks became frequent and continued until death at 35 hours.

Histology of the lungs showed marked atelectasis. Many terminal bronchioles and alveolar ducts were lined by hyaline membrane.

Summary: Severe respiratory failure with repeated apnoeic attacks. The blood oxygen saturation continued to drop despite the very high concentration of inspired oxygen. There was severe hypercapnia. The pH remained low although the blood bicarbonate was raised from 17 to 20 mEq/L by means of an infusion of bicarbonate. There was a large R-L shunt.

Pulmonary pathology in infants dying from respiratory failure in the first days of life

In our series 8 cases ended fatally. Seven of these died within 48 hours. The eighth case survived for 5 days (cf. Fig. 8, Case 23). Four of these were clinically typical cases of the respiratory distress syndrome. In the other four cases apnoeic spells dominated the clinical picture from the outset.

The pulmonary pathology of these two groups of cases was the same viz. gross atelectasis in all the cases with varying degrees of hyaline membrane in one half the cases. Although the hyaline membranes present a rather dramatic picture (cf. Figs. 2, 3, 15 and 16) we agree with James (1959) that the diagnosis of the syndrome should rest on "the history, symptomatology and clinical signs rather than the presence or absence of membranes".

Discussion

(i) R-L shunt in the newborn. It is known that in normal adults there is small R-L shunt amounting to about 2% of the cardiac output, resulting from shunts through the bronchial and Thebesian veins. No comparable information exists for the normal infant. The data shown in Fig.5 refer to premature infants in the first 16 hours of life. These infants showed only slight and transient symptoms, while respiratory function, as judged by arterial O_2-saturation and P_{CO_2}, was good. The data may therefore be useful as a guide to the level of shunt to be expected in healthy premature infants.

The mean value for R-L-shunt was 10.6%, seven of the ten cases gave values between 7 and 11%, and the highest value was 23%. No great accuracy can be claimed for these figures since at these low levels of shunt an error in measuring O_2-content of only 0.1 vols.% will alter the shunt value by 2%. That they are reasonably correct nevertheless, is suggested by the fact that using the same technique a normal adult gave a shunt value of 3%.

A comparison of these findings can be made with those for normal newborns by utilizing some data provided by Graham (1959), who measured the P_{O_2} of arterial blood in infants 3-50 hours old, while breathing 50% O_2. The mean value for arterial P_{O_2} was 153 mm. Hg, compared with an alveolar P_{O_2} of 317 mm. (as calculated by equation (2)), giving a difference between alveolar and arterial O_2-tensions of 168 mm. This figure corresponds to an O_2-content difference of 0.52 vols.%*

*Since physically dissolved O_2 increases by 0.00312 vols.% for each mm. Hg rise in P_{O_2} (Sendroy et al., 1934).

between pulmonary capillary blood and arterial blood, and to a shunt value (equation 3) of 9.4%. This figure for the R-L-shunt in normal newborns is about the same as the mean of 10.6% arrived at for the prematures studied.

Besides the anatomical sites available in the adult for R-L-shunts, the newborn infant possesses also the ductus arteriosus and the foramen ovale. Oliver, Demis and Bates (1961) studying infants in the first hour of life, found L-atrial blood to have a higher P_{O_2} than arterial (aortic) blood, and concluded that this must be due to some R-L-shunting through the ductus, a conclusion compatible with the bidirectional flow through the ductus noted by James (1959) in infants in the first hour of life.

R-L-shunting through the foramen ovale is also probably the rule for normal infants during the first few days of life, as was shown originally by Lind and Wegelius (1954) by means of angiocardiography, and recently by Stahlman, Merrill, Lequire and James (1961) using an ingenious dye-dilution technique.

Thus R-L-shunting occurs in the newborn infant at a number of sites outside the lungs, and this could account for the shunt values observed. Whether in addition there is an intra-pulmonary shunt is not known.

(ii) <u>The pulmonary defect in the respiratory distress syndrome.</u>

Comparing a series of cases of the respiratory distress syndrome of graded severity such as Cases 11, 12, 13 and 22 the findings range

from the case of moderate severity where there is an O_2-responsive hypoxia, a small shunt, and no hypercapnia, to the severe case where there is O_2-unsaturation even in high O_2-concentration, a very large R-L-shunt and gross hypercapnia.

If the same type of pulmonary defect is responsible for both moderate and severe forms of the respiratory distress syndrome, then a distribution defect would seem to cover the facts best. A distribution defect of the kind where a proportion of alveoli are non-perfused will at first lead to an increase in functional dead space, with an O_2-sensitive hypoxia, but no CO_2 retention, the pattern seen in Case 11. CO_2 retention is here absent because a small increase in ventilation suffices to remove any excess CO_2 via well-functioning alveoli. Further increase in the proportion of non-perfused alveoli will eventually lead to functional dead space approaching tidal volume. Removal of excess CO_2 being limited by the capacity to increase ventilation, CO_2 now accumulates.

This conclusion is in accord with the rather scanty facts available from earlier studies. An increase in functional dead space was the most prominent fault in respiratory function found by Karlberg, Cook, O'Brien, Cherry and Smith (1954) in their study of respiratory function in the respiratory distress syndrome; the ratio of functional dead space to tidal volume averaged 0.66 in three distressed infants, against 0.32 in normals. Nelson, Prod'hom, Lipsitz, Cherry and Smith (1961), whose study included measurement of alveolar-arterial gradients

for O_2 and CO_2, concluded that a severe degree of non-perfusion of alveoli was a prominent feature of these cases.

In addition, in the severe cases of respiratory distress syndrome there is a large R-L-shunt which may amount to 60% or more, as was pointed out by Strang and MacLeish (1961) and confirmed in our cases. The site of this shunt is at present not known. Rudolph and co-workers (1961) catheterised a series of distressed infants, studying particularly the question of shunts through the ductus arteriosus. In their cases with severe respiratory distress syndrome a large L-R ductal shunt was the most conspicuous feature; in some cases a concomitant R-L ductal shunt was also observed, but in only one of the 10 severe cases studied was this judged to be large. This infant while breathing pure O_2 gave a saturation of 80% in L-atrial blood and 63% in aortic blood. We have calculated that these figures imply that there was a "pre-ductal" R-L-shunt (through foramen ovale and/or lungs) of 50%, and one of 12% through the ductus. The only facts bearing on the foramen ovale as the site of R-L-shunting is a brief comment by Stahlman (1961) that such a shunt is demonstrable by dye-dilution techniques in normal newborns, and that in distressed newborns this "may be increased".

There is thus not much evidence to suggest that the very large amount of blood R-L-shunted in these cases all by-passes the lungs via the ductus and foramen ovale, although doubtless some of it does so. It seems probable that a considerable part of the shunt must be intra-pulmonary, much of the blood which flows through the lungs making no

contact with functioning alveoli. A diffusion defect, even if severe, is hardly compatible with the findings, because with such a defect 0_2-saturation is very sensitive to ambient 0_2 concentration, and we have found that the shunt effect in distressed infants is in general not less when breathing pure 0_2 than when breathing 40-80% 0_2(Table 2).

To summarise conclusions then, in the respiratory distress syndrome findings would be compatible with a distribution defect, whereby much of the inspired air goes to non-perfused alveoli and much of the perfusing blood goes to non-ventilated alveoli. Such a gross functional disturbance of the lungs is, of course, in keeping with the evidence of a similarly gross lung disorder obtained by auscultation (deficient air entry) by radiology (generalized mottling or ground-glass opacity of the lungs), and in fatal cases, by histology (extensive atalectasis with or without hyaline membrane).

(iii) Cases of respiratory failure with apnoeic attacks as the predominant feature. In fatal cases of the respiratory distress syndrome death is often preceded by a series of severe apnoeic attacks. We wish, however, to discuss a different problem, that presented by cases where apnoeic spells dominate the picture from the outset, while the typical features of the respiratory distress syndrome - tachypnoea, recession, expiratory moan - may be by comparison less conspicuous. Most of these infants are very premature. We have already given some account of the mildest forms of this clinical picture (Case 1, Fig. 6). In such infants tachypnoea with mild apnoeic spells occur in the

first 24-48 hours after birth, without any other evidence of respiratory failure.

There remains to be mentioned the problem of infants such as cases 19, 20 and 21 described, where the apnoeic spells are from the beginning severe and are associated with other evidence of respiratory failure. In these cases we have found (1) that the blood gas and acid/base findings are similar to those seen in the typical cases of the respiratory distress syndrome (Figs. 17, 18 and 19); (2) that the severe cases also have large R-L shunts (Figs. 18 and 19) (3) that the pulmonary pathology is the same viz. atalectasis as a constant finding plus hyaline membrane in half the cases. In spite of these similarities between the two groups of cases, we incline to the view that the group of cases where apnoeic spells are the predominant feature should be differentiated from the respiratory distress syndrome. A reasonable surmise would be that in the apnoeic group the symptoms arise primarily from central failure, with pulmonary change occurring secondarily; while in the respiratory distress syndrome there is primarily pulmonary failure, which may lead eventually to central failure as a consequence. That is as far as we can go at present. The principles of treatment discussed in the next section also apply to this group of cases.

Principles of treatment of the respiratory distress syndrome

1. Oxygen therapy. When the infant's needs for O_2 are being considered, the brain is usually thought of as the organ for which a good supply of O_2 is most essential. Yet the brain can function reasonably well with quite low O_2-tensions, as is clear from the normal development of the nervous system in many infants that survive with cyanotic heart disease. Oxygenation of the respiratory muscles, however, may be crucial for the infant with the respiratory distress syndrome, in that its survival may depend upon whether or not the respiratory muscles can continue to ventilate the lungs throughout the critical days when the illness is at its height. Some discussion of the work of breathing is therefore relevant.

The work of breathing in the normal infant at rest has been calculated to be much the same as for the adult, about 1% of the basal metabolism (Cook, Sutherland, Cherry, Mead, McIlroy, Segal and Smith, 1957). It is obvious from watching any infant with severe respiratory distress that the work of breathing must be very greatly increased. The conspicuous retraction of ribs and sternum demonstrates the abnormal resistance of the lungs to expansion (low compliance) (Cook et al., 1957). The respiratory rate of 80 or more reflects the effort to maintain a large minute volume in order to compensate for a large functional dead space (Karlberg et al., 1954).

The situation is somewhat analogous to the respiratory failure of the adult with advanced emphysema, where the increased work of breathing

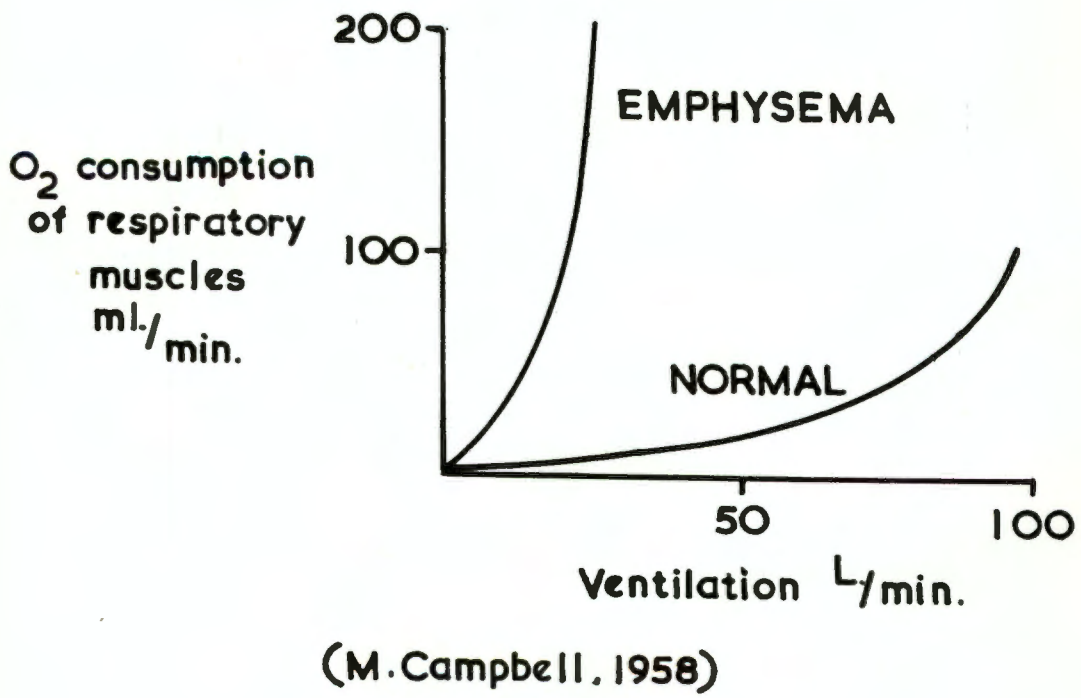


Fig. 20

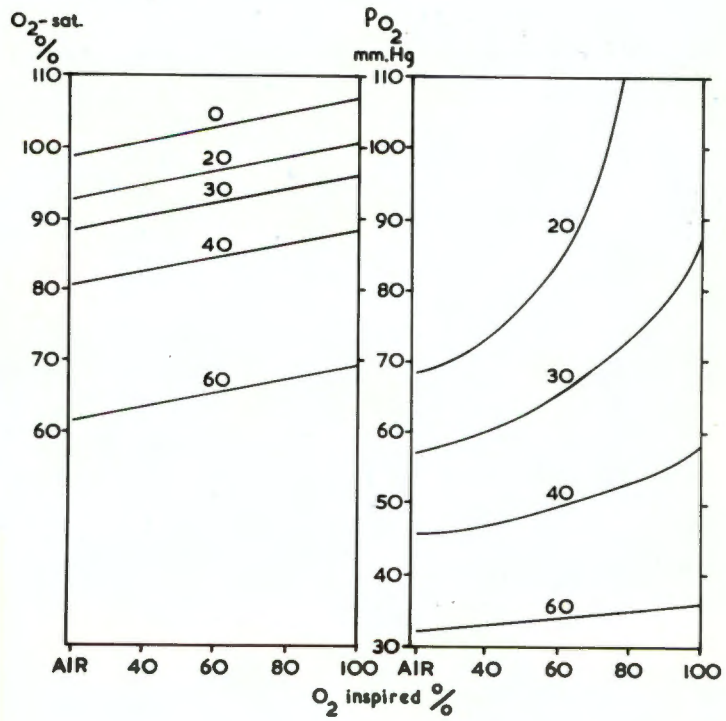
O_2 consumption of respiratory muscles in relation to ventilation in emphysematous patient and normal adult.
(see text)

is also due in part to the need to compensate for a large functional dead space by increased ventilation. In these cases the work of breathing rises steeply as ventilation is increased, and the point is soon reached where ventilation cannot be further increased because the O_2 cost of breathing is more than the extra O_2 taken in (Fig. 20) (Campbell, 1958).

The only study in which an attempt was made to measure the work of breathing in infants with the respiratory distress syndrome is that of the Boston team, Karlberg et al. (1954) and Cook et al. (1955). They concluded that these infants may be expending 4 to 10 times the normal amount of energy on breathing, and pointed out that fatigue of the respiratory muscles might often be the cause of death.

These considerations lead to the conclusion that the aim of O_2 therapy in the respiratory distress syndrome should be to maintain the P_{O_2} of blood supplying the respiratory muscles (i.e. of aortic blood) at a "high normal" level. As we have not measured P_{O_2} we have aimed at maintaining O_2-saturation at about 95-97%, corresponding to a P_{O_2} of 80-100 mm. Fall in $\left[HCO_3^-\right]$ has been regarded as a measure of the accumulation of lactic acid from imperfectly oxygenated respiratory muscles.

We must now consider how the O_2-saturation and O_2-tension of arterial blood are related to the concentration of inspired O_2. If there is no R-L-shunt, then any O_2-unsaturation present is due to pulmonary disorder and will largely disappear with a modest increase



(a) (b)

Fig. 21

Effect of concentration of inspired oxygen on (a) arterial oxygen saturation, (b) oxygen tension (P_{O_2}), at various levels of R-L-shunt, as shown by curves for 0, 20, 30, 40 and 60% shunt.

in the ambient O_2 to 30-40%, as already described.

The situation when a R-L-shunt is present is most simply displayed by the graphs shown in Fig. 21.* These show that with moderate shunts, up to 30%, O_2-therapy is able to restore arterial O_2-saturation to near normal, provided high concentrations are used. Thus for a 30% shunt, O_2-saturation in air is about 88%, and can be raised to 95% by breathing 90% O_2; the corresponding rise in P_{O_2} is from 57 mm. to 79 mm. Hg, a gain of 22 mm. With a 60% shunt, however, saturation will be 61% in air, raised to 68% by breathing 90% O_2, but at this point in the S-shaped HbO_2 dissociation curve the corresponding rise in P_{O_2} is from 32 to 36 mm., a gain of only 4 mm.

The use of high concentrations of O_2 up to 90% is seen to be fully justified in those cases where unsaturation is not abolished by lower levels of O_2, always provided that high concentrations of inspired O_2 are without toxic effects under these conditions (see later). Even with these high levels in the most severe cases (such as Case 13) the

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*The figures from which these graphs were constructed were derived as follows. Assuming a P_{CO_2} of 40 mm. and an R.Q. of 0.8, alveolar P_{O_2} was calculated from equation (2) for different concentrations of inspired O_2. Inserting these values in equation (1) (the correction factor 100/f was omitted) gave the corresponding O_2-content of pulmonary capillary blood, the O_2-capacity of which was taken as 20 vols.%. The values so obtained for O_2-content of pulmonary capillary blood, when inserted into equation (3) with an assumed arterio-venous O_2-content difference of 5 vols.%, enabled arterial O_2-content and saturation to be calculated for any shunt value (Fig. 21a). From these O_2-saturation values, corresponding values for P_{O_2} (Fig. 21b) were read off from a standard HbO_2 dissociation curve for adult blood (Severinghaus, 1958), data for foetal blood in that part of the curve lying above 95% saturation not being available.

large shunt present will still make it impossible to achieve anything approaching normal oxygenation. Nevertheless, even though the gain in arterial P_{O_2} may amount to only a few mm. Hg, this may yet be of significant help to the fatigued respiratory muscles.

In practice O_2 needs will usually have to be gauged in terms of cyanosis. We have found that in neonates central cyanosis can be recognized when the saturation falls below about 85%. which is well below the lowest level of 94% found in well prematures (Fig. 5). Saturations of 85%, 94% and 97% correspond to P_{O_2} values (adult Hb) of 52, 73, and 100 mm. Hg. Thus O_2 given at a concentration sufficient only to abolish cyanosis will give arterial P_{O_2} levels far below either the normal or the optimum. As a working rule therefore O_2 should be given at one-quarter higher concentration than the minimum needed to abolish cyanosis. Thus if there are signs of distress, but cyanosis is absent in air, O_2 at about 25% should be given. If cyanosis is abolished by 40%. O_2, then 50% O_2 should be given.

Oxygen toxicity. A clear distinction must be drawn between the possible local toxic effects of O_2 on the lungs, and the effects of O_2 at high tension in arterial blood upon organs such as the eye. As regards the latter, retrolental fibroplasia was common at a period when premature babies were indiscriminately exposed for long periods to high ambient O_2 concentrations, without regard to the resulting O_2-tensions in the blood and tissues. The principles which we have suggested should govern O_2 therapy, aim at maintaining a normal O_2-tension in the blood,

while in practice it is often impossible to attain a tension as high as this, however high the ambient O_2 concentration. The danger of retrolental fibroplasia in infants given O_2 according to this principle thus seems negligible on theoretical grounds, and no cases have been encountered.

The amount of danger (if any) to the lung itself of exposure to high O_2 concentrations is much harder to define. In experimental animals exposure to 70-100% O_2 for several days produces serious and often fatal lung lesions in the adult mouse, rat, rabbit, cat, dog and opossum. On the other hand the newborn of these species are very resistant to such damage and in them lung lesions can, in general (the guinea-pig is an exception), only be produced by combining exposure to O_2 with vagotomy, intratracheal injections of foreign material, or other insult (Tran Dinh De and Anderson, 1954; Smith et al., 1932; Berfenstam, Edlund and Zettergren, 1958; Patz, 1958; Buckingham and Sommers, 1959).

Less is known about the pulmonary effects in adult humans exposed to O_2 (at normal barometric pressures). The best controlled study is that of Comroe and co-workers (1945), who exposed adult males for 24 hours continuously to 100% O_2. Most developed symptoms such as substernal discomfort or pain and cough, although symptoms were never severe enough to interfere with the experiment. The only functional effect discernible was some reduction of vital capacity. Exposure to 75% O_2 likewise produced symptoms suggesting irritation of the

respiratory passages, but 50% O_2 was without effect. Becker-Freysing and Clamann (1950) breathed 90% O_2 for 65 hours, ceasing then because one of the subjects became ill with vomiting. Both subjects showed some reduction in vital capacity.

In human newborns, then, we need to know whether exposure to high O_2 concentrations for many hours is liable to produce moderate symptoms as in adults, or gross lung lesions as in adult experimental animals, or no effects at all as in newborn animals. Unfortunately there are few facts with which to answer this important question. In the period after 1954, when the role of oxygen in retrolental fibroplasia became recognized, the suggestion was often made that oxygen might play a part also in causing the lung lesions found in newborns dying from respiratory failure. No evidence for this has appeared since that time, nor (so far as can be ascertained) has there been any striking fall in the incidence of the respiratory distress syndrome in the many centres where, since about 1954, the use of high O_2 levels in nursing prematures has been greatly curtailed. Some have even suggested that the stricter use of oxygen was followed by some rise in mortality of prematures, and questioned whether this might not mean that infants with the respiratory distress syndrome needed more O_2 than they had been receiving (Avery and Oppenheimer, 1960).

We have concluded that on present evidence the possible harmful effect of O_2 on the lung do not outweigh the sound reasons that exist for using O_2 in the amounts required to oxygenate the distressed infant adequately.

2. The correction of acidosis. Usher (1961) focussed attention on the importance of acidosis in the respiratory distress syndrome and considered that its correction by intravenous $NaHCO_3$ with glucose increased survival rates. Some experimental support for this view came from Dawes and Shelley (1961) who found that the length of time that foetal lambs survived complete asphyxia increased some threefold when acidosis was corrected by infusion of Na_2CO_3 with glucose, but not by either alone.

Acid-base homeostasis inevitably breaks down in a severe case of the respiratory distress syndrome, where an initial respiratory acidosis with later a super-added metabolic acidosis, is the rule. To correct this acidosis appears rational, in view of the wealth of evidence that a major departure from the normal pH interferes with many of the fundamental enzyme processes in the body. If the pH is falling we have infused intravenously $NaHCO_3$ 100 mEq./L. in 10% glucose at an initial rate of 65 ml./kg./day (Usher, 1961). The total amount of $NaHCO_3$ given depends on serial pH measurements, so that in effect the baby is titrated to an arterial pH of about 7.4. To achieve this correction, an amount of Na may have to be given over 24-48 hours amounting to as much as half to two-thirds of the Na in the extracellular fluid (see Cases 12, 13). As might be expected, therefore, oedema is sometimes a complication of this treatment, although this has not proved of serious import. Although the same fluid may occasionally be successfully given by gastric tube, most of the

infants sufficiently ill to need this treatment fail either to retain or to absorb it by this route.

Where arterial specimens have not been available, pH has been measured on heel-prick blood, with sufficient accuracy for regulating the bicarbonate therapy.

3. Humidity. Babies with severe respiratory distress syndrome still continue to breathe through the nose, so that air entering the lungs must be assumed (as in adults) to be saturated with water vapour at body temperature. Therefore humidification of the ambient air can have no effect upon the lungs. The same applies to the inhalation of aqueous mist, and this treatment was found to be without effect on the pulmonary disorder of infants with the respiratory distress syndrome by Silverman and Anderson (1956).

Humidification does however reduce the normal losses of water from skin and respiratory tract, particularly the latter (O'Brien, Hanson and Smith, 1954). Reduction of water loss in this way may be desirable, if, for instance, fluid intake is withheld for several days, but under different circumstances, such as when fluid is being given intravenously, it might not be desirable.

Under average nursery conditions with a humidity of 30-40%, the newborn baby breathing quietly loses water via the respiratory tract at the rate of about 0.4 g./kg./hour, and this loss may easily rise to 0.8 g./kg./hour or more if the baby hyperventilates (Hooper, Evans and Stapleton, 1954; O'Brien et al., 1954). Eliminating this loss, as can

Fig. 22

Sternal traction.

The baby's weight was 950 g. and the traction 50 g.

be done by maximum humidification, is equivalent to cutting down the baby's losses by 0.5 cals./kg./hour*, which represents one quarter of its basal metabolism. Humidification must thus have the effect of enabling the distressed infant to maintain its body temperature while in an ambient temperature appreciably lower than would otherwise be the case (Silverman and Blanc, 1957). That the maintenance of a normal body temperature is of importance for survival seems probable on present evidence (Silverman, 1961).

4. Sternal traction. We have laid particular emphasis on the work imposed on the respiratory muscles in the respiratory distress syndrome. A mechanical means of lightening this load would therefore be a logical form of treatment. A number of different mechanical solutions to the problem have been tried (Donald and Lord, 1953; Benson et al., 1958), but the only one of which we have experience is sternal traction (Love and Tillery, 1953; Michelson, 1953). It is applicable to those cases of the respiratory distress syndrome where marked in-drawing of the lower sternum accompanies each downward excursion of the diaphragm, as is seen especially in small prematures, who, in addition to the stiff lungs typical of the respiratory distress syndrome, have a weak thoracic cage. Their situation can be likened to that of someone who is trying to pump a large volume of air using bellows with a defective framework lacking rigidity. When such bellows are forcibly opened to "inspire" air the framework tends to collapse, so that only a fraction of the potential "tidal air" of the bellows can be utilised. Despite

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*Since 1 ml. water evaporated at 37°C. loses 0.58 cals.

the large amount of work expended by the operator in trying to compensate for the mechanical defect by working the bellows faster, the "minute volume" he achieves is low.

The method we have used is to pass a suture through the tissues attached to the front of the xiphisternum. The suture is taken through a hole in the roof of the incubator vertically above and is attached to a counter-weight (Fig. 22). The amount of traction is adjusted to give optimum relief to breathing; usually about 5% of the infant's weight is adequate, but as much as 10% of the body weight may be needed to stabilize the sternum, a useful demonstration of the magnitude of the muscular forces involved in respiration in distressed infants.

The immediate effect of applying such traction in a suitable case is to allow the exaggerated diaphragmatic excursion to be much reduced. In a small series of cases we have been impressed by the mechanical effectiveness of the method, and by the obvious relief it can bring to the infant.

Summary

Respiratory failure accounts for a large, if not the largest percentage of deaths in the first 48 hours of life. It often manifests itself clinically as a recognizable syndrome, the respiratory distress syndrome, with certain characteristic features - tachypnoea, rib and sternal recession, an expiratory moan and poor air entry. Physiologically there is oxygen unsaturation, carbon dioxide retention (raised P_{CO_2}) and acidosis (low pH).

In this study we have tried to define the physiological disturbances found in the respiratory failure of the respiratory distress syndrome and to establish the principles which should govern the correction of these disturbances. We made a detailed study of a relatively small number of cases, observing them from the earliest stages of the illness until recovery or death, with serial measurements of the four variables, oxygen saturation, carbon dioxide tension (P_{CO_2}), pH and bicarbonate of arterial blood.

Before describing the details and conclusions of this study we have given an account of what is already known about the respiratory distress syndrome. This is followed by a historical review of the literature of what was originally known as hyaline membrane disease. We have tried to show how the emphasis has shifted from hyaline membranes to a more comprehensive clinical concept - the respiratory distress syndrome. Current views on the aetiology of the syndrome are also discussed.

The method for collecting anaerobic specimens of arterial blood by passing a catheter via the umbilical artery into the iliac artery is described. The samples of blood so collected were examined for oxygen content and capacity by the Roughton-Scholander syringe technique and the pH, P_{CO_2} and bicarbonate were measured by the Astrup method. The method for estimating right to left shunts is described in detail.

The findings in 10 "normal" premature infants are tabulated. Two of these cases are described in greater detail. The data obtained in these "normal" prematures acted as a useful base line.

Four typical examples of the respiratory distress syndrome of graded severity are described in detail with clinical histories, blood gas and acid/base findings.

Three cases of respiratory failure characterised by apnoeic attacks from the outset as a dominant feature are also described.

These results are followed by a summary of the pulmonary pathology in 8 fatal cases.

Conclusions

1. The R-L shunt in normal premature infants is estimated to average 11%. In severe respiratory distress the shunt increases as the illness progresses. The site of the shunt in distressed infants is not known, but is probably largely intrapulmonary.

2. The pulmonary disorder in the respiratory distress syndrome is probably a distribution defect.

3. The work of the respiratory muscles in infants with respiratory distress is greatly increased, and survival may depend on the capacity of these muscles to maintain a high rate of work. To provide optimum conditions for the respiratory muscles to work in should therefore be the aim of treatment.

Principles of treatment

a. Oxygen therapy is discussed in terms of oxygen concentration needed to restore normal arterial saturation. High concentrations up to 90% may be indicated. Oxygen toxicity is considered a lesser danger to the infant in respiratory failure than oxygen lack.

b. Acidosis, whether respiratory or metabolic should be corrected by infusing sodium bicarbonate with glucose.

c. Humidification reduces water losses from the respiratory tract, and hence also reduces heat losses from the body; to this extent it may be of value.

d. Sternal indrawing may be treated by sternal traction.

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