AETIOLOGICAL FACTORS IN THE RESPIRATORY DISTRESS SYNDROME OF THE NEWBORN

by

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INTRODUCTION

The respiratory distress syndrome of the newborn (RDS) is essentially a disease of prematurity. Its synonyms include 'hyaline membrane disease' and 'pulmonary syndrome of the newborn'. It occurs in approximately 20% of infants classified as premature, that is in those weighing 2,500 g (5 lb 8 oz) or less at birth. When infants above this weight are affected, they are almost invariably premature by gestation. Between a quarter and half of the infants may die, and mortality increases with decreasing gestation and birth weight. A pre-natal cause has been postulated, for the signs are present from birth, or develop within a very short time of it. Characteristically, the infant shows a raised respiratory rate, an expiratory grunt, indrawing of the ribs and sternum, and a reduced air entry on auscultation. Chest radiography shows a fine granular mottling of the lung fields with the air-filled tracheobronchial tree showing up clearly in relief. In unfavourable cases, cyanosis soon appears, and though at first this may be relieved by oxygen, the infant frequently develops periods of apnoea, increasing cyanosis, peripheral oedema and becomes unresponsive to stimuli. Death usually occurs within 24-72 hours of delivery, just as in the favourable cases recovery has often ensued by this time. Autopsy shows a widespread atelectasis, with over-distended terminal bronchioles and alevolar ducts containing an eosinophilic hyaline membrane. When death occurs within a few hours there may be little or no membrane formation, and it has never been seen in the stillborn infant.

This condition has exerted an almost hypnotic fascination for paediatricians, pathologists and physiologists over the past 60 years. In the past decade particularly, with new techniques available for

investigating the heart and lungs both in animals and humans, a picture of the functional changes which occur has emerged. The pulmonary surface active factor which makes the alveoli stable and prevents the lung from collapsing on expiration, is absent or greatly diminished. The resulting widespread atelectasis causes low lung compliance, this in turn leading to ventilatory insufficiency and right-to-left shunting. A respiratory acidosis, caused by under-ventilation, and a metabolic acidosis due to anaerobic glycolysis resulting from oxygen deficiency, both develop. The hyaline membrane, now thought considerably less important than formerly, is derived from a blood transudate and breakdown products of the lung itself.

Though the exact sequence of the cycle is uncertain, and many events in it are interrelated, their occurrence seems securely established. Striking aetiological factors, however, other than the one constant of immaturity, have eluded clinicians and though brave and skilful attempts have been made to treat the disease, it remains a leading cause of perinatal mortality. Prevention cannot be attempted without a more certain knowledge of aetiology. Clinical analyses of related factors have been few, and insufficient attention has been paid to comparing carefully cases of like weight and gestation, for it seems likely that complicating factors may vary with gestational age. The purpose of this work has been therefore to make such an analysis of all mothers who gave birth to infants weighing 2500 g (5 lb 8 oz) or less over a 6-year period, in an effort to establish some positive factors.

HISTORICAL REVIEW

The respiratory distress syndrome has acquired a large literature, and though the analysis has been concerned with aetiology only, a complete understanding of the functional and pathological changes is necessary so that possible influencing factors may be critically evaluated.

The first description of RDS is probably that of Hochheim (1903), who reported a peculiar membrane in the lungs of two infants dying after birth. Further histological descriptions of larger numbers of cases were given some 20-30 years later (Johnson, 1923; Johnson and Meyer, 1925; Farber and Sweet, 1931; Farber and Wilson, 1932), establishing the essential features of widespread resorption atelectasis with eosinophilic membranes lying adjacent to those portions of aerated lung - usually over-dilated terminal bronchioles and alveolar ducts. The membranes, certainly an arresting sight under the microscope, were considered all-important, and the cause of the atelectasis. They were variously interpreted as a form of neonatal pneumonia (Johnson, 1923), due to the effect of respiratory effort on aspirated amniotic sac contents, particularly vernix (Farber and Sweet, 1931; Farber and Wilson, 1932) or derived from degenerating epithelial cells (Rosenthal, 1935). They remained the centre of attraction for another 25 years, though Gruenwald (1953) alone disclaimed their importance, calling them 'eosinophilic red herrings'. He argued that the atelectasis which accompanied them was the prime cause of respiratory difficulty and that they were a secondary development, perhaps associated with the oedema fluid which he recognised was almost invariably present. In support he pointed out that infants with typical respiratory distress

dying within a few hours of birth showed an identical widespread atelectasis with virtually no membrane formation. Others had shown that radiographic changes in such cases were identical with those in which membrane formation could later be demonstrated at autopsy (Donald and Steiner, 1953). He also believed respiration to be necessary for membrane formation for he had never seen it in still-births (Gruenwald, 1955, 1958). His views have been amply confirmed and he has continued to make important additions to this subject.

The fact that the membrane was derived from the circulation became firmly established in the 1950's. Its predominantly fibrinous nature was demonstrated using a fluorescent antibody technique by Gitlin and Craig (1956), with other workers making contributory studies mainly with histochemical methods (Reutter, 1954; Laufe and Stevenson, 1954; Hadders and Dirken, 1955; Duran-Jorda, Holzel and Patterson, 1956; Lynch, Mellor and Badgery, 1956). Though its precipitation may be helped by thromboplastin from inhaled amniotic fluid (Laufe and Stevenson, 1954), interaction of inhaled acid mucopolysaccharide from respiratory or gastro-intestinal mucus or amniotic fluid with plasma proteins especially fibrinogen leaking from the pulmonary capillaries, seems more likely (Carone and Spector, 1960; Aherne, 1964). Electron microscope studies (Campiche, Jaccottet and Juillard, 1962) have confirmed the earlier views of Rosenthal and later supporters (Tregillus, 1951; Barter and Maddison, 1960) that epithelial necrosis is present and its products incorporated in the membrane. Thus it seems that membrane formation in RDS mirrors that seen in the lung in other pathological conditions which have in common capillary damage or altered capillary permeability such as phosgene poisoning (Groll, 1921), aspiration of kerosene (Barter, 1962), influenza (Martin, Kunin, Gottlieb, Barnes, Liu and Finland,

1959) and rheumatic pneumonitis (Goldring, Behrer, Brown and Elliott, 1958). Nevertheless the widespread atelectasis which is such a notable feature of RDS is lacking. Deficiency of fibrinolytic activators (Lieberman, 1959; Lieberman and Kellogg, 1960) and low levels of plasma profibrinolysin (Phillips and Skrodelis, 1958) may well contribute to the inability of the premature baby to deal with the membranes once formed. It seems certain then that the membrane is a blood transudate, probably drawn out by a high alveolar surface tension (see below), though increased pulmonary capillary permeability due to asphyxia may well play some part (Warren, Petersen and Drinker, 1942). It has been suggested that such permeability is greater in the premature (Celander, 1964).

Perhaps one of the most important advances in the understanding of this condition also occurred in the 1950's. Though both von Neergard (1929) and Gruenwald (1947) had supposed that surface tension played an important part in lung elasticity, the basic work on surface tension and lung stability was done by Pattle (1955, 1958, 1960) with complementary studies by Clements (Clements, 1957; Clements, Brown and Johnson, 1958). It can be summarised by saying that in order to be normally ventilated a lung must be lined with an alveolar cell layer secreting a material, now known as pulmonary surface active factor or pulmonary surfactant which has the remarkable property of changing surface tension with surface area, and achieving very low tension at reduced areas. This attribute makes the terminal air spaces stable, and acts, in Clements' words, as an 'anti-atelectasis factor'. The substance is a lipoprotein (Pattle and Thomas, 1961), mainly dipalmitoyl alpha-lecithin (Brown, 1964), derived from the mitochondria of the alveolar cells (Klaus, Reiss, Tooley, Piel and Clements, 1962). It has been demonstrated as a thin fluorescent line at the air-tissue interface on ultraviolet microscopy in guinea-pigs

(Bolande and Klaus, 1964) and in newborn infants (de Sa', 1965). Though Pattle (1958) first suggested it might be absent in RDS, it was Avery and Mead (1959) who established that this was so. Their work has been confirmed, using different techniques (Pattle, Claireaux, Davies and Cameron, 1962; Gruenwald, 1964; Reynolds, Orzalesi, Motoyama, Craig and Cook, 1965). Gruenwald, while demonstrating that poor pulmonary stability and immaturity are intimately connected, also showed that lungs of certain fresh stillbirths were involved, so emphasizing that the basic lesion originates before birth. Pulmonary surface active factor is present in foetal lung shortly after the transition from cuboidal to glandular epithelium occurs (Pattle, 1961; Campiche, Gautier, Hernandez and Reymond, 1963), that is from approximately 24 weeks gestation in the human. In very small premature infants the quantity of active phospholipid components is low (Adams, Fujiwara, Emmanouilides and Scudder, 1965). Foetal lung fluid, studied in lambs, chemically different from amniotic fluid and thought to be an ultrafiltrate of foetal plasma (Adams, Moss and Fagan, 1962; Adams, Fujiwara and Rowshan, 1963) contains pulmonary surface active factor but amniotic fluid does not (Fujiwara, Adams and Scudder, 1964). Since amniotic fluid is probably contributed to by lung fluid, this may indicate dilution or inactivation of the surfactant. A preliminary report that it is inactivated by fibrinogen has also appeared (Abrams and Taylor, 1964).

The fact that a deficiency of pulmonary surface active factor is seen in the massive lung collapse which occasionally follows operations involving a cardio-pulmonary by-pass and hence non-perfusion of the lung alveoli for a period, and also after experimental pulmonary artery occlusion, suggested that alterations in blood supply to the foetal lung might be of prime importance in the pathogenesis of RDS (Tooley, Gardner, Thung and Finlay, 1961). Experimental work in the newborn lamb has shown that the pulmonary vascular bed is very

labile and sensitive to many pre-natal and post-natal influences, important among them asphyxia (Cook, Drinker, Levison and Strang, 1963; Cassin, Dawes, Mott, Ross and Strang, 1964; Cassin, Dawes and Ross, 1964). Preliminary evidence to show that pulmonary vasoconstriction and diminution in pulmonary blood flow are present in RDS has been presented (Chu, Clements, Cotton, Klaus, Sweet, Thomas and Tooley, 1965), supporting the hypothesis that hypo-perfusion of the alveoli may be of great importance in pathogenesis. A tantalising pointer to the importance of the pulmonary circulation has been provided in a case report by Bozic (1963). An infant dying from RDS was found at autopsy to have three anomalous arteries from the descending aorta supplying the inferior section of the left lower lobe. Atleectasis and hyaline membrane formation were widespread, except in that part of the lung supplied by the aberrant aortic vessels, which was normally aerated.

The extensive atelectasis in this disease gives rise to retraction, often striking, of the ribs and sternum, and it is obvious that the work of breathing is considerable. Low levels of tissue carbohydrate, most marked in heart, liver and respiratory muscles, found in infants dying with RDS reflect this increased work and the energy demands of these infants (Shelley, 1964). Vital capacity and tidal volume are reduced as the illness progresses unfavourably, the physiological dead space becomes relatively greater in relation to tidal area, and that available for gas exchange less (Karlberg, Cook, O'Brien, Cherry and Smith, 1954). Lung compliance is greatly reduced (Cook, Sutherland, Segal, Cherry, Mead, McIlroy and Smith, 1957). Thus it appears there is a ventilatory failure involving large volumes of lung tissue. Vascular shunts which could theoretically take place through

the foramen ovale, ductus arteriosus and unventilated areas of the lungs have been shown to occur. Right-to-left shunting has been revealed by gas analysis (Strang and Macleish, 1961; Warley and Gairdner, 1962; Nelson, Prod'Hom, Cherry, Lipsitz and Smith, 1963). Dye dilution curves show a right-to-left shunt through the foramen ovale (Stahlman, 1964), but the catheterisation studies of Rudolph/ Drorbaugh, Auld, Rudolph, Nadas, Smith and Hubbell (1961) suggest that there is more likely to be a left-to-right shunt through the ductus than vice versa. The right-to-left lung shunts proposed by Nelson and colleagues may therefore assume greater importance. The decreased alveolar ventilation results in carbon dioxide retention and hence a respiratory acidosis (Blystad, 1956); decreased oxygen saturation results in anaerobic glycolysis and a metabolic acidosis as well (Usher, 1961). All infants in fact have some degree of acidosis at birth, but normal respiration blows off carbon dioxide to correct the respiratory acidosis, and after several hours the metabolic acidosis has usually been corrected as well by conservation of bicarbonate (Oliver,/1961). Demis and Bates, Mothers shown to have low arterial and intervillous space oxygen tension have produced infants with a more marked respiratory and metabolic acidosis, who went on to develop RDS (Bruns, Cooper and Drose, 1961), lending further support to the role played by asphyxia in pathogenesis.

Hyaline membrane formation has been produced in experimental animals, the studies having formation of pulmonary oedema in common; for instance as in hyaline membrane seen in oxygen poisoning (Bruns and Shields, 1954) and following bilateral vagotomy (Milley and Casarett, 1965). Atelectasis, however, is not an invariable accompaniment, and perhaps more relevant are those experiments which have tried to produce the clinical picture of respiratory distress in the animals. This has now been done in a number of ways, which have in common either the pre-natal asphyxiation of the mother, or the asphyxiation of the premature newborn animal, leading to a histological

picture very like the human disease, and with the same lack of pulmonary surface active factor. The asphyxial insults, however, have usually been rather severe (Stahlman, Lequire, Young, Merrill, Birmingham, Payne and Gray, 1964; Adamson, Behrman, Dawes, James and Koford, 1964; Davis and Stafford, 1964; Reynolds, Jacobson, Motoyama, Kikkawa, Craig, Orzalesi and Cook, 1965).

By comparison reports on the clinical associations have been relatively few in number. While events at delivery and after may certainly aggravate the disease, the concept that aetiological factors must operate before birth to produce it was slow to gain acceptance, because for some time it was supposed that the infants were normal at delivery and only developed symptoms after several hours. Careful clinical observations however showed that this was not so, and that respiratory difficulty started at once in the great majority (Miller, Behrle and Smull, 1958). Further support came from the demonstration of the absence of pulmonary surface active factor or poor stability of expansion in certain stillbirths (Avery and Mead, 1959; Gruenwald, 1960, 1964).

There is an undisputed association with prematurity (Miller and Jennison, 1950; Silverman and Silverman, 1958; Cohen, Weintraub and Lilienfeld, 1960; Usher, 1961). Its occurrence in the most immature has often been doubted (Blystad, Landing and Smith, 1951) but this view does not tally with the surface tension findings, and has doubtless arisen from the earlier preoccupation with the membrane. The majority of very immature infants, usually weighing less than 1000 g at birth, die within a few hours of delivery, and the amount of membrane formation can largely be correlated with age at death (Potter, 1952). The type of atelectasis seen in hyaline membrane disease is present, even if the membrane itself is lacking (Briggs and Hogg, 1958). Maternal diabetes has become accepted as an

aetiological factor (Winter and Gellis, 1954; Gellis and Hsia, 1959) and the syndrome is considered the chief cause of death among such infants (Driscoll, Bonirschke and Curtis, 1960). Maternal diabetics are most frequently delivered prematurely and often by Caesarean section. The incidence of antepartum haemorrhage is considered to be significantly increased in infants dying from RDS (Rogers and Gruenwald, 1956; Cohen, Weintraub and Lilienfeld, 1960). The latter authors, who presented a careful statistical analysis of maternal factors associated with RDS deaths among 2001 infants 'below 2500 g' suggested that the disease resulted from a process of intrauterine asphyxia manifested in many instances by maternal bleeding. The role of delivery by Caesarean section in the pathogenesis of RDS has been more controversial. It has been considered a predisposing factor by many (Blystad, Landing and Smith, 1951; Bloxsom, 1953; Cardell, 1953; Winter and Gellis, 1954; Nesbitt and Anderson, 1956; Snyder, 1959a and b; Klein, 1960; Potter, 1952; Usher, 1964). Others, notably Clayton (1956), Strang, Anderson and Platt (1957), Hess (1958), and Brudenell (1959) differ. The disagreement between the two groups has largely centred on whether or not the procedure itself is harmful as opposed to the threatening complications such as antepartum haemorrhage, fulminating toxaemia, or foetal distress which may lead to its performance. Two other studies must be mentioned in this content. It has been shown that infants delivered this way have a greater quantity of amniotic fluid in their stomachs at birth than infants delivered vaginally (Gellis, White and Pfeffer, 1949). It has also been demonstrated, using dye dilution techniques, that both left and right ventricular outputs are significantly less, and pulmonary blood flow lower in infants delivered abdominally than in those delivered vaginally (Gessner, Kroveta, Benson, Prystowsky, Stengor and

Eitzman, 1965).

Once the physical process of delivery is over, the circulatory readjustment occurring with clamping of the umbilical cord and start of respiration establish the newborn infant as an individual capable of independent life. Both these vital steps have been implicated in the development of RDS. If the umbilical cord is left unclamped after delivery, and the infant's position is lower than that of the mother, blood is transferred to him from the placenta, average amounts varying between 100 and 166 ml (Gunther, 1957; Usher, Shephard and Lind, 1963). In a mature infant this would constitute about one-third of the estimated blood volume, and variations in obstetric practice could lead to differences in this volume. Recently Redmond, Isana and Ingall (1965) have suggested that a placental transfusion is an 'inevitable physiological consequence' of initial pulmonary expansion. They measured the amount of blood (residual placental volume) collected when the placenta was suspended from a height for 20 minutes after the cord had been cut. Significantly higher residual volumes collected when the cord had been clamped ten seconds or more before as opposed to the same time after the onset of respiration. They maintained that the occurrence of a placental transfusion after initial lung expansion was evident irrespective of the interval between delivery of the infant's chin and clamping of the cord. If these observations are confirmed it would mean that some of the interpretations made in previous studies would have to be re-evaluated. Nevertheless, as Redmond and colleagues acknowledge, in general the longer the interval between delivery of the chin and cord clamping, the less the volume of blood remaining in the placenta. So the results of various studies noting lower haematocrits and lower systemic and pulmonary arterial pressures with early

clamping (Buckels and Usher, 1965; Arcilla, Oh, Lind and Gessner, 1966); increased transverse diameter of the heart (Burnard and James, 1963), and increased central venous pressure with delayed clamping (Jegier, Blankenship and Lind, 1963) may still be valid. Speculations about these physiologic differences being associated with RDS have led to trials of delayed cord clamping in newborn infants, two of which claim beneficial effects (Bound, Harvey and Bagshawe, 1962; Moss, Duffie and Fagan, 1963) and one offered no confirmation (Taylor, Bright and Birchard, 1963). It is clear that more data will have to be collected to settle this issue, particularly in view of the probable relationship with onset of respiration cited above.

Finally, birth asphyxia or abnormal delay in the onset of spontaneous respirations after birth has been reported frequently (Latham, Nesbitt and Anderson, 1955; Miller, Behrle and Smull, 1958; James, 1959) among infants dying from RDS. A significant excess of males over 1500 g developing severe RDS was reported by Miller (1963).

APPRAISAL

Firstly the wealth of investigative work may be summarised very briefly by saying that deficiency of the pulmonary surface active factor can account for all the main features of RDS; the atelectasis and hence decreased lung compliance, ventilatory insufficiency, vascular shunts and the respiratory and metabolic acidosis. The consensus of opinion favours pre-natal asphyxia with its secondary effects on the pulmonary circulation as the most likely cause, though very recently a few of the workers reproducing RDS in animals have concluded that prematurity may be of equal if not greater importance.

Secondly the clinical surveys have shown that RDS is highly correlated with prematurity. An association with antepartum haemorrhage, maternal diabetes, birth asphyxia and the male sex also appears undisputed, while delivery by Caesarian section seems more controversial.

Since the summation of investigative work at present points to intra-uterine asphyxia as a likely cause of alterations in pulmonary blood flow, there has been little substantial evidence of this forthcoming, with the exception of antepartum haemorrhage. While criticism of the investigations which have established the functional and pathological features of the disease would be presumptuous without knowledge of the highly specialised techniques involved, an appraisal of the clinical analyses may be attempted. Many of them are retrospective, with the hazards involved of incomplete data. In the great majority the 'incidence' of RDS is taken as synonymous with deaths showing the classic atelectasis and hyaline membrane formation. This must inevitably lead to a false weighting of cases, for at least half of infants with RDS will survive and any investigation into aetiological factors should properly include them. This inclusion by pathological criteria has also led to the exclusion in the majority of the surveys of those very immature infants, most of whom have atelectasis but no membrane formation. Reasons have been given to show that they belong to the same disease entity. In those papers where statistical analysis has been made of the relevance of maternal factors, the controls have usually been those infants classified as premature by weight who did not develop the disease. While these are the only possible controls, if taken en bloc, babies of unlike gestation and birth weight may be compared with each other.

MATERIAL AND METHODS

The infants, who with their mothers form the basis of this report, were all classified as premature by birth weight, and thus were 2500 g (5 lb 8 oz) or under at delivery. All were born alive in the Nuffield Maternity Home, Oxford, between 1st January, 1959 and 31st December, 1964 inclusive, and comprise all such infants. The vast majority, unless delivered during the writer's absence on vacation, were examined personally. The records of all the mothers were looked at personally, and relevant details of the pregnancy, labour and delivery abstracted, along with those of the infant. This was done, except during vacations, within 24 hours of delivery, so that any uncertainties about the maternal data could be checked with the obstetric staff.

The following were recorded and analysed:-

Maternal age, parity and gestation;

Pregnancy complications;

Toxaemia (blood pressure 140/90 or above, with oedema and/or albuminuria) and essential or malignant hypertension (blood pressure of 140/90 or above);

Antepartum haemorrhage - degree of bleeding considered significantly abnormal by obstetric staff;

Urinary infections;

Anaemia (Hb below 70%);

Diabetes mellitus;

Threatened miscarriage;

Hydramnios.

Abnormalities of umbilical cord (recorded if cord prolapsed, was known to be compressed by presenting part, was wound

firmly round neck or body, or contained true knots);

The presence of an episiotomy;

Interval between membrane rupture and delivery;

Length of labour (from beginning of 1st stage until delivery) and length of 2nd stage of labour;

Analgesics and sedatives given within 4 hours of delivery;

Anaesthetics given during labour and delivery;

The presence of foetal distress (recorded if meconium appeared in the amniotic fluid in vertex presentations, if the foetal heart rose above 160 beats/minute or fell to below 120 beats/minute on more than one occasion during labour, and if the foetal heart could not be heard during any part of labour);

Mode of delivery;

Birth weight - infants were further subdivided according to the International Classification into 5 subgroups as follows:-

Less than 1000 g (less than 2 lb 3 oz)
1000-1500 g (2 lb 3 oz - 3 lb 4 oz)
1501-2000 g (3 lb 5 oz - 4 lb 6 oz)
2001-2250 g (4 lb 7 oz - 4 lb 15 oz)
2251-2500 g (5 lb - 5 lb 8 oz)

but they weren't

Sex;

Birth asphyxia (recorded as present if spontaneous respirations were not established within 2 minutes of delivery). This was further subdivided in an arbitrary manner into three grades of severity:-

Grade I - respiration established between 2 and 5 min
Grade II - " " " 5 and 10 min
Grade III - " " at varying times from 10 min

Respiratory distress syndrome - infants were regarded as having this if the following signs were present, and persisted for more than 3 hours after delivery:-

Sternal or intercostal retraction,
Expiratory grunting,
A respiratory rate greater than 65/minute,
A rise in respiratory rate of more than 15 per minute over the highest recorded during the first hour after birth.

A small number of infants, all of whom were extremely immature and who died, were classified as having RDS although they did not satisfy the above criteria in that their respirations did not reach the rate specified. Nevertheless all showed the typical histological findings of widespread resorption atelectasis, usually with some hyaline membrane formation at autopsy. Chest X-rays showing the characteristic diffuse reticulo-granular mottling were further confirmatory evidence in a number of babies, but were done to exclude other causes of respiratory difficulty such as pneumothorax or pneumomediastinum, diaphragmatic hernia and congenital heart disease, if the slightest doubt existed, and not routinely. When the data were complete, the infants were divided into two groups, depending on whether or not they showed signs of the respiratory distress syndrome. These two groups were then contrasted and compared for each of the remaining factors recorded above. Each group was further subdivided according to the single criterion of birth weight, and infants weighing 1500 g and less were contrasted with those of similar weight in the second group, and with infants weighing 1501-2500 g in their own group. Although it would have been more satisfactory to compare infants above and below a certain gestation, too many of the mothers

were uncertain of their dates, so that birth weight, accurately measured in each case, was preferred. Chi-squared tests of significance were then applied.

The value of an analysis conducted in this way was thought to have certain limitations in view of the large number of variables considered, and their uncertain relationship one with another, and with the all-important feature of prematurity by gestation. In order to overcome this difficulty a regression analysis was performed (see 'Acknowledgements'), so that significant results obtained by the simple analysis could be more critically assessed. Three samples were given to the computer. The first consisted of a random sample of 540 infants, all singletons delivered vaginally, 93 of whom had respiratory distress. The second consisted of 132 infants delivered by Caesarian section, of whom 36 had RDS. The third random sample consisted of 85 singletons weighing 1500 g and less, of whom 45 had RDS. A correlation matrix was then performed to show which of the variables had a significant correlation one with another.

RESULTS

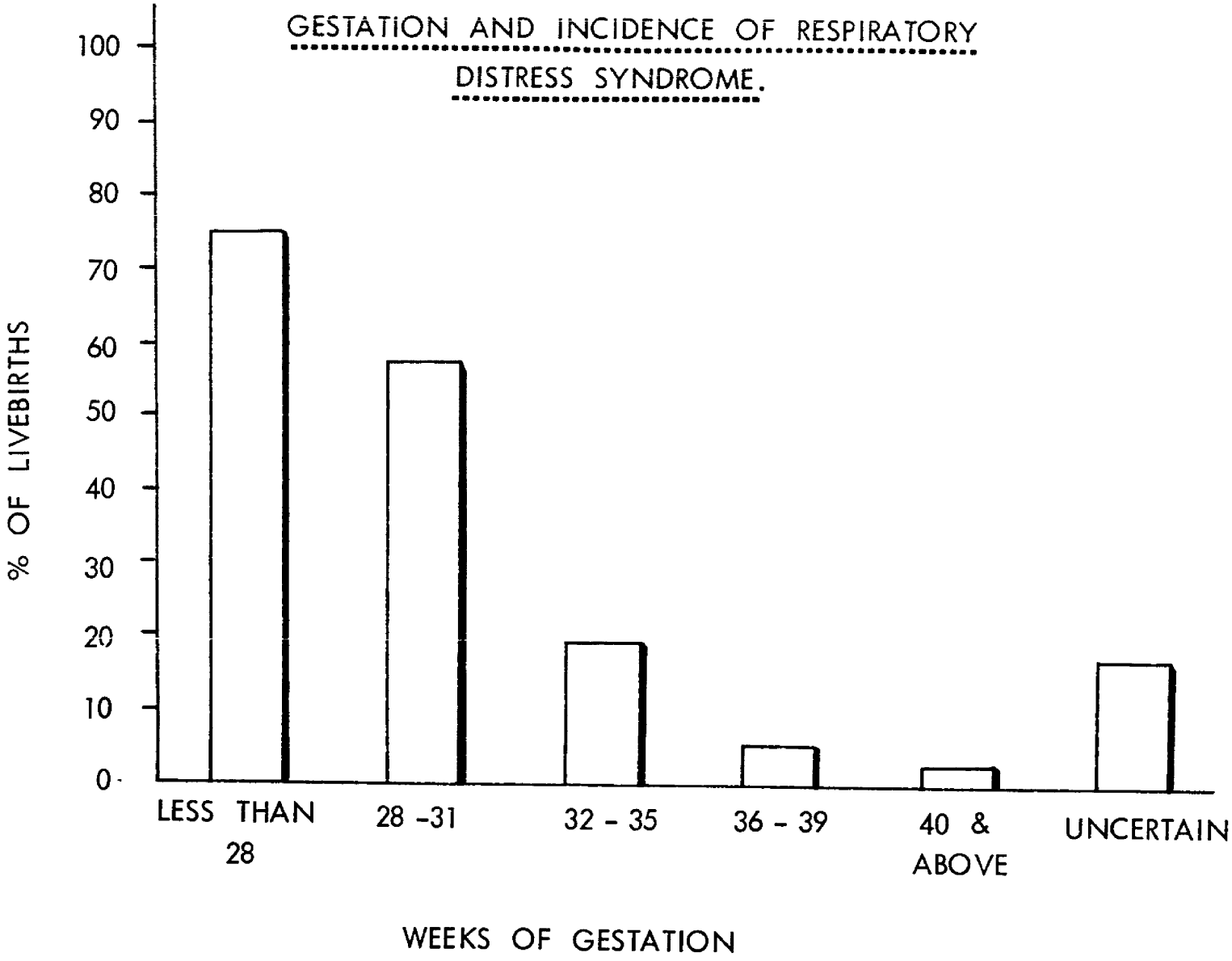
GESTATION AND INCIDENCE OF RESPIRATORY DISTRESS SYNDROME.
% OF LIVEBIRTHS
100
90
80
70
60
50
40
30
20
10
0
LESS THAN 28
28 -31
32 - 35
36 - 39
40 & ABOVE
UNCERTAIN
WEEKS OF GESTATION

FIG. 1

A. SIMPLE ANALYSIS

Between 1st January, 1959 and 31st December, 1964, 1126 mothers delivered 1244 infants weighing 2500 g (5 lb 8 oz) or under at birth. Of these, 219 mothers produced 255 infants who developed RDS and the remaining 907 mothers delivered 989 infants who did not. Of the 255 infants with RDS, 115 were 1500 g or less, and 140 were 1501-2500 g at birth. Eighty-two of the infants without RDS were 1500 g or less at birth, and 907 over this weight.

Maternal Age. (Table I, Appendix, p. 58). There were no significant differences in the ages of mothers who delivered infants with RDS compared with those who did not.

Parity. (Table II, Appendix, p. 59). The incidence of primiparity between the groups was not significantly different.

Gestation. (Table III, Appendix, p. 60 , Fig. 1, p. 19). Gestation was uncertain in 13.7% of the total sample. In the remainder, significantly more infants with gestations both less than 28 weeks, and 28-32 weeks developed RDS ($P = < 0.001$). Between 32 and 36 weeks, the number of infants having and not having RDS did not differ. However, when this group was broken down by birth

weight, fewer infants 1500 g and less developed RDS ($P = < 0.05$) whereas the incidence of RDS was significantly higher at this gestation among infants weighing 1501-2500 g ($P = < 0.001$).

Pregnancy Complications. (Table IV, Appendix, p. 61). Those mothers giving birth to infants with RDS had significantly more complications than those who did not ($P = < 0.001$). The group whose infants had RDS had a higher incidence of antepartum haemorrhage ($P = < 0.001$), a lower incidence of anaemia ($P = < 0.001$), and a higher incidence during the pregnancy of threatened miscarriage ($P = < 0.001$). When comparison was made within the two birth weight groups, in infants 1500 g and less, the only one of these differences that still held, though at a lower level of significance ($P = < 0.01$), was that of anaemia, and a new difference, a lower incidence among RDS babies of toxaemia and essential hypertension appeared ($P = < 0.01$). Between 1501-2500 g the results were as for the total group.

Interval Between Membrane Rupture and Delivery. (Table V, Appendix, p. 62). Significantly more infants with RDS had membranes ruptured for more than 48 hours before delivery ($P = < 0.05$), and significantly fewer of them had membranes ruptured for between 12 and 24 hours ($P = < 0.05$) and 24-48 hours ($P = < 0.01$). Comparison of the weight subgroupings one with another, however, revealed no significant differences.

Duration of Labour. (Table VI, Appendix, p. 63) There were no significant differences.

Length of 2nd Stage of Labour. (Table VII, Appendix, p. 64) More infants with RDS had a very short 2nd stage, less than 25 minutes ($P = < 0.05$), whereas more infants without RDS had second stages lasting between 15 and 30 minutes ($P = < 0.05$) and 30 and 60 minutes ($P = < 0.01$). However the number of infants in whom the second stage was not accurately known, or who were delivered by Caesarian section or forceps before the second stage was reached was significantly greater in RDS cases ($P = < 0.01$) so that the foregoing results may not be valid. There were no significant differences when the two weight subgroups were compared.

Analgesics and Sedatives Given Within 4 Hours of Delivery. (Table VIII, Appendix, p. 65) There were no significant differences.

Anaesthetics Given During Labour or Delivery. (Table IX, Appendix, p. 66) In the total group of 1244 infants analysed, 12.4% had no anaesthetic of any kind administered, but in the group with RDS this percentage was significantly higher ($P = < 0.001$). When infants weighing 1500 g and less were compred, this relationship held good, but at a reduced level of significance ($P = < 0.05$). However, there was no significant difference in this respect in infants weighing 1501-2500 g. A higher proportion of infants with RDS were given a general anaesthetic ($P = < 0.05$) and while this was still so for infants 1501-2500 g ($P = < 0.01$) the difference was not present in infants 1500 g and less.

Foetal Distress. (Table X, Appendix, p. 67) More infants with RDS had foetal distress ($P = < 0.01$). When the two weight groups were considered, the difference in incidence between infants

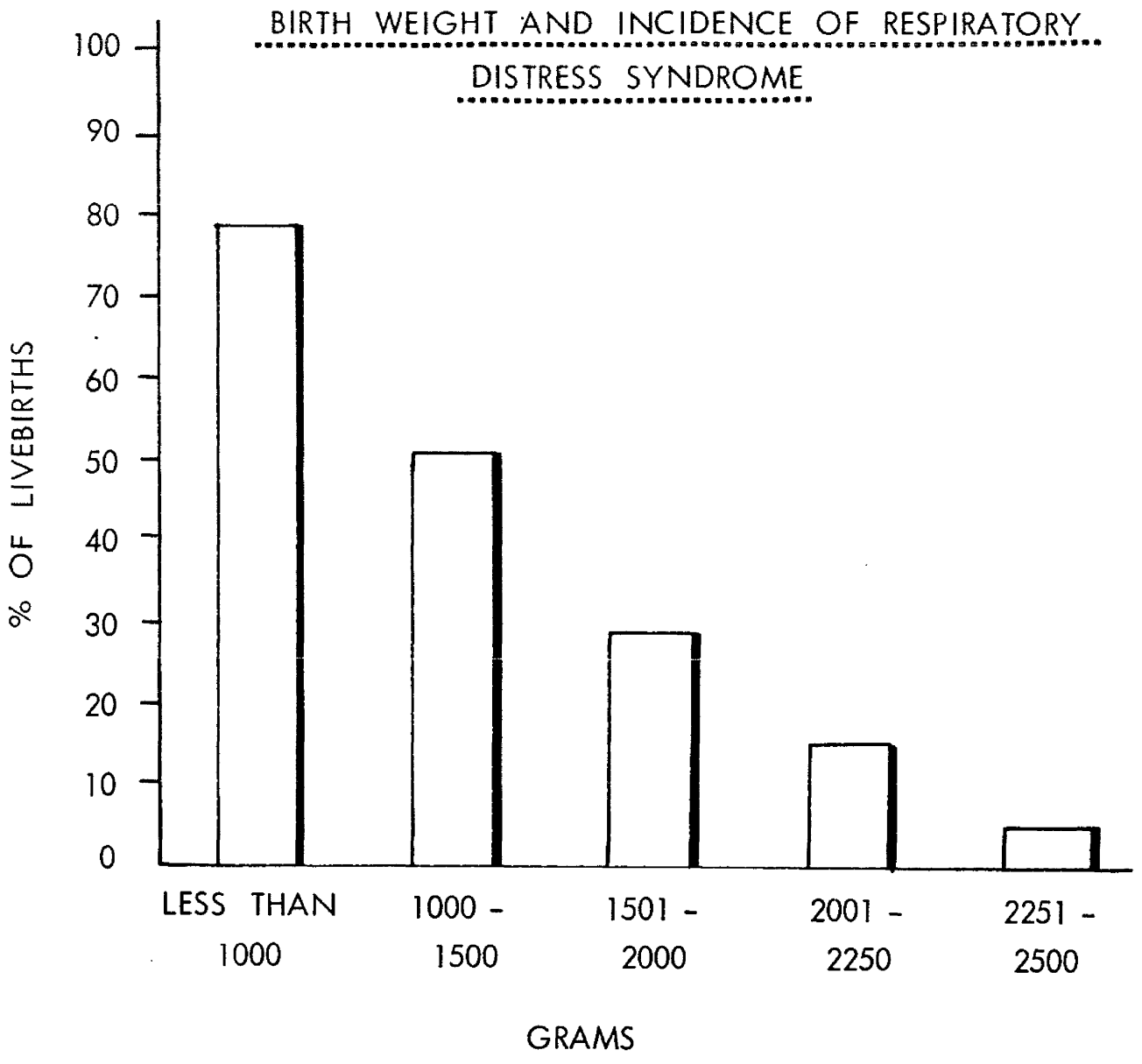
BIRTH WEIGHT AND INCIDENCE OF RESPIRATORY DISTRESS SYNDROME
% OF LIVEBIRTHS
100
90
80
70
60
50
40
30
20
10
0
LESS THAN 1000
1000 - 1500
1501 - 2000
2001 - 2250
2251 - 2500
GRAMS

FIG. 2

more than 1500 g was highly significant ($P = < 0.001$) but in those 1500 g and below this was no longer present.

Presence of Episiotomy. (Table XI, Appendix, p. 68). There were no significant differences.

Mode of Delivery. (Table XII, Appendix, p. 69) Of infants with RDS significantly more were delivered by the breech ($P = < 0.01$) and by emergency Caesarian section ($P = < 0.05$) and significantly fewer by forceps ($P = < 0.001$). However, when infants 1500 g and below were compared, none of these differences held; and above 1500 g, only the increased incidence of emergency Caesarian sections remained ($P = < 0.05$).

In order to examine further the question of whether the significance of Caesarean section could be affected by such associations as antepartum haemorrhage and foetal distress (themselves significantly correlated with RDS), a further analysis of all infants delivered abdominally (whether as an emergency or electively) was made according to whether or not these two complications were present.

They were compared with the relevant infants delivered vaginally (Table XIII) and it can be seen that in the absence of either complication, Caesarean section was still more significantly associated with RDS ($P = < 0.05$).

Since the time of clamping of the umbilical cord was known accurately in only a very small number of cases, no observations about this procedure have been included.

Birth Weight. (Figure 2). The incidence of RDS was inversely proportional to birth weight. Using the standards of birth weight and gestation for singletons derived from the National Birthday Trust's Perinatal Mortality Survey of 1958, the infants were further

9/8/80

Survey of 1958. It should be noted that these standards relate to the country as a whole, and may have limited application to any one Maternity Unit, but they have been used in the absence of standards for Oxford infants, and as they are the most up-to-date standards available for British babies.

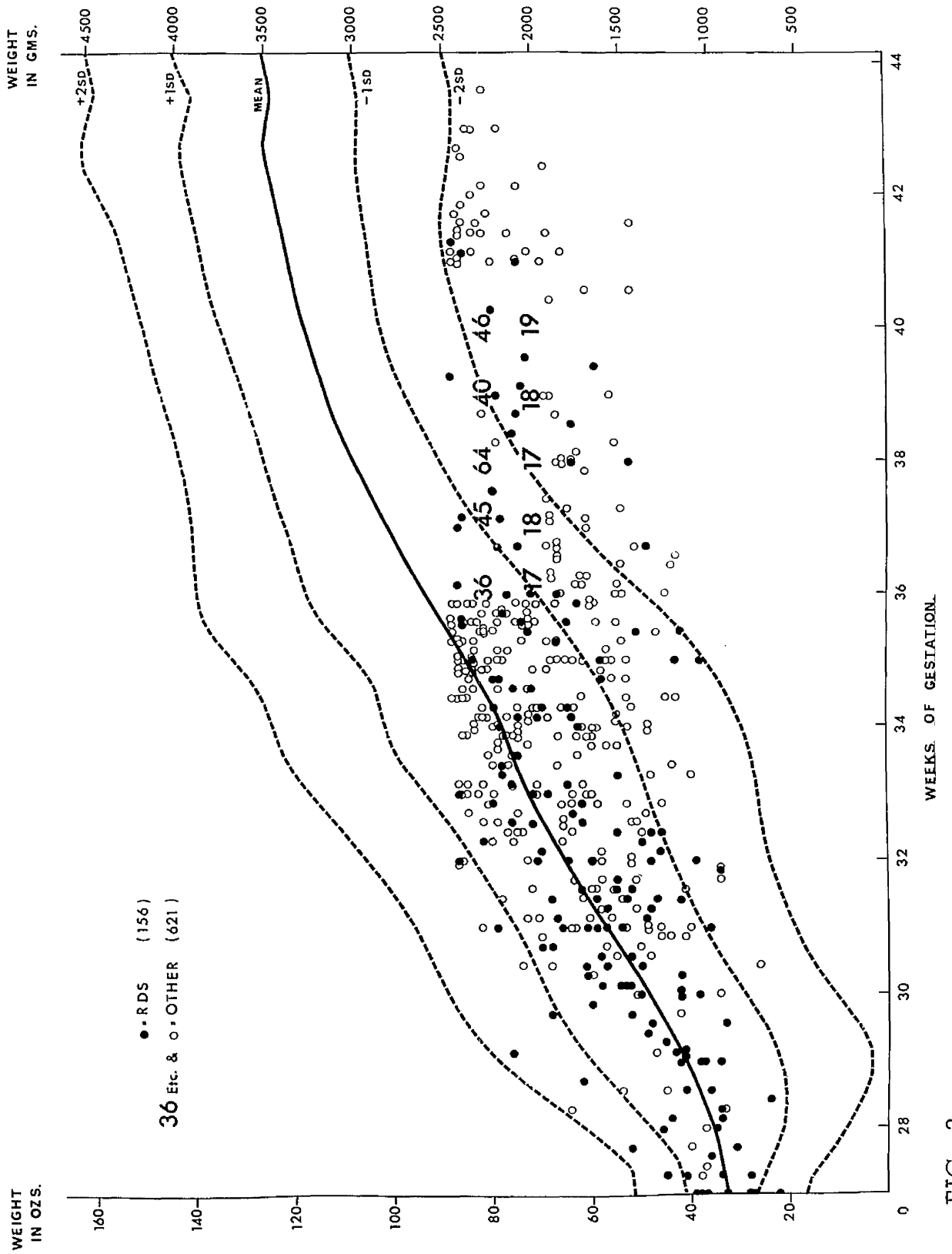

FIG. 3

subdivided according to whether or not they were above or below the expected mean for their gestation (Table XIV, Appendix, p. 71). Figure 3 (opp.) demonstrates this graphically for singletons in the study. Significantly more infants with RDS were found the mean and less than one standard deviation above or below it ($P = < 0.001$) and significantly fewer of them were more than one standard deviation below the mean ($P = < 0.001$). These relationships held when infants above and below 1500 g were examined separately, though at 1500 g and below the levels of significance were lower ($P = < 0.01$ and < 0.05 respectively).

Sex. (Table XV, Appendix, p. 72) More males developed RDS than females ($P = < 0.001$). This relationship remains when infants 1501-2500 g are examined, but is no longer present in infants 1500 g and below.

Birth Asphyxia. (Table XVI, Appendix, p. 73) Infants who later developed RDS failed to establish regular respirations within 2 minutes of delivery more often than the remainder ($P = < 0.001$), and among these asphyxiated infants there were a larger number in whom the degree of asphyxia is severe ($P = < 0.001$). This is true in both the total sample, and the two weight subgroups.

Summary of Results from Simple Analysis

The respiratory distress syndrome appears to be significantly correlated with antepartum haemorrhage, a low incidence of pregnancy anaemia, threatened miscarriage, foetal distress, prolonged rupture of membranes, a greater use of general anaesthesia but a lower use of other anaesthetics, with more frequent delivery by Caesarian section and the breech, and less frequent delivery by forceps, with immaturity, low birth weight, severe birth asphyxia, and the male

sex. A more rapid second stage of labour appeared also to be significantly correlated with RDS, but among these infants there were a larger number in whom duration of the 2nd stage was unknown or not reached, so that this association may be invalid.

When a second comparison was made between infants who did and did not develop RDS above and below a weight of 1500 g it became strikingly apparent that in infants 1500 g and less at birth the majority of these differences disappeared and the only factors remaining significantly correlated were the lowered incidence of anaemia, lessened use of anaesthesia and severe birth asphyxia. In addition the new variable of a lowered incidence of maternal essential hypertension and toxaemia appeared.

B. REGRESSION ANALYSIS

(With the help of Dr. A. Barr and Miss E. Whitwell.)

1) A random sample of 540 infants, all singletons delivered vaginally, were analysed, of whom 94 had RDS. The following variables differentiated the two groups at the 10.0% significance level ($P = < 0.1$).

a. Gestation (mean for RDS cases 31.83 weeks, and for remainder 36.68 weeks).

b. Birth weight (mean for RDS cases 3.8 lb and for remainder 4.8 lb).

c. Infants with birth weights more than one standard deviation below mean for gestation (less common in RDS).

d. Antepartum haemorrhage (more common in RDS cases).

e. An absent foetal heart at some stage in labour (more common in RDS cases).

f. Hydramnios (less common in RDS infants).

g. Male sex (more common in RDS infants).

h. A foetal heart heard above 160/minute on more than one occasion during labour (more common in RDS infants).

i. Grade III (severe) birth asphyxia (more common in RDS infants).

At the 5% significance level ($P = < 0.05$) these variables remained with the exception of (f) and (i). At the 1.0% significance level ($P = < 0.01$) (h) was eliminated, and at 0.1% significance level ($P = < 0.001$) (g) was eliminated. Thus when $p = < 0.001$, the distinguishing variables between infants with and without RDS were gestation, birth weight, infants more than one standard deviation below expected mean birth weight for gestation, antepartum haemorrhage, and foetal heart not heard during labour.

When the variables gestation, birth weight, vertex, breech and forceps delivery from these 540 infants were fed to the computer to test the hypothesis that mode of delivery had some bearing on the development of RDS as suggested by the simple analysis, birth weight and gestation were found to be the most powerful discriminants.

2) A regression analysis of 132 infants delivered by Caesarian section was made, of whom 36 had RDS.

At the 10% significance level ($P = < 0.1$) the following variables distinguished the two groups.

a. Gestation (mean for RDS cases 32.88 weeks, and for remainder 36.23 weeks).

b. Birth asphyxia (Grade I) (more common in RDS cases).

c. Cord round neck (less frequent in RDS infants).

d. Use of gas and oxygen before delivery (more common in RDS infants).

e. Male sex (more common in RDS infants).

f. Maternal age 20-25 (less common in RDS infants).

g. Maternal age 30-35 (more common in RDS infants).

h. Use of general anaesthesia for delivery (more common in RDS infants).

i. Use of an analgesic within 4 hours of delivery (more common in RDS infants).

At the 5% significance level ($P = < 0.05$) the last four variables, (f), (g), (h) and (i), were eliminated. At the 1% significance level ($P = < 0.01$) only (a), (b) and (d) remained, and at the 0.1% significance level ($P = < 0.001$) only (a) and (b) remained. Thus when $P = < 0.001$, the distinguishing variables between infants with and without RDS delivered by Caesarian section were gestation, and a mild degree of birth asphyxia.

3) A regression analysis of 85 infants weighing 1500 g and less was then made of whom 45 had RDS.

No significant variables were found to distinguish the two groups.

4) Finally a correlation matrix was performed, on the 540 singleton vaginal deliveries and the following paired variables have been selected as showing significant positive or negative correlation, one with the other:-

Antepartum haemorrhage and birth asphyxia (Grade II) - positive correlation;

Antepartum haemorrhage and gestation - negative correlation, indicating an increasing incidence of antepartum haemorrhage with decreasing gestation;

Rapid foetal heart and birth asphyxia (Grade III) - positive correlation;

Gestation and birth asphyxia (Grade III) - a negative correlation,

indicating a higher incidence of birth asphyxia with decreasing gestation;

Threatened miscarriage and infants more than 1 standard deviation above the mean for gestation - positive correlation;

Threatened miscarriage and infants less than 1000 g - positive correlation;

Threatened miscarriage and infants 1000-1500 g - positive correlation.

Summary of Regression Analysis Findings

Infants delivered vaginally and developing RDS later can be distinguished from infants not developing RDS by the variables of low gestation, low birth weight, by having a birth weight more than one standard deviation below the mean less frequently, by antepartum haemorrhage, and by foetal distress characterised by an inaudible foetal heart during labour. Those delivered by Caesarian section and later developing RDS are distinguished from those similarly delivered but not developing RDS by a lower gestation, and by the more frequent presence of mild birth asphyxia. All these distinctions between the two groups are highly significant ($P = < 0.001$). At a level of lower significance ($P = < 0.05$), foetal distress shown by a rapid foetal heart during labour, and a preponderance of the male sex also characterised RDS infants delivered vaginally, and the use of gas and oxygen more often before delivery and a preponderance of the male sex characterised infants delivered by Caesarian section who later developed RDS. Those who did not had the umbilical cord round the neck more frequently.

When a sample of infants weighing 1500 g and less at birth were examined, no significant variables to distinguish infants who did and did not develope RDS were found.

A correlation matrix showed that birth asphyxia was significantly associated with antepartum haemorrhage, low gestation and a rapid foetal heart during delivery; and that threatened miscarriage was a feature in the pregnancies of women who delivered infants weighing 1500 g and under, and who had infants rather larger than expected for gestation.

DISCUSSION

It will be noted that the analysis has been of live births only, although certain stillbirths show, in Gruenwald's words, 'poor stability of lung expansion'. Without, however, some specialized investigation into surface active properties of these lungs, such infants may not properly be included. In view of the relatively small numbers which would have been involved, it seems unlikely that they would have made appreciable difference to the results. These results show some new factors which may be incriminated in the aetiology of this fascinating condition.

Both the simple and the regression analyses show yet again the outstanding importance of low gestation and low birth weight. The previously reported associations of antepartum haemorrhage, birth asphyxia and the male sex are all confirmed as significant. Since the majority of diabetic mothers produce infants whose birth weights are larger than expected for gestation, and frequently more than 3000 g, it is not surprising that the group considered here contained few such mothers and their infants, and can therefore contribute nothing to this aspect. The question of whether delivery by Caesarean section per se predisposed to RDS has been answered in the affirmative for the material analysed. While in the simple analysis a significantly increased incidence among RDS babies was found only when the operation was done as an emergency and not as an elective procedure, the figures for the latter were so small as to make further differentiation desirable. This was done as outlined in Table 13 (Appendix, p. 70). The operation is frequently performed because of antepartum haemorrhage and foetal distress, of themselves conditions linked with RDS. When neither

was present there was still a significant association with such a delivery and the syndrome. The regression analysis on a random sample of 132 infants delivered this way gave further confirmation by showing that at the highest level of significance only a lower mean gestation and an increased incidence of mild birth asphyxia differentiated RDS infants from the others. These data do not support the contention then that Caesarean section is only of importance in RDS because of the threatening associated conditions. This is in agreement with the studies of Klein (1960) and Usher (1964), both of whom have reported larger series than others and have differentiated carefully between such conditions, and their association with prematurity before coming to the conclusion that the operation of itself was important. The simple analysis had suggested that breech delivery was significantly associated with RDS and delivery by forceps significantly less common. However when the regression sample of 540 singletons delivered vaginally was re-examined with only the variables of weight, gestation and mode of delivery, it was found that only gestation and birth weight were the discriminating factors. This may be interpreted as showing that the excess of breech deliveries among RDS infants occurred by virtue of immaturity. Forceps, on the other hand, were never used to deliver infants under 1000 g, and the likelihood of their use seemed to increase with maturity, thus accounting for the findings on simple analysis alone.

Since intrauterine asphyxia has been postulated as an aetiological factor in RDS, it is of interest that a significant association with foetal distress has been demonstrated by the survey for the first time. The indications taken for foetal distress ; the recording of a high or low foetal heart rate, or its disappearance, with or

without the passage of meconium in the liquor, are crude ones. They were regarded as one group in the simple analysis, but the regression found an inaudible foetal heart during labour, and a rapid one, to be the constant discriminating factors. Some other significant variables, not previously reported, appear though their relevance in some cases may be questioned. For instance a significantly lower incidence of anaemia among RDS mothers may only reflect that the infants are delivered earlier in gestation, perhaps before this has time to develop. Similarly the decreased incidence of toxaemia could be explained on the same basis. An increased incidence of hydramnios among non-RDS infants may reflect a larger number of congenital abnormalities in this group. In the simple analysis threatened miscarriage during pregnancy was found significantly more often in the mothers of RDS infants. This did not appear as a powerful discriminatory factor in the regression, but the correlation matrix showed a positive association between this and birth weights of 1500 g or less, and with birth weights larger than expected for gestational ages, both more likely with RDS. A higher incidence of long ruptured membranes, and of general anaesthesia were also present in mothers of RDS infants, the latter probably reflecting the greater incidence of Caesarean sections, and there were significantly fewer infants small for the period of gestation among affected babies.

While the regression analysis confirmed these differences when the factors were considered separately, in the final sorting the most powerful discriminating factors between infants with RDS and those without, were the low birth weight and gestation of RDS infants, birth weight more than one standard deviation below the mean for gestation, significantly less common in the RDS group, antepartum

haemorrhage and foetal distress as shown by an inaudible foetal heart at some stage of labour, both more common in RDS. The correlation matrix puts some of these factors into perspective. Thus both antepartum haemorrhage and severe birth asphyxia were negatively correlated with gestational age, indicating that as this became lower, the incidence of haemorrhage and asphyxia increased. Foetal distress as shown by a rapid foetal heart was positively correlated with severe birth asphyxia. So it would seem that there is an intricate pattern of interdependency of many of the significant associated factors, and assignment of their true importance is difficult. Perhaps however the most important finding of the whole survey is that when infants weighing 1500 g or less were considered separately neither the simple analysis nor the regression could show any convincing points of difference between those with and without RDS. Since nearly half of all these cases of RDS fell within this weight range, it seems logical to conclude that these infants have inherent in them the conditions necessary for development of the syndrome, whereas above this weight some insult may be necessary to induce it.

The lungs of all infants are partially distended by fluid at delivery, and this must be replaced quickly by air to allow oxygen uptake by the pulmonary circulation. This intrinsic foetal lung fluid has an electrolyte content resembling plasma, but a lower protein content (Adams, Fujiwara and Rowshan, 1963). Amniotic fluid has a higher protein content. During prenatal asphyxia in the rat, lung capillary permeability has been shown to be altered, with protein leakage into the pulmonary alveoli (Seller and Spector, 1964). Proteins do not pass easily into the pulmonary circulation, and serum, which is only slowly absorbed by the lymphatics, may persist in the lungs for varying periods (Courtice and Phipps, 1946). It has been shown

in animals that the foetus is likely to make inspiratory gasping movements in uteru if it becomes hypoxic (Windle, Becker, Barth and Schultz, 1939), and it is a well established fact that amniotic debris, squames and occasionally meconium may be seen in the air passages and alveoli at autopsy in infants who have shown signs of distress during labour. Intrauterine hypoxia, then, by causing either aspiration of amniotic fluid or increased capillary permeability or both, may result in an excess of a high protein fluid to be cleared from the airways at birth. Aherne and Dawkins (1964) have recently indicated the sequence of events. Demonstrating a fall in the wet weight of the newborn rabbit lung in the first two hours after delivery, they observed that as fluid disappeared from airways and alveoli, it transiently increased in the loose periarterial tissues with coincident dilatation of the lymphatic vessels running in them. Hypoxic insults to the doe before birth increased the wet weight of the lung, lengthened the time period of periarterial tissue distension and was accompanied by alveolar resorption collapse. This work has been extended and complemented by two other studies. Boston, Humphreys, Reynolds and Strang (1965) found a slower rate of fluid removal in immature lambs, associated with a relative lack of pulmonary surface active factor, the resulting higher surface tension causing greater retractive pressure to suck fluid back into the alveoli during expiration. De Sa' (1966) has found a significant association between increased fluid content in the human infant lung at autopsy and loss of pulmonary surface active factor; and a steady decline in pulmonary fluid with increasing birth weight. Adopting the experimental method of producing respiratory distress used by Davis and Stafford (1964), he has also shown that asphyxiation alone did not increase the amount of lung fluid in the newborn rabbit, but that it occured a short time

after, during a period of transudation which was accompanied by loss of alveolar lining layer and hence pulmonary stability. Therefore this vital substance may literally be washed away by oedema fluid or perhaps be diluted to impotence. Since pulmonary blood flow has been reduced by perivascular oedema in the isolated dog lung (West, Dollery and Heard, 1964), the periarterial distension noted by Aherne and Dawkins (1964) could be responsible both for the pulmonary hypoperfusion in RDS cited by Chu, Clements, Cotton, Klaus, Sweet, Thomas and Tooley (1965), and for tissue hypoxia resulting in alveolar epithelial damage. Such damage may in fact be a perpetuation of that occurring prenatally, and again due to alveolar hypoperfusion, for the sensitivity of the pulmonary circulation to hypoxic insults in utero has been demonstrated.

The results of the analysis show that there are definite grounds for supposing that intrauterine asphyxia occurs in a certain number of RDS infants. Disturbances of the utero-placental circulation such as are seen in antepartum haemorrhage and threatened miscarriage, could cause such hypoxia. An absent foetal heart, and a too rapid one, are also evidence of it. Brady and James (1962) have suggested as a result of clinical and biochemical correlations that tachycardia is an earlier sign of foetal distress than brachycardia. At delivery by Caesarean section there is often considerable handling of the uterus before the foetus is extracted, and these stimuli may conceivably cause gasping. In addition abdominal delivery robs the infant of the thoracic compression afforded by the muscles of the birth canal which serves to squeeze some of the lung fluid out through mouth and nose.

So the stage is set for an increase in fluid content of the

lungs of these infants as indicated above, either by the addition of inspired amniotic fluid to intrinsic lung fluid or to hypoxic transudation from pulmonary capillaries, or both, though the latter seems more important (de Sa', 1966). The amount of pulmonary fluid at birth and its rate of clearance are quite clearly of outstanding importance to the infant's wellbeing. These two factors may hold a clue to the anomalous situation revealed by the analysis of infants 1500 g and less, for whom no significant aetiological factors could be found. For de Sa's (1966) work shows that their lung fluid content is higher than that of larger infants. If to this were added the delayed rate of fluid clearance shown by Boston, Humphreys, Reynolds and Strang (1965) to be present in immature lambs, it is easy to see that the predisposing factors for RDS are already present in them, whereas in the large infants these conditions do not exist without the appearance of an asphyxial insultadding to the pulmonary fluid content. While this does not explain why some infants under 1500 g, albeit a minority, escape RDS, it may be that much more sophisticated methods of measuring foetal hypoxia are needed than the crude yardsticks used here.

Infants more than one standard deviation below the mean were significantly less likely to develop RDS. To a large extent this is a reflection of their greater maturity, and Dunn (1965) has pointed out that low birth weight is related to RDS only in so far as it in turn is related to immaturity. A glance at the gestation grid (Figure 3) shows how steeply the number of "small for dates" infants increases after 36 weeks gestation, a time when RDS becomes less and less likely to occur. Nevertheless the percentage of infants between 32 and 36 weeks more than one standard deviation below the mean and without RDS is increased, and before leaving the question of lung fluid

content, that of water content of the foetus as a whole should be discussed. The percentage of tissue weight which is water in the foetal rhesus monkey decreases in a linear manner as total foetal weight and gestation increase; this is also true of the percentage of water in plasma and whole blood (Behrman, Seeds, Battaglia, Hellegers and Bruns, 1964). These same workers have shown a significant reduction in total foetal water content following injection of sucrose into the amniotic fluid, or the intravenous infusion of either a disaccharide solution or a sodium chloride solution (Bruns, Hellegers, Seeds, Behrman and Battaglia, 1964). Some infants who are small for their gestation often appear wizened and dehydrated at birth, and capillary haematocrit readings between 60 and 80%or more have been obtained in certain infants consistently during the first 72 hours of life (Ainsworth, Davies and Mitchell, 1966), suggesting a greatly reduced water content in their blood which may mirror that in other tissues, since oedema is very rarely seen, and weight gain with liberal feeding after birth is rapid. Significantly lower haematocrit values have been reported for infants with RDS (Inall, Bluhm, Kerr, Douglas, Hope and Hutchison, 1965) when compared with other infants, 2500 g and less, who did not have it. While this may reflect the greater degree of immaturity likely in RDS cases, the contrast with certain small-for-dates babies is nevertheless striking. On the other hand, infants of diabetic mothers, notoriously large for their gestation and very prone to RDS, have significantly less total body and extracellular water than is normal (Osler, 1960) and it is presumed that their excessive weight is mainly due to increased fat deposition. Farquhar (1962) has pointed out too that it is those of them 3000 g and below who are more likely to develop RDS than those much above 3000 g. While it seems certain from the analysis

that infants of average weight for gestation or above are more prone to develop RDS, it is difficult to know how they can be linked with infants of diabetic mothers. The latter have recently been shown to have a greater adrenocortical activity than controls on urinary assay (Cathro and Forsyth, 1965), so that changes in body water could perhaps be present. It has been suggested that certain mothers may deliver successive infants who develop RDS (Graven and Misenheimer, 1965). Two groups of mothers have been compared; one delivering several infants below 2500 g who developed RDS, and another group who delivered similar-sized infants who did not become distressed. Whereas the mean birth weight in the two groups was almost identical, and was considered to be at the 50th percentile for the RDS group, the gestational age was somewhat higher in the non-distressed group, suggesting they were smaller than expected. Since patterns of birth weight for gestation may be constant in certain mothers (Ounsted, 1965, 1966) it would be particularly interesting to know in these two contrasting groups whether differences in utero-placental blood flow, and osmotic gradients across the placenta existed, for their relevance to infants with RDS might be considerable.

The role of the central nervous system in the development of RDS has not received a great deal of attention, though with pulmonary oedema an invariable concomitant, this is perhaps surprising. Buckingham and Sommers (1960) have suggested that an abnormal autonomic stimulation could result in the hypersecretory lung changes. We have seen that vagotomy in experimental animals leads to pulmonary oedema and membrane formation, and loss of surface activity has also been demonstrated after bilateral vagotomy in guinea pigs (Klaus, Reiss, Tooley, Piel and Clements, 1962). It has been suggested that anoxic damage to the brain stem or upper cervical cord might interrupt

vagal-phrenic reflexes (Belter and Friedrich, 1959). Absence or marked decrease of cerebellar Purkinje cells has also been noted (Schneck and Neubuerger, 1962), and a degenerative change in the dorsal vagal nuclei in infants dying of RDS (Buckingham and Sommers, 1960). The role of the autonomic system, however, in the regulation of the pulmonary circulation does not seem well understood (Fishman, 1961). Nevertheless if intrauterine asphyxia be a significant factor in RDS as it seems to be cerebral hypoxia and its effects on the respiratory centres of the brain may be closely linked.

Severe birth asphyxia was the one important significant association that distinguished infants 1500 g or less with RDS from others of this weight group, as it did in fact the group as a whole, and infants 1501 g and above, though in the simple analysis only. Birth asphyxia itself, however, is highly correlated with immaturity, with foetal distress and with antepartum haemorrhage, so that its importance as a factor on its own recedes. Nevertheless, such delay in establishing respiration after birth will almost certainly mean a delay in the establishment of effective pulmonary blood flow. Since this will not increase until alveolar ventilation is occurring, its importance in aggravating RDS should probably not be underestimated. Aherne (1964) has emphasized the tremendous mechanical disadvantage facing the very immature infant, with his greatly reduced lung compliance, relatively soft thoracic cage and weak respiratory muscles. When gestation has reached the stage at which pulmonary surface active factor is being produced, even if in smaller amounts than later on, these mechanical factors are likely to be almost as important as the dilution or inactivation of surfactant in preventing lung expansion, another point which could explain the absence of other aetiological factors in this group of lowest birth weight.

Although there are no observations presented here, it is possible that the relatively early clamping of the umbilical cord which often takes place at Caesarean section, may not only deprive the infant of placental blood, but as he is more often above the level of the placenta, actually lead to some siphonage of blood from his circulation. This, like birth asphyxia, may be an aggravating factor. Lastly the special predisposition of the male to RDS is not clearly understood. Though he may have a birth weight on average some 4 oz above the female at comparable gestation, his greater morbidity and mortality are by no means confined to RDS where the neonatal period is concerned.

The optimistic, perhaps naive thoughts which prompted this survey, those of finding some preventable factor in RDS, have certainly not been realized. Only the all-too-obvious one of prematurity presents itself as a recurring theme, and prevention of prematurity is a question with very wide social and economic implications, already receiving considerable attention in the quest for improved antenatal care. It has been shown that foetal distress (and hence by implication intra-uterine asphyxia) as defined by the practising obstetrician is significantly more common in RDS, confirming the postulations of physiologists and experimental workers who believe the pulmonary circulation to play a vital role. Nevertheless the indisputable fact remains that 67.5% of infants who later developed RDS did not have any foetal distress recorded, and 30.6% of mothers of RDS infants had no recognised complication of pregnancy, much less one which is known for certain to cause intrauterine asphyxia. These anomalies are further underlined by the finding that infants of 1500 g and less with RDS had really no helpful distinguishing features at all when compared with the remainder of like birth weight.

It seems clear that much more sophisticated measurements of intra-uterine conditions are needed, particularly in terms of oxygenation and blood flow, and perhaps maternal acid-base balance in labour. More attention might profitably be paid to factors governing transfer of fluid to and from the foetus, in view of the suggestion that infants more than one standard deviation below mean birth weight for gestation are less likely to develop RDS.

CONCLUSIONS

An examination has been made of possible aetiological factors in the production of the respiratory distress syndrome of the newborn. All infants classified as premature (birth weight 2500 g or 5 lb 8 oz and less) born in the Nuffield Maternity Home, Oxford between 1st January, 1959 and 31st December, 1964 have been studied, and simple, regression and correlation analyses made of maternal factors relating to the pregnancy and labour, and certain infant details. During this period 1126 mothers gave birth to 1244 such infants.

255 (20.5%) developed RDS using strict criteria for diagnosis.

The previously acknowledged significance of antepartum haemorrhage, birth asphyxia and the male sex as aetiological factors has been confirmed.

Foetal distress was significantly more common among infants with RDS. Regression analysis showed that an inaudible foetal heart at some stage during labour, and a rapid foetal heart in labour, were the most powerful factors discriminating between RDS infants and others in this respect.

Delivery by Caesarean section of itself predisposed to RDS, regardless of the indications for its performance.

Infants more than one standard deviation below the mean birth weight for gestation were significantly less likely to develop RDS.

The results of a correlation matrix showed that many of the significant factors were correlated one with another, indicating that a multiplicity of interrelating factors may be important in production of RDS.

When infants with a birth weight of 1500 g and less were considered separately, with all variables, those who developed RDS did not have any important aetiological features to distinguish them from the others. This finding stresses that immaturity is the single outstanding factor in pathogenesis of the disease.

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APPENDIX

All tables in the simple analysis (with the exception of Table 13) are set out similarly, with figures for the entire group (2500 g. or less) in the left-hand column, figures for infants 1500 g or less in the middle column, and figures for infants 1501-2500 g in the right-hand column.

These columns are further divided into infants with respiratory distress (designated RDS) and infants without (designated OTHER). Numbers and percentages are given, and the results of chi-squared tests inserted where relevant.

After a preliminary analysis of twins had been made, and it was found the results did not differ materially from singletons, it was decided to present the analysis of all infants together. Thus where data relate to mothers only the totals will be fewer (1126) than when relating to infants (1244).

Table 1 : MATERNAL AGE (1126 MOTHERS)

Maternal age, years	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
15–19	30	13.7	89	9.8	13	13.3	8	11.4	17	14.9	81	9.7
20–24	66	30.1	262	28.9	32	32.7	15	21.4	34	28.1	247	29.5
25–29	56	25.6	232	25.6	28	28.6	18	25.7	28	23.1	214	25.6
30–34	38	17.3	174	19.2	16	16.3	12	17.1	22	18.1	162	19.4
35–39	26	11.9	116	12.8	7	7.1	12	17.1	19	15.7	104	12.4
40–44	3	1.4	31	3.4	2	2.0	5	7.1	1	0.8	26	3.1
45–49	0	0.0	2	0.2	0	0.0	0	0.0	0	0.0	2	0.2
50+	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1
TOTAL	219	100.0	907	100.0	98	100.0	70	99.8	121	99.8	837	100.0

TABLE 2 : PRIMIPARITY (403 OF 1126 MOTHERS)

	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Primiparae	70	32.6	333	36.7	31	31.6	26	37.1	39	32.2	307	35.5

TABLE 3 : GESTATION (1244 INFANTS)

Gestation, weeks	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501-2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 28	44‡	17.2	15	1.5	44†	38.3	15	18.3	0	0.0	0	0.0
28-32	82‡	32.2	61	6.2	45	39.1	29	35.4	37‡	26.4	32	3.5
32-36	74	29.0	254	25.7	9*	7.8	17	20.7	65‡	46.4	237	26.1
36-40	23‡	9.0	396	40.0	2	1.7	4	4.9	21‡	15.0	392	43.2
> 40	3‡	1.2	121	12.2	1	0.9	2	2.4	2‡	1.4	119	13.2
Uncertain	29	11.4	142	14.4	14	12.2	15	18.3	15	10.7	127	14.0
TOTAL	255	100.0	989	100.0	115	100.0	82	100.0	140	99.9	907	100.0

*P = < 0.05
†P = < 0.01
‡P = < 0.001

TABLE 4: PREGNANCY COMPLICATIONS (1126 MOTHERS)

Pregnancy complications	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Pre-eclamptic toxaemia and/or essential hypertension	31	14.1	133	14.7	11†	11.2	20	28.6	20	16.5	113	13.5
Antepartum haemorrhage	69‡	31.5	116	12.8	32	32.6	19	27.1	37‡	30.6	97	11.6
Urinary infection	7	3.2	36	4.0	2	2.0	1	1.4	5	4.1	35	4.2
Abnormalities of umbilical cord	13	5.9	54	5.9	3	3.1	5	4.1	10	8.3	49	5.8
Anaemia	11‡	5.0	150	16.5	1†	1.0	7	10.0	10‡	8.3	143	17.8
Diabetes	1	0.4	4	0.4	0	0.0	0	0.0	1	0.8	4	0.5
Threatened miscarriage	30‡	13.7	25	2.7	23	23.5	10	14.3	7‡	5.8	15	1.8
Hydramnios	13	5.9	46	5.1	6	6.1	4	5.7	7	5.8	42	5.0
None	67‡	30.6	379	41.8	28	28.6	26	37.1	39‡	32.2	353	42.3
TOTAL MOTHERS	219		907		98		70		121		837	

(*P = < 0.05)
†P = < 0.01
‡P = < 0.001

TABLE 5 : INTERVAL BETWEEN MEMBRANE RUPTURE AND DELIVERY

(1244 INFANTS)

	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
⩽ 12	163	63.9	626	63.3	66	57.4	53	64.6	97	69.3	573	63.2
12–24	16*	6.3	115	11.6	3	2.6	5	6.1	13	9.3	110	12.1
24–48	5†	1.9	75	7.6	0	0.0	0	0.0	5	3.6	75	8.3
> 48	41*	16.1	104	10.5	23	20.0	12	14.6	18	12.8	92	10.1
Uncertain	30	11.8	69	7.0	23	20.0	12	14.6	7	5.0	57	6.3
TOTAL	255	100.0	989	100.0	115	100.0	82	99.9	140	100.0	907	100.0

*P = < 0.05
†P = < 0.01

TABLE 6: DURATION OF LABOUR, FIRST AND SECOND STAGES (1244 INFANTS)

Duration, hours	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 12	149	58.4	632	63.9	68	59.5	43	52.4	84	60.0	589	64.9
12–24	42	16.5	148	14.9	14	12.2	10	12.2	28	20.0	138	15.2
24–48	4	1.6	45	4.6	2	1.7	3	3.7	2	1.4	42	4.6
> 48	2	0.8	19	1.9	2	1.7	4	4.9	0	0.0	15	1.7
Uncertain	21	8.2	69	7.0	18	15.7	10	12.2	3	2.1	59	6.5
Not in labour	37*	14.5	76	7.7	14	12.2	12	14.6	23†	16.4	64	7.1
TOTAL	255	100.0	989	100.0	115	100.0	82	100.0	140	99.9	907	100.0

*P = < 0 01
†P = < 0.001

TABLE 7: DURATION OF SECOND STAGE OF LABOUR (1244 INFANTS)

Duration, minutes	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 15	76*	30.6	230	23.2	40	34.8	27	32.9	36	27.1	203	22.4
15–30	43*	16.9	240	24.3	14	12.2	15	18.3	29	20.7	225	24.9
30–60	29†	11.4	197	20.0	8	7.0	7	8.5	21	15.0	190	20.9
> 60	13	5.1	65	6.6	5	4.3	3	3.7	8	5.7	62	6.8
Uncertain or not in labour	92†	36.1	257	25.9	48	41.7	30	36.6	44	31.4	227	25.0
TOTAL	255	100.1	989	100.0	115	100.0	82	100.0	140	99.9	907	100.0

*P = < 0.05
†P = < 0.01

TABLE 8: DRUGS GIVEN WITHIN 4 HOURS OF DELIVERY (1244 INFANTS)

Drug	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Analgesic	86	33.7	362	36.6	35	30.4	26	31.7	51	36.4	336	37.0
Sedative	15	5.9	73	7.4	6	5.2	4	4.9	9	6.4	69	7.6
Both	33	12.9	86	8.7	18	15.7	8	9.7	15	10.7	78	8.6
None	121	47.5	468	47.4	56	48.7	44	53.7	65	46.4	424	46.7
TOTAL	255	100.0	989	100.0	115	100.0	82	100.0	140	99.9	907	99.9

TABLE 9: ANAESTHETICS GIVEN DURING LABOUR OR DELIVERY (1244 INFANTS)

Anaesthetic	Birthweight 2500 g or less				Birthweight 1500 g or less				Birthweight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Gas + air or oxygen	93*	37.3	455	46.0	39	33.9	37	45.1	56	40.0	418	46.1
General anaesthetic	52*	20.4	139	14.1	19	16.5	14	17.2	33*	23.6	125	13.7
Local, spinal or caudal	60	23.5	289	29.2	21	18.3	18	21.9	39	27.9	271	29.9
None	48*	18.8	106	10.7	36*	31.3	13	115.9	12	8.6	93	10.3
TOTAL	255	100.0	989	100.0	115	100.0	82	100.0	140	100.1	907	100.0

*P = < 0.05
**P = < 0.01
***P = < 0.001

TABLE 10: FOETAL DISTRESS (IN 313 OF 1244 INFANTS)

	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Foetal distress	83*	32.5	230	23.2	29	25.2	24	29.3	54†	38.6	206	22.7

*P = < 0.01
†P = < 0.001

TABLE 11: EPISIOTOMY FOR VAGINAL DELIVERY (IN 554 OF 1095 DELIVERIES)

	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Episiotomy	101	43.3	453	51.6	37	36.6	32	48.5	64	54.7	421	51.9

TABLE 12: MODE OF DELIVERY (1244 INFANTS)

Delivery	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Vertex	135	52.9	535	54.1	63	54.8	41	50.0	72	51.4	494	54.5
Breech	53†	20.8	129	13.1	30	26.1	14	17.1	23	16.4	115	12.7
Forceps	30‡	11.8	213	21.5	8	6.9	11	13.4	22	15.7	202	22.3
Caesarean (emergency)	34*	13.3	84	8.5	14	12.2	13	15.9	20*	14.3	71	7.8
Caesarean (elective)	3	1.2	28	2.8	0	0.0	3	3.6	3	2.2	25	2.7
TOTAL	255	100.0	989	100.0	115	100.0	82	100.0	140	100.0	907	100.0

*P = < 0.05
†P = < 0.01
‡P = < 0.001

TABLE 13: COMPARISON OF CAESAREAN AND VAGINAL DELIVERIES, WITH INCIDENCE OF RDS

Foetal distress	Antepartum haemorrhage	Caesarean delivery				Vaginal delivery			
		RDS		Other		RDS		Other	
		No.	%	No.	%	No.	%	No.	%
+	+	7	18.9	6	5.3	32	14.7	26	3.0
+	-	1*	2.7	31	27.7	43	19.7	167	19.0
-	+	7	18.9	16	14.3	23	10.6	68	7.8
-	-	22*	59.5	59	52.7	120	55.0	616	70.2
TOTAL		37	100.0	112	100.0	218	100.0	877	100.0

*P = < 0.05.

TABLE 14 : BIRTH WEIGHT AND GESTATION STANDARDS (1244 INFANTS)

Birth weight/Gestation	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501-2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Mean and <±1 SD	173‡	67.8	347	36.1	83†	72.2	43	52.5	90‡	64.3	304	33.5
> + 1 SD	7†	2.7	5	0.5	2	1.7	0	0.0	5†	3.6	5	0.6
> - 1 SD	46‡	18.1	491	49.6	16*	13.9	24	29.2	30‡	21.4	467	51.5
Uncertain	29	11.4	146	14.8	14	12.2	15	18.3	15	10.7	131	14.4
TOTAL	255	100.0	989	100.0	115	100.0	82	100.0	140	100.0	907	100.0

*P = < 0.05
†P = < 0.01
‡P = < 0.001

The standards used are those of the National Birthday Trust's Perinatal Mortality Survey of 1958. It should be noted that these standards relate to the country as a whole, and may have limited application to any one Maternity Unit, but they have been used in the absence of standards for Oxford infants, and as they are the most up-to-date standards available for British babies.

TABLE 15: SEX DISTRIBUTION (1244 INFANTS)

	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Male	152*	59.6	468	47.3	60	52.2	45	54.9	92*	65.7	423	46.6
Female	103	40.4	521	52.7	55	47.8	37	45.1	48	34.3	484	53.4
TOTAL	255	100.0	989	100.0	115	100.0	82	100.0	140	100.0	907	100.0

*P = < 0.001

TABLE 16: BIRTH ASPHYXIA (1244 INFANTS)

Asphyxia	Birth weight 2500 g or less				Birth weight 1500 g or less				Birth weight 1501–2500 g			
	RDS		Other		RDS		Other		RDS		Other	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Grade I	31	12.2	127	12.8	9*	7.8	17	20.7	22	15.7	110	12.1
Grade II	80‡	31.4	154	15.6	44	38.3	29	35.4	36‡	25.7	125	13.8
Grade III	45‡	17.6	15	1.5	39‡	33.9	2	3.7	6*	4.3	12	1.3
None	99†	38.8	693	70.1	23†	20.0	33	40.2	76†	54.3	660	72.8
TOTAL	255	100.0	989	100.0	115	100.0	82	100.0	140	100.0	907	100.0

Grade I - Respirations established between 2 and 5 minutes.
Grade II - " " between 5 and 10 minutes.
Grade III - " " at varying times after 10 minutes.

*P = < 0.05
†P = < 0.01
‡P = < 0.001

REGRESSION ANALYSIS AND CORRELATION MATRIX

(Dr. A. Barr and Miss E. Whitwell)

REGRESSION OF 540 SINGLETONS DELIVERED VAGINALLY

	Regression coefficient	Standard error	T value
5.0% significance level			
RDS			
Ante-partum haemorrhage	-.9927/-01	.3934/-01	2.52
Hydramnios	.1866/ 00	.9307/-01	2.00
Gestation	.1752/-01	.4169/-02	4.20
Rapid foetal heart	-.6210/-01	.4416/-01	1.41
Inaudible foetal heart	-.2046/ 00	.8418/-01	2.43
Sex	-.6186/-01	.2887/-01	2.14
Weight < 1000 g	-.3624/ 00	.9755/-01	3.72
Weight 1000-1500 g	-.2224/ 00	.6293/-01	3.53
Weight 1501-2000 g	-.1481/ 00	.4054/-01	3.65
Weight 2001-2250	-.7384/-01	.3741/-01	1.97
Weight > - 1 SD	.9317/-01	.3171/-01	2.94
1.0% significance level			
RDS			
Gestation	.1793/-01	.4181/-02	4.29
Weight < 1000 g	-.3419/ 00	.9670/-01	3.54
Weight 1000-1500 g	-.2022/ 00	.6145/-01	3.29
Weight 1501-2000 g	-.1214/ 00	.3849/-01	3.15
Weight > - 1 SD	.1041/ 00	.3168/-01	3.29
Ante-partum haemorrhage	-.1043/ 00	.3949/-01	2.64
Sex	-.6745/-01	.2898/-01	2.33
Inaudible foetal heart	-.1957/ 00	.8424/-01	2.32
0.1% significance level			
RDS			
Gestation	.1895/-01	.4175/-02	4.54
Weight < 1000 g	-.3261/ 00	.9686/-01	3.37
Inaudible foetal heart	-.2078/ 00	.8443/-01	2.46
Weight > - 1 SD	.1072/ 00	.3178/-01	3.37
Ante-partum haemorrhage	-.1075/ 00	.3963/-01	2.71
Weight 1000-1500 g	-.2049/ 00	.6169/-01	3.32
Weight 1501-2000 g	-.1179/ 00	.3863/-01	3.05

(10.0% significance level results have been omitted.)

CAESAREAN REGRESSION - 132 INFANTS

	Regression coefficient	Standard error	T value
5.0% significance level			
RDS			
Cord round neck	- .5337/ 00	.2211/ 00	2.41
Gas and oxygen during labour	.6954/ 00	.2183/ 00	3.19
Sex	.1273/ 00	.6499/-01	1.96
Asphyxia (grade I)	.3305/ 00	.6985/-01	4.73
Gestation	- .5555/-01	.9441/-02	5.88
1.0% significance level			
RDS			
Gas and oxygen during labour	.6808/ 00	.2241/ 00	3.04
Asphyxia (grade I)	.2987/ 00	.7021/-01	4.25
Gestation	- .5468/-01	.9694/-02	5.64
0.1% significance level			
RDS			
Asphyxia (grade I)	.2775/ 00	.7207/-01	3.85
Gestation	- .5158/-01	.9945/-02	5.19

REGRESSION OF 85 INFANTS 1500 g AND LESS

	Regression coefficient	Standard error	T value
RDS			
Consultant A	.1782/ 00	.3258/ 00	0.55
Consultant B	.5517/ 00	.3201/ 00	1.72
Consultant C	.1714/ 00	.3674/ 00	0.47
Cord round neck	.1609/ 01	.1680/ 01	0.96
Prolapsed cord	-.1947/ 01	.4316/ 01	0.45
Ante-partum haemorrhage	-.1191/ 00	.2808/ 00	0.42
Pre-eclamptic toxaemia	-.3128/ 00	.8231/ 00	0.38
Anaemia	.2079/ 01	.2000/ 01	1.04
Urinary infection	.1269/ 01	.1242/ 01	1.02
Threatened miscarriage	-.2169/ 00	.2856/ 00	0.76
Essential hypertension	-.4192/ 00	.1156/ 01	0.36
Hydramnios	-.7947/ 00	.7929/ 00	1.00
Parity	-.3035/-01	.1502/ 00	0.20
Previous miscarriages	.5359/-01	.1589/ 00	0.34
Age 15-19	.2322/ 00	.4208/ 00	0.55
Age 20-24	-.6990/-01	.4816/ 00	0.15
Age 25-29	-.5811/ 00	.5936/ 00	0.98
Age 30-34	-.5904/ 00	.8316/ 00	0.71
Age 35-39	.3027/-01	.5581/-01	0.54
Gestation	.1664/ 01	.9239/ 00	1.80
Rapid foetal heart	.6965/ 00	.8398/ 00	0.83
Slow foetal heart	.7640/ 00	.9444/ 00	0.81
Meconium-stained liquor	.1365/ 00	.3726/ 00	0.37
Inaudible foetal heart	.7871/-01	.3293/ 00	0.24
Membranes ruptured < 12 hours	.8331/ 00	.6883/ 00	1.21
Membranes ruptured 24-48 hrs	-.1646/ 01	.7088/ 03	0.00
Labour < 12 hours	-.2099/ 01	.7088/ 03	0.00
Labour 12-24 hours	-.1704/ 01	.7088/ 03	0.00
Vertex delivery	-.2739/-01	.3023/-01	0.91
Breech delivery	-.1047/ 01	.7088/ 03	0.00
Forceps delivery	-.9914/ 00	.7088/ 03	0.00
Emergency Caesarean section delivery	.2474/ 01	.7088/ 03	0.00
Gas and oxygen during labour	.3236/ 00	.3004/ 00	1.08

(continued)

(continuation)

	Regression coefficient	Standard error	T value
General anaesthesia	-.2743/ 00	.8490/ 00	0.32
Local anaesthesia	-.2917/ 01	.3101/ 01	0.94
Spinal anaesthesia	-.821 / 00	.6367/ 00	1.29
Caudal anaesthesia	-.2630/ 01	.3042/ 01	0.86
Analgesic within 4 hours of delivery	-.2957/ 01	.3703/ 01	0.80
Sedative within 4 hours of delivery	-.3652/ 00	.3913/ 00	0.93
Both within 4 hrs of delivery	-.8516/ 00	.7404/ 00	1.15
Sex	-.1258/ 01	.1083/ 01	1.16
Weight < 1000 g	-.6034/ 00	.5006/ 00	1.21
Weight 1000-1500 g	-.2025/ 00	.5450/ 00	0.37
Weight > 1 SD below mean for gestation	.5507/-01	.2016/ 00	0.27
Weight < ± 1 SD	-.1488/ 00	.3403/ 00	0.44
Weight > 1 SD above mean for gestation	.2014/ 00	.4237/ 00	0.48
Birth asphyxia (grade II)	.8116/ 00	.1041/ 01	0.78
Birth asphyxia (grade III)	.1956/ 00	.5511/ 00	0.36
Intubation	-.3008/ 00	.5883/ 00	0.51
Time of delivery	.2696/-01	.3835/ 00	0.07
Date of delivery	.1010/-01	.2101/-01	0.48
Accoucheur - house officer	-.2224/-01	.1182/-01	1.88
" - registrar	-.8909/ 00	.4141/ 00	2.15
" - consultant	.1736/ 00	.7650/ 00	0.23
" - pupil midwife	-.6020/ 00	.2331/ 00	2.58
" - staff midwife	-.1234/ 01	.9340/ 00	1.32
" - medical student	-.2815/ 00	.2688/ 00	1.05

CORRELATION MATRIX N= 540

1													
-019	2												
-004	-492	3											
009	-272	-315	4										
039	-056	-020	024	5									
026	036	-050	011	-018	6								
-032	060	-004	-031	-006	105	7							
-075	133	-065	-036	-007	-018	284	8						
-195	005	-003	-002	-038	001	-033	078	9					
115	-007	002	030	-039	-027	031	-039	-083	10				
107	-009	-061	002	-034	-006	-029	-034	-015	-022	11			
-002	-094	018	044	-015	-038	-013	-015	-022	-054	052	12		
056	-008	-011	067	-016	110	-013	-016	-054	024	-043	-033	13	
-195	043	-025	-036	-018	-045	-015	088	129	-096	-083	-038	-039	14
073	-081	042	087	-018	084	-016	-018	-071	-098	-059	-038	010	15
-018	-009	-020	-036	-007	-018	-006	-007	-038	-039	029	-015	-016	16
070	029	007	-031	-013	-033	-011	-013	027	056	008	-028	105	17
013	-081	023	011	146	075	024	-023	005	-109	154	216	019	18
-036	013	068	-055	-010	033	-033	-010	018	-061	009	017	-001	19
-060	048	-050	-000	037	008	-026	037	-016	-023	-004	-064	031	20
-032	047	-036	-039	-062	-005	-054	028	-017	009	-035	-063	-026	21
027	-000	-004	031	-048	066	015	-048	039	-006	-084	-003	-032	22
024	-005	040	-008	127	-032	093	014	008	037	050	079	045	23
023	-093	056	013	-027	-036	-023	-027	-018	-024	082	016	013	24
410	-091	026	039	003	049	017	-056	-196	157	080	074	005	25
-103	-017	-078	038	034	085	048	-032	065	057	-029	-066	-005	26
059	-026	044	008	035	004	-027	035	022	-015	022	-000	091	27
058	-038	-031	047	-019	033	-017	079	-102	007	008	007	-042	28
-198	-001	040	-045	-015	-038	129	108	120	-026	021	-032	-033	29
-071	114	080	-058	-116	-045	-048	019	070	-018	012	-064	-012	30
000	-053	-024	066	-033	-005	-029	-033	-042	110	-059	085	-042	31
058	-023	-061	034	-025	105	071	-025	-054	069	026	026	023	32
019	-045	-008	-006	050	064	-013	-048	031	-025	107	057	061	33
-017	073	027	-015	-045	-047	021	060	-025	-035	-088	-042	-072	34
074	-034	001	057	-024	-061	-021	-024	-089	128	-072	-051	063	35
133	048	-102	010	-031	-028	-039	-004	-086	141	-023	-069	-005	36
-023	045	-051	-096	057	065	-004	-130	-041	-145	050	073	011	37
-096	037	-015	048	-032	-081	047	098	120	-067	-000	-035	024	38
109	-083	078	076	-040	-007	-035	072	-051	221	-058	-056	-033	39
019	-028	-032	-018	-003	-009	-003	-003	-019	094	-017	-007	-008	40
-004	062	040	-035	-091	-066	-029	-005	-011	155	-127	-106	030	41
026	-000	-023	003	-045	048	045	-045	-048	-146	042	036	-051	42
-030	-031	000	045	-017	001	-015	091	085	079	000	-037	066	43
061	-013	008	045	-042	-037	-036	066	-016	060	-057	-035	039	44
046	-110	083	088	-014	-036	-012	-014	-014	192	-000	-030	-031	46
003	015	029	-046	012	030	-014	-031	-032	-068	-003	-092	-057	47
047	-050	009	025	-026	065	-022	-026	-025	093	018	137	-018	48
001	-004	-018	022	-032	-024	-027	034	019	133	020	031	026	49
-149	065	033	-023	047	-008	028	047	064	015	-052	-045	-012	50
-238	029	027	-042	-015	-037	-013	-015	040	-079	-069	-031	-032	51
-234	007	025	-043	-025	-029	-021	055	113	-040	-074	-052	-015	52
-145	038	-011	000	064	-018	024	010	089	004	-048	-090	036	53
007	-042	058	-000	-044	-068	-038	007	000	026	019	-067	004	54
-248	-008	022	012	027	031	-002	027	031	-055	-050	024	-049	55
202	053	003	019	-010	033	059	-010	-011	072	056	-026	012	56
152	-062	-021	013	010	-040	-037	-043	-110	041	032	015	010	57
-085	023	-001	-050	-030	-077	-026	037	093	-069	-021	-030	031	58
-094	-028	057	-018	-003	-009	-003	-003	097	-019	-017	-007	-008	59
-071	011	-046	061	-027	-038	-024	-027	-006	121	-035	-022	010	60
-110	099	-028	-016	016	017	-034	129	198	109	-056	-056	-005	61
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66				
-192	67			
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-306	-269	-103	-367	70

ABSTRACT

Previous investigations into the respiratory distress syndrome have established that the infants lack pulmonary surface active factor, and thus alveolar stability. Inactivation or greatly reduced production of this substance is more likely than congenital absence. The extensive atelectasis which ensues leads to decreased lung compliance, ventilatory insufficiency, vascular shunts and respiratory and metabolic acidosis. It has been shown to be largely a condition of premature gestation, and significant associations found with antepartum haemorrhage, maternal diabetes, birth asphyxia and the male sex. Largely as the result of animal studies on the pulmonary circulation, and the experimental production of respiratory distress, prenatal asphyxia has been postulated as a likely cause.

An analysis has been made of maternal and infant factors relating to premature births over a six-year period. Infants developing the respiratory distress syndrome as defined by strict criteria, and their mothers, have been compared with those who avoided this complication. Since immaturity is known to be the one constant factor in aetiology, it was realized that an en bloc comparison of these two groups might lead to mothers and their infants of dissimilar gestation being compared, so that in addition, infants in the two groups above and below a birth weight of 1500 g have been contrasted with each other as well, and chi-squared tests of significance used. Since there were many factors being analysed, there was much to be gained by regression and correlation analyses as well, to discriminate the most important variables between the groups and their association one with another.

The results confirm the already published associations. They are also considered to show that Caesarean section predisposes of itself to the development of RDS, a question previously controversial. They establish that pre-natal asphyxia as judged by relatively crude manifestations of foetal distress is indeed likely to be significantly associated in certain infants; and that infants who are small for their gestation period are less likely to develop the syndrome. When infants 1500 g or below were analysed separately there were found to be no helpful factors discriminating RDS infants from others.

It is suggested, since many of these significantly associated conditions are shown to be interrelated, that the syndrome may develop in response to any one of a number of factors or to a combination of them. Inspiratory gasping in utero and increased pulmonary capillary permeability, due to pre-natal asphyxia, may be the cause of the increased fluid content which has been shown present in these infants' lungs. Such an increase, in the larger infants, may then parallel the amount of fluid normally found in the lungs of very small infants, an amount which decreases with birth weight. This fluid and delay in its removal may compromise the pulmonary circulation further, leading to alveolar cell damage and hence decreased production of pulmonary surface active factor, already diluted or inactivated by the extra fluid. In the most immature, the sheer mechanical disadvantage of breathing may be equally important.