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The Current Status of the Respiratory Distress Syndrome of the Newly Born

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ABSTRACT

The respiratory distress syndrome (RDS) occurs in 14% of premature infants and is twice as common and twice as lethal in males as in females. Recent work suggests that, during the intrauterine period a disturbance in nutrition of the lung resulting from fetal pulmonary vascular constriction results in alveolar-cell damage and a decrease in pulmonary surface activity with resultant atelectasis. Data on respiratory work levels, oxygen consumption and arterial oxygen tension suggest that there is an oxygen debt in the acute stage of the disease. Such data have further clarified the pathogenesis of the metabolic and respiratory components of the acidosis and the secondary effects thereof. In prevention, prophylaxis of prematurity is of major importance. A program of treatment designed to combat the various aspects of the pathophysiological disturbances is described in the form of a case profile. Modern methods of observation, biochemical control and treatment, as well as the necessity for critical evaluation, suggest that infants with RDS are best cared for in special centres.

SOMMAIRE

Le syndrome de détresse respiratoire (SDR) survient chez 14% des prématurés et est deux fois plus fréquent et entraîne deux fois plus de décès chez les garçons que chez les filles. Une étude récente évoque la possibilité que, durant la vie intra-utérine, un trouble de la nutrition pulmonaire à la suite d'une vaso-constriction pulmonaire chez le fœtus, se traduise par une lésion alvéolo-cellulaire et une diminution de l'activité de la surface pulmonaire et, partant, par de l'atélectasie. Des analyses sur la fonction respiratoire, la consommation d'oxygène et la tension d'oxygène artérielle permettent de croire qu'il existe un déficit durant la phase aiguë de la maladie. Ces données ont part ailleurs permis d'élucider la pathogénie des éléments métabolique et respiratoire de l'acidose et ses effets secondaires. Au point de vue prophylactique, la prevention de la prématurité est d'une importance capitale. Un plan de traitement destiné à combattre les divers éléments des troubles physiopathologiques est évoqué par le truchement d'une histoire clinique. La nécessité de recourir à des méthodes d'observation modernes, à des analyses et à des traitements biochimiques, ainsi que le besoin de procéder à une évaluation critique conduit à la conclusion que les nourrissons atteints de SDR doivent être hospitalisés dans des centres spécialisés.

THE purpose of this communication is to review, in conjunction with our own studies, recent knowledge of the respiratory distress syndrome (RDS) of the newly born and to indicate how this knowledge may be used in practice.

Clinically the disease is almost exclusively found in prematures and has a 2:1 predominance in the male, both in incidence and mortality.[82] It is also associated with maternal conditions such as diabetes mellitus and obstetrical complications, including those leading to Cesarean section. The incidence is approximately 14% of premature live births[55] and the mortality varies from 17% to

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55%.[82] Death usually occurs during the first 48 hours of life.

In 1962 Dawes[1] proposed a unified concept of the disease in which a number of possible processes, notably intrauterine asphyxia, by causing pulmonary vasoconstriction, could result in reduced pulmonary blood flow. This could lead to alveolar cell damage, with subsequent uneven alveolar distension.

This concept is supported by the chance occurrence of a fatal case of hyaline membrane disease (HMD) in which one lobe was spared.[3] This lobe had a separate arterial supply from the aorta, which presumably prevented damage from reduction in blood flow.

Two other groups of workers[4, 5] as well as Dawes and his associates[6] have now demonstrated the occurrence of alveolar cell damage and atelectasis with structures resembling hyaline membranes in animals as a result of certain maneuvers or drugs administered to the mother producing fetal asphyxia and HMD.[7-10] The key to the problem may be the quantitative effect on uteroplacental blood flow as well as the qualitative alteration in the maternal blood. Thus both maternal acidosis[8-10] and alkalosis[11, 12] have been shown to result in fetal acidosis. Maternal alkalosis is thought to have a vasoconstrictor effect on the fetal blood vessels in the placenta, leading to fetal asphyxia.

We then have a number of possible mechanisms which, by causing fetal asphyxia, could lead to a reduction in fetal or neonatal pulmonary blood flow as proposed by Dawes, initiating the sequence of alveolar cell damage, surfactant deficiency and atelectasis which is the main morbid anatomical lesion.

Several workers[14-17] have demonstrated a deficiency or inactivation of the surface active molecular lining of the alveolus during the first two days of the disease. From the third day, increasing surface activity has been detected[18] and presumably parallels clinical recovery.

The alveolar surfactant probably consists of di-palmitoyl alpha-lecithin, forming a polarized molecular layer on the alveolar surface.[19, 20] This layer has the property of stabilizing the alveolar space at low inflation volumes. A reorientation of polar molecules on compression of the surface film reduces the surface tension, tending to collapse the alveolus, which is at its maximum when the alveolar diameter is smallest. It can be calculated that, if the surface tension of the alveolar fluid is that of most biological fluids (40 dynes/cm.^{2}), a distending pressure of approximately 40 cm. of water would be required to maintain patency of the alveolus at the end of expiration. In fact only about 1-2 cm. of water distending pressure is necessary under normal conditions to prevent end expiratory alveolar closure.

Reduction in normal alveolar surface activity leads to atelectasis, diminishing total lung capacity,

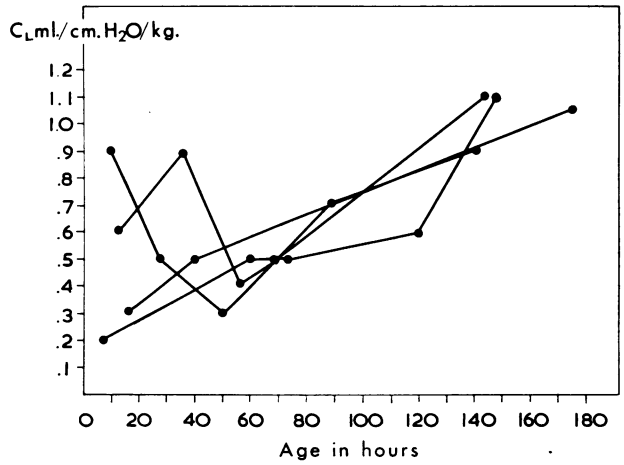


Fig. 1.—Serial measurements of lung compliance in four cases of respiratory distress syndrome. The normal lung compliance is 1.6-1.9 ml./kg. body weight.[13, 89]

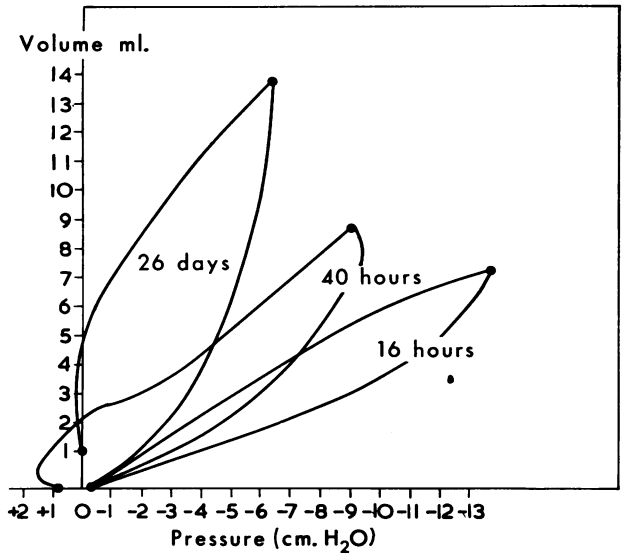


Fig. 2.—Serial respiratory pressure/volume diagrams in one patient with respiratory distress syndrome showing at 16 hours a high negative intrapleural pressure with a low tidal volume, which by 26 days had returned to normal.

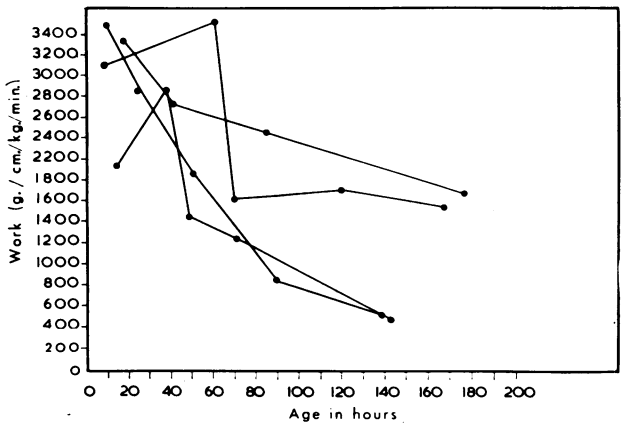


Fig. 3.—Serial measurements of respiratory work done on the lungs showing high initial values returning towards the normal 400 g./cm./kg./min. on recovery.

"crying vital capacity" and functional residual capacity.[21, 28] A reduction in the number of ventilating alveoli together with edema and exuda-

tion lowers lung compliance[25-29] (Figs. 1 and 2). An increase in respiratory work[27-29] (Fig. 3) accompanies the larger negative intrapleural pressures generated at an increased respiratory rate[29, 30] (Fig. 4) to maintain alveolar ventilation. Negative

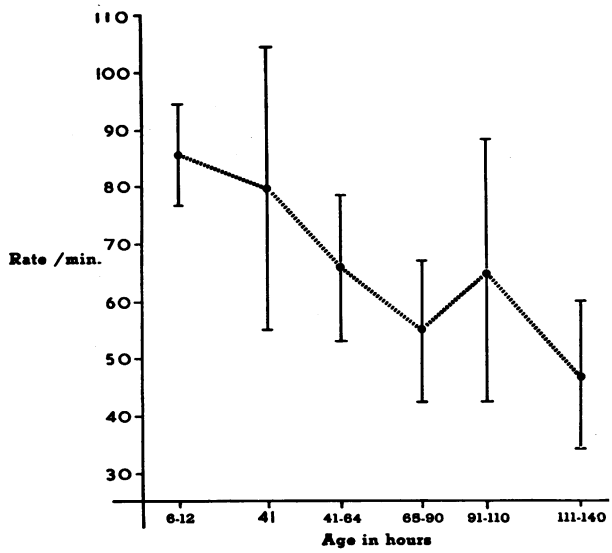


Fig. 4.—The course of the mean respiratory rate in 28 newborn infants with respiratory distress syndrome (four of whom died). Vertical bars represent ± SE of the mean.

intra-esophageal pressures > 35 cm. have been required.[31-34] The large negative intrapleural pressure in inspiration, opposing the increased alveolar surface tension, results in a large capillary transmural gradient outwards. This gradient causes transudation and hyaline membrane formation.[35]

The result of these morbid anatomical changes is a decrease in alveolar ventilation[25, 36, 37] which is not fully compensated by the increase in minute volume (Fig. 5) owing to the accelerated respiratory rate (Fig. 4). Alveolar hypoventilation results in carbon dioxide retention, a rise in arterial carbon dioxide tension, an increase in blood carbonic acid in relation to bicarbonate and hence a respiratory acidosis[38] (Fig. 6).

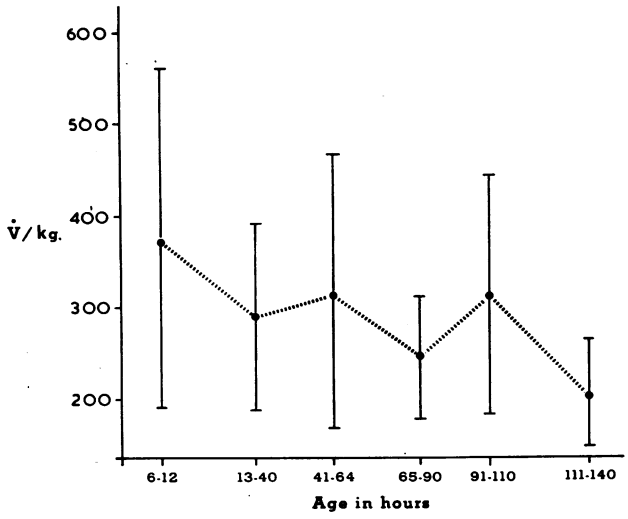


Fig. 5.—The course of the minute volume (B.T.P.S. = Body Temperature and Pressure Saturated with water vapour) in 28 newborn infants with respiratory distress syndrome (four of whom died). V̇ = minute respiratory volume. Other symbols same as in Fig. 4. Reproduced from *Biologia Neonatorum*[57] by permission of the Editor and Publisher (S. Karger, Basel/New York).

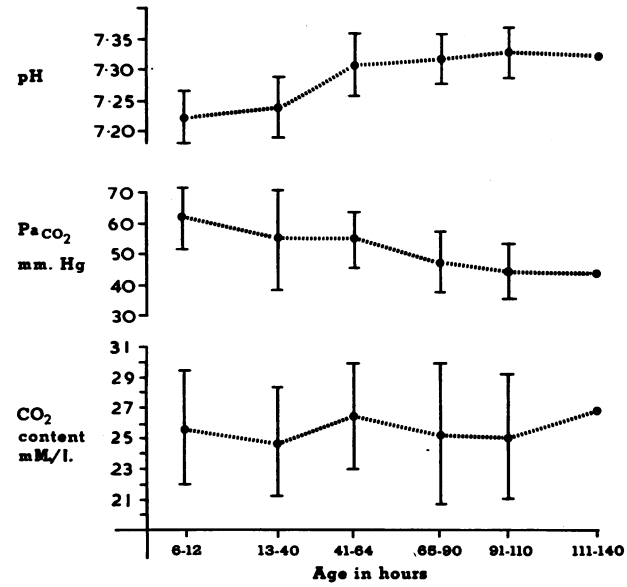


Fig. 6.—Serial measurements of acid-base parameters in 11 infants with respiratory distress syndrome. $PaCO_2$ = partial pressure of CO_2 in arterial blood. Other symbols same as in Fig. 4. Reproduced from *Biologia Neonatorum*[57] by permission of the Editor and Publisher (S. Karger, Basel/New York).

Alveolar hypoventilation also results in hypoxemia while breathing air.[25, 37, 39-42] Inadequate arterial saturation may possibly be further augmented by a diffusion defect[43, 44] in the alveolar capillary membrane, or by uneven distribution of oxygen molecules to alveoli from mechanical changes or obstruction within the airways. However, the chief cause of inadequate arterial saturation is deficient or absent alveolar ventilation in relation to pulmonary blood flow, resulting in an intrapulmonary right-to-left (R→L) shunt. If high oxygen concentrations are breathed up to > 95%, the diffusion and distribution defects are eliminated as causes of hypoxemia (Table I), but the shunt effect remains.

TABLE I.—THE CAUSATION OF ARTERIAL HYPOXEMIA WHILE BREATHING AIR AND 100% OXYGEN

HYPOXIA IN AIR	HYPOXIA IN 100% O_2
1. ↓ alv. Vent.^{n}	Abolished by 100% O_2
2. Uneven distribution to alveoli	Abolished by 100% O_2
3. Diffusion defect	Abolished by 100% O_2
4. R → L shunt (perfusion non vent.^{d} alveoli; fetal channels)	R → L shunt

Under these circumstances it is possible, by an analysis of the difference in oxygen tension between

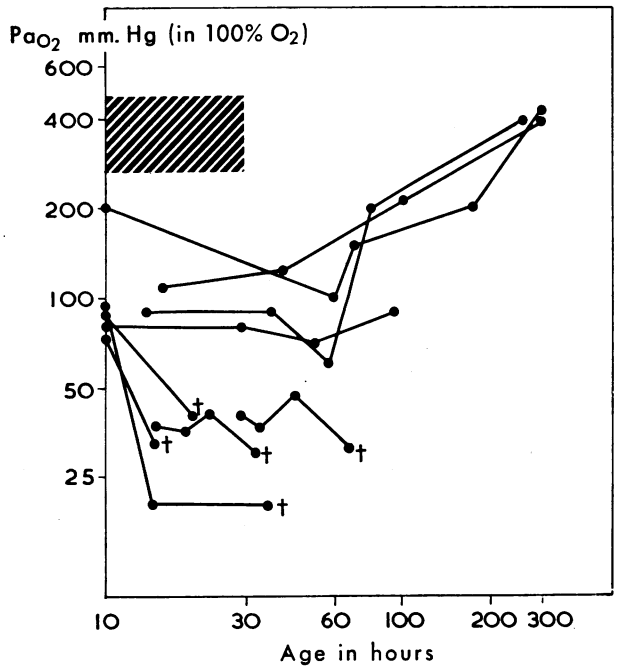


Fig. 7.—Serial arterial oxygen tensions in eight infants with respiratory distress syndrome, four of whom died, measured after 30 minutes' breathing 100% oxygen. The shaded area represents normal levels for infants.[25]

alveoli and arterial blood, to calculate the volume of R→L shunt.[25, 40-42, 45] It is this shunt which is the cause of arterial hypoxemia in RDS while breathing high concentrations of oxygen. If the arterial oxygen tension is 40 mm. or less, while breathing > 95% oxygen, a R→L shunt of > 70% of the cardiac output is present.[25, 37, 40, 41, 46] The mortality under these circumstances is very high and such serial measurements are probably the best guide to prognosis currently available (Fig. 7).

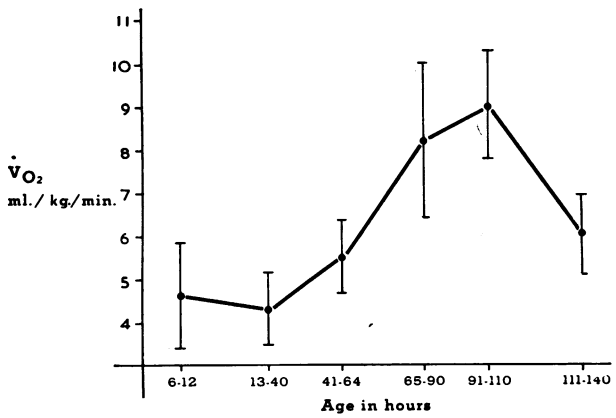


Fig. 8.—Serial oxygen consumption (S.T.P.D. = Standard Temperature and Pressure, Dry) in 28 infants with respiratory distress syndrome, four of whom died. $\dot{V}O_2$ = oxygen consumption per minute. Other symbols same as in Fig. 4. Reproduced from *Biologia Neonatorum*[57] by permission of the Editor and Publisher (S. Karger, Basel/New York).

Such data only give information on the volume of the shunt relative to the total cardiac output and do not give an absolute value. Thus in the presence of a low cardiac output, while the proportion of a R→L shunt may be large, its absolute volume may well be relatively small. The cardiac output and its distribution between the lungs and systemic circulation deserve further study. The present evidence, derived from dye dilution curves[47] and cardiac catheterization[48] studies, indicates pulmonary-to-systemic flow ratios, in severe cases, of over 3 to 1. The very labile nature of the pulmonary vascular bed and its sensitivity to many prenatal and postnatal influences has been pointed out by Dawes[1, 2, 88] and documented in a number of subsequent studies.[49-51] Changes in pulmonary vascular resistance and blood flow may yet prove to play a decisive part both in the etiology and pathophysiology of the disease.

Tissue hypoxia is an invariable concomitant of all serious cases of RDS and results in anaerobic metabolism[25, 33, 34, 38, 52-55, 57] and lactate accumulation[52, 53] adding a metabolic component to the respiratory acidosis already described. This suggestive evidence of an oxygen debt has recently been confirmed by studies showing low oxygen consumption[56, 57] in the first 60 hours of the disease (Fig. 8), when metabolic demand is highest, as judged by increased mechanical work of breathing[27, 29] (Fig. 3) and low core temperature[57] (Fig. 9).

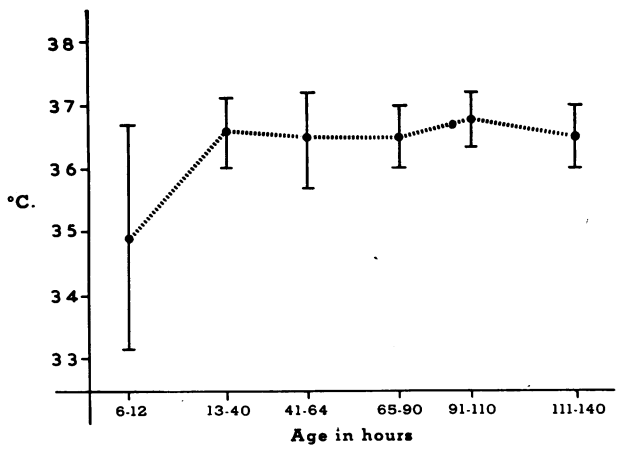


Fig. 9.—Serial measurements of colonic temperature in 28 newborn infants with respiratory distress syndrome. Symbols same as in Fig. 4.

There is evidence that the low oxygen consumption is related to circulatory defects. Our surviving patients with low oxygen consumption and metabolic acidosis during the first 60 hours of the disease had arterial oxygen tensions which, while lower than predicted for infants breathing > 95% oxygen, were consistent with full arterial hemoglobin saturation (Fig. 7).[57] This indicates a low systemic blood flow to explain the deficient volume of oxygen delivered to the tissues as reflected by the lowered oxygen uptake. Our patients dying with RDS also showed reduced oxygen consumption and had arterial oxygen tensions less than 40 mm. Hg (Fig. 7). However, we have recently demonstrated that, even in the presence of an arterial oxygen tension of 20 mm. Hg in cyanotic infants with cardio-

pulmonary disease,[58] a normal or increased oxygen uptake is possible, presumably as a result of a compensating increased blood flow. Thus we have indirect but suggestive evidence of reduced systemic blood flow in the acute stage of RDS. It is also possible that there is a parallel defect in pulmonary blood flow, thus reducing the absolute volume of blood oxygenated/unit of time. In fatal cases the oxygen uptakes remain low, but if recovery occurs oxygen consumption rises significantly above the initial levels to satisfy the increased metabolic demand, falling to normal on full recovery[57] (Fig. 8). There is some clinical, electrocardiographic and radiological evidence that heart failure is implicated, especially terminally.[59-61]

The consequence of the pulmonary and hemodynamic changes is a profound respiratory and metabolic acidosis which in itself induces a train of secondary effects.[54, 55, 62, 63] A vicious cycle (Fig. 10) is initiated by carbon dioxide retention and

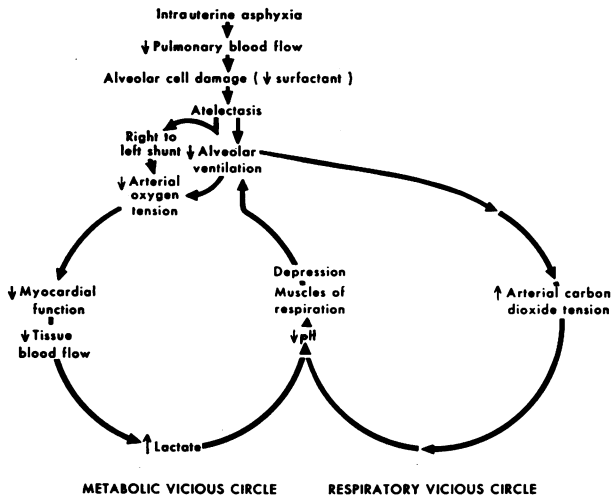


Fig. 10.—Schematic diagram to show the etiology of respiratory distress syndrome and its pathophysiological consequences.

tissue hypoxia, leading to lactic acidemia, reduction in pH, damage to cell metabolism, poor myocardial function, and reduced peripheral blood flow, which further potentiates the tissue hypoxia. Changes in cell membranes and cellular acidotic damage lead to leakage of potassium[62] from the intracellular space and entry of hydrogen ion and sodium ion to the cell. While plasma potassium rises, plasma calcium may fall reciprocally.

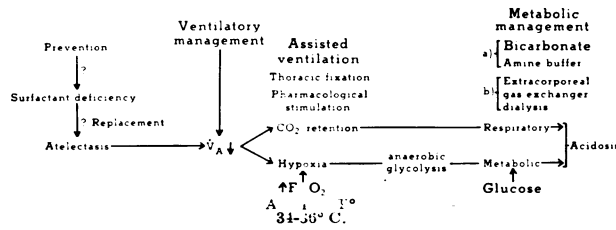
The metabolic derangement is further compounded by the increased demands for energy substrate, as well as oxygen, consequent on the increased work of breathing.

It has been shown that both infants[64] and animals[65] with respiratory distress, dying within 60 hours of birth, have low levels of tissue carbohydrate, especially in the heart, liver and muscles that have been extensively used, particularly the muscles of respiration. Blood sugar levels were found to be less than 4 mg. % terminally in about half of the infants studied.[64]

Thus the starved premature infant with negligible body fat stores and deficient carbohydrate reserves is forced to catabolize protein[63] to provide energy, to the further detriment of muscular respiratory function.

In the absence of a clear picture of the etiology, which would permit specific therapy or prevention, rational management of the disease process calls for a multiple approach in which each abnormality in the cycle of events is specifically countered by the appropriate treatment (Table II). It is the

TABLE II.—SCHEMATIC DIAGRAM OF MANAGEMENT OF THE RESPIRATORY DISTRESS SYNDROME



multifactorial nature of the problem that makes treatment and its scientific evaluation so difficult in this condition. Nevertheless, there is an increasing body of evidence to suggest that an improvement in the prognosis of the severely affected infant can be attained by such a multiple approach. Such evidence may be indirect and is derived from an extensive literature on the benefits of counteracting hypoxia, acidosis[66, 69] and providing energy substrate in conditions such as traumatic or hemorrhagic shock,[67, 68] following extracorporeal circulations for cardiac surgery,[70] acidosis due to poisoning, or artificially induced asphyxia in animals.[6, 71-73] There is also suggestive, but not conclusive, direct evidence that the early counteraction of acidosis and provision of energy substrate reduces the mortality of RDS.[74-76] However, such metabolic treatment cannot be given in isolation. A severely ill infant needs controlled oxygen therapy,[39, 77] careful attention to the thermal environment so that undue demands are not made on the metabolism for maintaining body temperature,[78, 79, 85-87] assisted ventilation in the event of respiratory failure,[32-34, 47, 80, 81] adequate fluid intake, possibly cardiac stimulants,[47] and treatment aimed at correcting such electrolyte disturbances as hypocalcemia[47] or hyperkalemia.[40]

It is appropriate here to mention that hyperbaric oxygenation has been tried by others in the treatment of RDS.[75, 84] The results have not been encouraging, either biochemically or in terms of survival.

In a previous communication[82] we indicated that, as a result of the morbidity and mortality of respiratory distress from all causes, particularly RDS, an Intensive Care Unit was organized with the object of studying the pathophysiology of the disease and improving its management. As a result

of the new knowledge of the pathophysiology of RDS obtained in this unit and elsewhere, we now believe that there is a case for admitting all infants with RDS to such a unit so that intensive treatment can be given for the derangements that have been revealed by recent research.

The methods currently in use in our Intensive Care Unit are outlined below in the form of a profile of a recent admission.

CASE REPORT

Baby T.B. was born at 9:58 p.m. on January 4, 1965, weighing 2100 g. The mother was a known diabetic who had been well controlled during pregnancy. She was aged 28 and had had one previous infant who had died from HMD. She went into labour prematurely at 36 weeks and was delivered promptly by Cesarean section. The infant was cyanosed at birth but became pink with mask oxygen. Within a short time respirations became grunting and indrawing.

The infant was transferred to the Intensive Care Unit of The Hospital for Sick Children (Toronto) at the age of 4½ hours, when he was in severe respiratory distress with marked retraction of the lower ribs. There was restricted air entry but no rales on auscultation. The respiratory rate was 90/min. The apex rate was 150/min., but there were no murmurs, and the liver was 1 cm. below the right costal margin. He required 70% oxygen to maintain a good central colour. The chest radiograph (Fig. 11) disclosed the typical

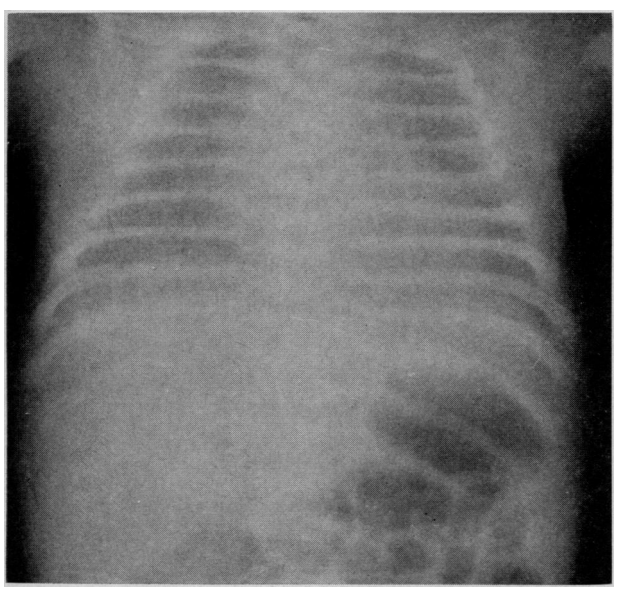


Fig. 11.—Radiograph of Baby T.B. at one day of age showing the typical generalized opacity of the lung fields in severe respiratory distress syndome.

ground glass appearance[83] of early RDS. His acid-base status, blood gases and therapy over the acute stage of the disease are recorded in Fig. 12. By 10 hours of age his clinical condition was worsening and a No. 5 French polyethylene catheter was passed through an umbilical artery to the arch of the aorta above the ductus. At that time the arterial oxygen tension while breathing more than 95% oxygen was 40 mm. Hg and by 17¼ hours hours it had fallen to 25 mm. Hg, the pH had fallen to 7.08, while the arterial carbon

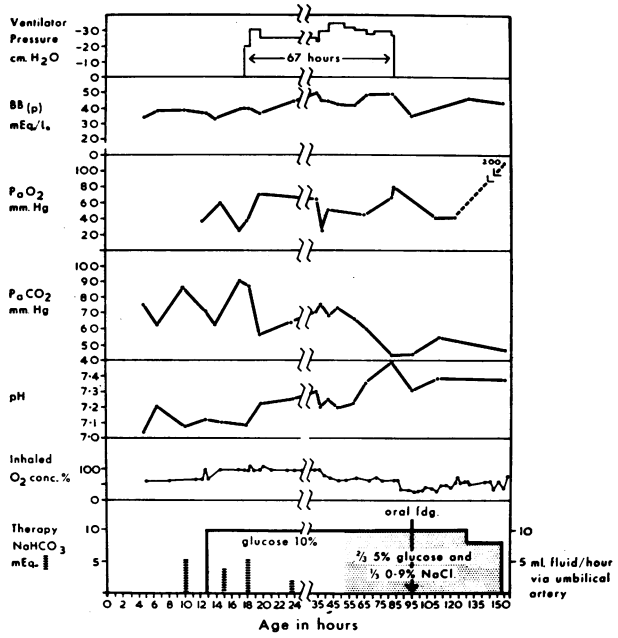


Fig. 12.—Biochemical and therapeutic details concerning Baby T.B. during the course of his disease to recovery. BB = Buffer base in plasma.

dioxide tension had risen to 90 mm. Hg. The infant was in a critical condition with a severe mixed metabolic and respiratory acidosis and a low blood sugar of 25 mg. %. Slow intra-arterial infusions of 8.4% sodium bicarbonate, 50% glucose by syringe injections, and 10% glucose by continuous drip infusion were given as indicated in Fig. 12.

At 17¾ hours of age the infant was gasping and grey. He was placed in a negative pressure ventilator* with the initial pressure at 20 cm. of water, later raised to 30 cm. of water. The inspiratory time was 0.35 sec. and the expiratory time 0.7 sec. The respirations were controlled at 55/min. and 90-95% oxygen was administered. The electrocardiogram was monitored continuously.

From 19¾ hours on it can be seen that the pH was maintained above 7.23. The arterial carbon dioxide tension fell at once and with some fluctuations continued to fall until controlled ventilation was discontinued at 84 hours of age (66½ hours controlled ventilation). Arterial oxygen tension was generally maintained between 40 and 80 mm. Hg or between 80 and 100% saturation while breathing 70-95% oxygen, and he did not develop a metabolic acidosis.

At 24 hours of age the serum calcium had fallen to 6.9 mg. % and 5 ml. of 10% calcium gluconate was added to infusion fluid. This was repeated at 50 hours, and since the calcium was still only 6.8 mg. % a further 10 ml. was given at 58 hours. Thereafter, oral feeding was started at 96 hours with a supplement of calcium gluconate,† 1 g. four times daily for two days, by which time the serum calcium had risen to normal levels.

The infant was digitalized at 21 hours of age with intramuscular digoxin, .06 mg./kg. in divided doses over 24 hours, followed by 1/10 of the digitalizing dose every 12 hours for three days. He also received

*Isolette-Respirator, Air-Shields, Inc., Hatboro, Pennsylvania, U.S.A.
†As calcium glucono-galactogluconate (Sandoz) syrup.

SR penicillin, 20,000 units, with streptomycin 20 mg. intramuscularly every 12 hours for the first week.

By 154 hours of age the arterial oxygen tension had risen to 200 mm. Hg while breathing 70% oxygen, the pH was 7.37, and the arterial carbon dioxide tension 47. The umbilical artery catheter was removed at 154 hours and supplemental oxygen was discontinued. The infant subsequently made a satisfactory recovery. Prolonged follow-up will be required, but there is no obvious neurological deficit at three months of age, the electrocardiogram showed no abnormality, and the optic fundi were normal.

He was discharged to his home at the age of 45 days, weighing 2780 g.

SUMMARY AND CONCLUSIONS

The respiratory distress syndrome (RDS) occurs in 14% of premature infants and is twice as common and as lethal in males.

The etiology is thought to be related to maternal-placental influences which have the effect of constricting the unstable vasculature of the gestationally immature lung, with resulting alveolar cell damage and reduction in pulmonary surface activity.

Loss of lung surface activity leads to alveolar atelectasis with alveolar hypoventilation, carbon dioxide retention and respiratory acidosis. Changes in pulmonary and systemic blood flow and the distribution of the cardiac output between the pulmonary and systemic vascular beds via persistingly patent fetal channels, together with perfusion of collapsed lung, result in tissue hypoxia and low total body oxygen consumption. A metabolic component due to anaerobiosis is added to the respiratory acidosis. Secondary changes in intracellular and extracellular distributions of hydrogen, sodium, potassium and calcium ions occur. There is depletion of body energy substrate reserves and hypoglycemia is frequent.

A full program of therapy should take account of the multifactorial nature of the etiology and pathophysiology. Prevention of prematurity and good obstetrical practice are important prophylactically. In the treatment of the established condition attention must be paid to regulation of blood gases, electrolytes, energy substrate reserves, body and environmental temperature control and assisted ventilation.

Modern methods of observation, biochemical control and treatment as well as the necessity for critical evaluation suggests that infants with RDS are best cared for in special centres.

ADDENDUM

Since this paper was written Chu *et al.* (*Pediatrics*, 35: 733, 1965) have produced preliminary evidence that pulmonary vasoconstriction and diminution in pulmonary blood flow is an important pathophysiological factor, adding further support to Dawes' hypothesis. They have proposed renaming RDS the "Pulmonary Hypoperfusion Syndrome".

We thank the physicians at The Hospital for Sick Children for allowing us to study and care for their patients and the staff of the Neonatal Intensive Care Unit, particularly Miss Pat Gemmell, for indispensable nursing care, Mr. D. McIntosh for technical assistance and Miss Carol MacLennan for secretarial help.

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The Possible Role of Hypnosis in Homograft Retention:
A Preliminary Report

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ABSTRACT

Hypnosis was used to alter body image in an attempt to enable a woman to retain a skin homograft from an unrelated male donor. The man also acted as a non-hypnotized control by receiving a homograft from the hypnotized woman. One-inch square full-thickness skin homografts were exchanged between the upper arms of the two volunteers. The homograft on the arm of the woman is still viable after eight months; the homograft on the man was rejected within two weeks. A second experiment in which the same subject was told under hypnosis to reject the homograft failed to produce rejection.

Definite conclusions are not yet justified. Among factors to be considered in the present case are an unusual compatibility, schizophrenia as an inhibitor of the rejection mechanism, hypnotically induced irreversible acceptance, or other unknown mechanisms.

SOMMAIRE

On a utilisé la méthode hypnotique pour modifier l'image somatique du sujet et tenter de permettre à une femme de retenir une greffe cutanée provenant d'un homme sans lien de parenté avec elle. L'homme a servi également comme sujet témoin, non hypnotisé, alors qu'il était receveur d'une greffe provenant de la femme hypnotisée. Des greffes cutanées d'une superficie d'un pouce carré de peau totale ont été ainsi échangées entre la partie supérieure des bras des deux volontaires. L'homogreffe sur le bras de la femme est encore viable huit mois après l'opération; l'homogreffe sur le bras de l'homme a été rejetée en deux semaines. Une seconde expérience au cours de laquelle le même sujet reçut l'ordre, sous hypnose, de rejeter l'homoeogreffe n'aboutit pas au rejet de la greffe.

Il n'est pas encore justifié de tirer des conclusions définitives. Parmi les facteurs à considérer dans le cas actuel figurent une compatibilité exceptionnelle, l'existence d'une schizophrénie susceptible d'inhiber le mécanisme de rejet, une acceptation irréversible induite par hypnotisme ou d'autres mécanismes inconnus.

IN recent years surgical and medical advances have made technically feasible the transplantation of tissue from one individual to another. However, the greatest barrier to progress in this field is still the rejection by the recipient of such homografts.

The rejection process is believed to be initiated by the release of mucopolysaccharides from the homograft. These sensitizing substances are then transmitted through the lymphatics to the regional lymph nodes where proliferation of mononuclear cells occurs.

During the preliminary period of two to four days the homograft is not distinguishable from an autograft. Vascularization occurs and the graft appears healthy and viable. However, after this initial period, mononuclear cells (mainly lymphocytes and plasma cells) infiltrate the graft; this is

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