1962

Respiratory distress syndrome (hyaline membrane disease)

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RESPIRATORY DISTRESS SYNDROME
(HYALINE MEMBRANE DISEASE)

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

March 22, 1962

Omaha, Nebraska

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Respiratory distress syndrome (hyaline membrane disease) is responsible for more deaths than any other single entity in the newborn infant.[3] Including the 40 to 60 per cent who survive, this is then by far the most commonly encountered serious problem in the nursery. Pulmonary hyaline membrane was first described in this country by Johnson and Meyers in 1925.[4]

This entity which accounts for a small number of deaths in the full-term group, is increase in infants delivered by cesarean section, accounts for approximately half the deaths of premature infants, and nearly all the mortality of infants born of diabetic mothers.[3]

At postmortem examination typical pulmonary findings include atelectasis, congestion, and hyaline membrane formation. Associated subarachnoid or intraventricular hemorrhages are a frequent find-ing. The minimal life span of the child to produce the membrane has been found to be from one and a half hours in prematures to a longer time in full term infants, usually the second or third day of life.[4]

The cause of hyaline membranes is not known and HMD is not recognized as a clinical entity. There is no mention of it in the Standard Nomenclature of Disease. There is marked disagreement as to its chemical and physical nature, little knowledge of the mode or modes of production and little understanding of its treatment.

The diagnostic signs of the RDS are chest retraction, exp-iiratory grunting and decreased air entry on auscultation, present

during and persisting beyond the first three hours of life. The labored respirations and especially the pathognomonic grunt, are sometimes not apparent until one hour after birth when the infant has quieted down and begins to breathe regularly and without crying or irritability.[1] Unless death supervenes during the first forty-eight hours, the respiratory distress reaches a peak within two to three days, after which gradual recovery takes place.

PATHOLOGICAL DESCRIPTION

The lungs appear pruplish and when cut look like liver as histologically there is widespread reabsorption of air and the walls of many alveolar ducts and most alveoli are collapsed giving a solid appearance to the lung parenchyma microscopically. The resorption atelectasis described above is associated with an intense capillary engorgement which is responsible for the gross color and increase in weight.

The feature from which the disease derived its name is a homogenous acidophilic material that lines the inner surfaces of the alveolar ducts, terminal bronchioles and some alveoli. This material, the HM, is thought to serve as a mechanical barrier to normal respiratory exchange by blocking alveolar-capillary perfusion.[14] If an attempt is made to expand the H lung with air after removal from the body, the proximal spaces become greatly hyperdistended and the distal ones more collapsed.[15] If fluid is injected the lung spaces gradually open.

Recent authors have depreciated the role of the hyaline membrane itself and emphasized the importance of atelectasis of the alveoli as the chief pathology.[26] Landing notes that the presence of HM seems to correlate with an absence of other lethal factors such as severe congenital heart disease.[27] Smith considers pneumonitis and pulmonary hemorrhage to be unrelated findings since they are seen with equal incidence, both with and without HMD.

Fourteen percent of premature infants have RDS. The incidence in regard to weight: 50 per cent of infants weighing 1000 to 1500 gm. and only 5 per cent weighing 2000 to 2500 gm.

Mortality rate: 66% of the 1000 to 1500 gm. infants die and 31 per cent of the 2000 to 2500 gm. infants. Four out of every 5 infants who die of respiratory distress syndrome die between 12 and 72 hours of age. The mortality rate among distressed infants who are still alive at 48 hours of age is 25 per cent; among those who survive 72 hours it is 11%.

It is evident that the mortality rate is closely related to the degree of prematurity and is 10 times greater in 1200 gm. babies as in 2400 gm. babies. Eleven per cent of premature infant females die from RDS. When the syndrome affects one member of twin or triplet sets, all members are affected, although the last-born is usually the most severely affected.

The syndrome is doubled when delivery is by cesarean section. This effect seems to be due to the operation itself rather than the

indication for which it is done; as the RDS occurs as often after elective sections as after emergency sections such as for placenta praevia.

The etiology does not seem to be related to the difficulty of the delivery, since those factors which tend to produce trauma, asphyxia or depression during delivery do not affect the incidence of RDS. It is not more common in breech deliveries, among second twins, after prolonged labors or with analgesia, anesthesia, asphyxia neonatorum or placental insufficiency syndrome. These potentially harmful factors do, however increase the mortality rate among affected infants.

In a study by Usher, infants of more than 37 weeks gestation and 3000 gm. birthweight born at the hospital did not have the syndrome whether they were delivered by section or by vaginam. It is therefore important to avoid iatrogenic prematurity by avoiding elective sections before absolutely necessary. Some obstetricians avoid this hazard by awaiting the onset of labor before performing repeat cesarean sections, while others allow spontaneous vaginal delivery after a previous section.

The syndrome probably originates in utero, for it is usually evident from the first breath. Also the analysis of the factors which affect incidence suggests that the RDS originates in utero before delivery, and is caused by some process other than fetal asphyxia. Whatever the cause, it seems to affect all the infants present in the uterus when it is present. This etiological agent

affects only premature infants, or possibly it affects only pregnancies which deliver prematurely.[1]

Clinical signs and symptoms have been classified by Silverman graded from 0-10, the former indicating no disease and the latter severe distress. This classification is based on five signs and symptoms: 1) retraction of the chin, 2) xiphoid retraction, 3) intercostal retraction, 4) grunting respiration, and 5) a comparsion of chest and abdominal movement.

Using Silvermans method of quantitative registration of the respiratory distress syndrome in 363 prematures Bauman found that the degree of immaturity and age at which the retractions were scored were closely related to the presence of distress, age at death and occurrence of PHD. In babies with the distress syndrome a greater fatality rate and higher incidence of PHM occurred than in those in whom these phenomena were absent.[7]

From the statistical analysis of various lesions in the lungs of 125 infants dying at the age of 7 days or less it follows that atelectasis occurs in association with pulmonary immaturity, emphysema and hyaline memoranes. Pulmonary hemorrhage is associated only with acute pneumonia and visa-versa. The presence of squamous cells in alveoli shows a significant positive association only with emphysema. Pulmonary immaturity shows a positive relation to female sex and occurs in infants with hyaline membranes, atelectasis and interstial emphysema. The frequency curves of lesions in the lungs according to the age of newborn infants showed an early peak for hyaline

membranes in contrast to the later peaks of acute pneumonias, pulmonary edema, hemorrhage and the presence of squamous cells in the alveoli.[8]

ETIOLOGY

The cause of the disease is obscure, but the histochemical, physiological, and experimental approaches to hyaline membrane disease can be divided into three main theories. These are 1) aspiration of amnionic or gastric contents, 2) transudation on the basis of some special type of heart failure thought possible only in the neonatal cardiovascular setup, and exudation due to toxic external influences like oxygen poisoning.

The aspiration theory: Snyder has demonstrated that respiratory-like movements of the fetus occur at least fairly frequently in many animals including man.[29,30] Potter has shown that the human fetus swallows and breathes Thorotrast containing amniotic fluid.[29] These experiments were done in early pregnancies in which the mothers were candidates for therapeutic abortion. In fetuses nearer term, proof of respiration by x-ray demonstration of Thorotrast in the fetal lungs was possible in only a few of the cases. In both animal and human experiments of this type there is evidence of foreign material in the lung apparently due to absorption of the amniotic fluid in the lung.

Hypoxia or anoxia in the fetus in many animal species causes exaggerated respiratory movements in the fetus in mid-pregnancy but

does not produce these in fetuses near term.[30] However, in fetal sheep it has been shown that certain activities may be normally inhibited by certain nervous system centers. Anoxia can be shown to depress these centers if it is of sufficient degree and may allow the release of activity. Progressive anoxia will in time supress all activity.

Farber considered the hyaline membrane to be fused, resolving exudate consisting of necrotic mononuclear cells, leukocytes, red cells, altered fibrin, or aspirated amniotic sac contents. He compared the infant hyaline membrane with a membrane seen in influenza pneumonia in adults. The location of the membrane was thought to represent mechanical dispersion of foreign material toward the periphery of the air sacs by violently inspired air. He showed that horse serum, India ink, or fibrinopurulent exudate instilled into the trachea of various experimental animals who were subject to vigorous artifical respiration in the Drinker respirator seemed to fulfill these criteria.

Claireaux notes that special stains of the hyaline membrane indicate the presence of fat and polysaccharides. Cells can be seen in areas of hyaline membrane that are still organizing and these are identifiable as flat squamous cells from the liquor amnii. Samples of centrifuged amnionic fluid sediment resuspended in saline and incubated at 37 degrees C. lose cellular outlines and become eosinophilic. If this material is inoculated into the trachea of a live rat, the picture in the drowned lung resembles hyaline membrane. Absorption of large volumes of water by the fetal lung would also create a concentrated amnionic sediment.[33]

Landing emphasizes that two factors are necessary: a large amount of amnionic fluid to provide the necessary particulate matter and a definite period of air breathing to mechanically compress the material against the wall of the lung passages.[29] Landing has shown that the squamous cell count in amnionic fluid rises in the latter months of pregnancy. He correlated this with an increased incidence of squamous incorporated in the hyaline membranes seen in infants born near term.

Negative evidence is provided by Lelong, who, along with other authors[34,29,35] notes that in certain cases of obvious massive amnionic aspiration with accumulation of cornified cells in many air cavities no hyaline membrane is formed in spite of survival of several hours to days. In the only human experiment reported, Potter was unable to demonstrate hyaline membrane in the lungs of an anencephalic monster who died several hours after the introduction of 80 cc. of amnionic fluid via tracheal catheter.[29]

Ahvenainen refines the aspiration theory by suggesting the role of aspiration of vomited amnionic fluid.[36] He notes that there is occasional desquamation of bronchial epithelium and emphasizes the role of acid gastric juice in hyaline membrane formation. Gellis and other authors[37,38] have observed that the stomachs of infants born by cesarean section, especially those of diabetic mothers, contain excessive amounts of fluid, and feel that routine aspiration of the stomach at delivery has reduced the incidence of respiratory complications in their nurseries.

The most complicated theories of hyaline membrane formation may be grouped under the heading of transudation or exudation. The simplest scheme is advanced by Reuther, who feels that anoxia is the etiologic factor in hyaline membrane disease. He feels that this causes increased capillary permeablity with exudation into the alveoli from the vascular alveolar walls.[39,40] This liquid material is then pressed against the alveoli by respiratory movement.

Indirect evidence for a vascular component contributing to hyaline membrane is found in certain diseases in which an apparently classical hyaline membrane is produced in the lung;[2,12,13] chicken pox, poliomyelitis, sulfonamide hypersensitivity, subacute bacterial endocarditis, metastatic carcinoma of the lung, Hodgkin's disease, uremia, milk aspiration, radiation pneumonitis, influenza pneumonia, rheumatic pneumonia, war gas pneumonitis, and plague. The hyaline membranes seen in these conditions were described as the result of vascular damage with increased capillary permeability. Further evidence to support the role of the vascular tree in the production of hyaline membranes is offered by Gilmer, who describes the appearance of hyaline membrane beneath the endothelial basement membrane but electron microscope studies seem to confirm its presence.

The most impressive evidence for an endogenous source of the hyaline membrane is provided by authors who describe histochemical techniques. Arwaka using isotopically labeled I^{131} attached to blood alpha g obulins in guinea pigs, showed that the hyaline membrane

produced by oxygen poisoning involves localized increased capillary permeability.[14] Duran-Jorda identifies hyaline membranes chief component by ultraviolet spectrograph as a member of the cytochrome group. He links it with blood-derived protein and pigment and compares it chemically to eosinophilic material found in thrombi, glomerulus precipitate, and pulmonary edema.[41] Hadde.s produced h line membrane in rats by tracheal injection of rabbit serum. He also succeeded in producing hyaline membranes by promoting the passage of blood plasma from the lung capillaries by intrathoracic injection of vasodilator substances. He used Cardophyllin, Duphyllin, and histamine successfully.[42] Hadders suggests that the sudden increase in perfusion of lung tissue by the change in circulation at birth could cause filtration of the plasma from blood into air spaces. Possibly then, some degree of hyaline membrane formation is a normal occurrence.

Gitlin using a fluorescent antibody, identifies the main component of hyaline membrane as contracted masses of fibrin. He showed that newborn infants with other illnesses do not have significant amounts of fibrin in the lung and that there is not enough fibrin in concentrated amniotic fluid to account for hyaline membrane. He postulates an alveolar effusion as the probable beginning of hyaline membrane formation and notes that the deposition of fibrin from this effusion would be enhanced by the presence of aspirated amniotic

fluid since this contains thromboplastic material.[43] Fresh amniotic fluid cuts the clotting time of plasma in half in the presence of calcium.[44,45]

Further evidence for the dual origin of hyaline membrane is presented by Stevenson and Laufe. They use a combination of amniotic fluid and plasma injected into the tracheas of live guinea pigs and succeeded for the first time in all experiments of hyaline membrane production in getting the full triad; hyaline membrane, atelectasis, and engorgement. They suggest that the sequence of events is as follows: 1) the newborn infant aspirates amniotic fluid; 2) the lungs exude a high protein fluid as a result of vagal injury, irritation from amniotic fluid, high oxygen tension, anoxia, or other cause; 3) amniotic fluid clots the exudate and, as fluid is absorbed, a membrane is formed; 4) clotted exudate plugs produce atelectasis as resorption of trapped air occurs; 5) anoxia increases and the infant asphyxiates unless the changes are minimal and phagocytes can destroy the membrane and reverse the picture.[46]

Lynch notes that the experimental studies of pulmonary edema invariably preceeded hyaline membrane formation.[47] Farber explained vagotomy induced pulmonary edema as a release of strong tonic vasoconstrictor effects causing capillary dilatation, blood stasis and edema. Vagal stimulation influences the rate of pulmonary edema formation in massive saline infusions in experimental animals.[32]

Drinker states that lung capillaries are physiologically different from those elsewhere in the body and cites the rapid production of pulmonary edema by two methods: the systemic injection of alpha naphthyl thiourea, and the introduction of fibrin forming mixtures, whole blood or particulate matter like India ink into the cisterna magna.[49]

Investigation of the fibrinolytic-enzyme system in the lungs of newborn infants now clearly indicates that pulmonary hyaline formation is significantly associated with an inability of lung tissue to activate plasminogen. This enzymatic derangement is shown to be due to the presence of a potent inhibitor to the plasminogen activator that is characterized by its ability to adhere to the particulate matter containing the enzyme.[49]

Pulmonary hyaline membranes were studied by Aronson in their dissolution in vitro by proteolytic enzymes: by streptokinase and by urea with and without added thioglycollic acid. Pepsin, trypsin and chymotrypsin dissolved the hyaline membranes both in sections of human lungs as well as in sections of mouse lung with the experimentally produced disease, whereas, streptokinase alone failed to do so. The combination of 8 molar urea with 2 per cent thioglycollic acid partially removed the hyaline membranes from lung slices. These findings are consistent with the view that fibrin is one important component of pulmonary hyaline membrane disease. Four possible therapeutic agents were evaluated by Aronson in experimental HMD in

mice, which was produced by a prolonged exposure to a high concentration of oxygen. Chymotrypsin, trypsin and chloropromazine did not influence the mortality rate or incidence of pulmonary lesions. Heparin treatment led to a striking increase in mortality and to an increased incidence of pulmonary hyaline membranes.[18]

Turner in his in vitro tests concluded that fibrinogen is affected considerably by fibrinolysin but that fibrinolysin has no specific action on fibrin. This lack of specificity together with inactivation at body temperature suggests that large and frequent doses would be necessary to maintain an effective plasma fibrinolytic level. In their opinion a better method of assay of fibrinolytic activity is needed.[55]

Recently, Fleming and his co-workers reported that total body irradiation affected the plasminogen-activator activity of lung in human beings and in dogs. The lungs need not receive the radiation directly.[50]

A new theory regarding the pathogenesis of hyaline membrane formation considers the placenta as the site from which the abnormal inhibitor arises. The placenta was found to contain high levels of this inhibitor, and it is suggested that placental infarction related to maternal diabetes or impending abortion releases this inhibitor into the fetal circulation. The presence of this inhibitor would thus prevent the dissolution of intra-alveolar fibrin, resulting in its retention and subsequent formation of hyaline membranes.[49]

The role of heart failure in hyaline memorane disease: The

first discussion in the literature by Gellis denied any causal relationship, as he found no sign of enlarging liver, edema, venous distention and in 60 per cent of his series no significant cardiomegaly by x-ray or post-mortem examination.[51] Lendrum suggests a rather elaborate heart failure etiology by fluid draining into the alveolar spaces, resulting in re-establishment of right to left flow through the ductus and foramen ovale with a re-vision of the circulation to a fetal pattern and some bypassing of the lungs. As capillary pressure in the lung drops, edema fluid is reabsorbed and the protein component is concentrated.[52] This theory has been criticized by Polacek who notes that there is no evidence of left heart burden at birth and remarks that the oxygenation of both ventricle muscle masses depends on a common origin of coronary circulation; therefore the left heart failure from Bendrum's theory is not feasible.[53]

Vascular pressure and volume changes may also be involved and could explain the picture of atelectasis characteristic of hyaline membrane. Jukka after doing perfusion experiments on atelectatic lungs decided that pulmonary parenchyma was to some degree an erectile tissue. Capillary filling of his excised lung specimens caused partial alveolar expansion when the bronchi were in contact with air.[54]

Cook has data showing that vascular distention does produce some decrease in pressure required to maintain a given lung volume in adult dogs. He feels that in view of the large initial

pressure necessary to overcome surface tension forces within the lungs in newborn animal and humans the apparently small effect of vascular distention cannot be very important.[55]

In Rudolph's et. al studies hemodynamic measurements were made by means of cardiac catheterization. These measurements were obtained in 38 infants in the first 30 hours after birth. Nineteen were normal, 9 had mild respiratory distress and 10 had severe respiratory distress.

The circulatory systems of infants with mild repiratory distress did not apprecially differ from normal. Some infants in both these groups showed evidence of patency of the ductus arteriosus with a small left to right shunt for the first 10 to 15 hours after birth. The infants with severe respiratory distress had widely patent ducti with large left to right shunts and in some cases right to left shunts. The pulmonary arterial and systemic arterial pressures were lower in these infants as compared to the normal and those with mild respiratory syndrome. These characteristics of the severely distressed infants could be related to the disease process but may be due to prematurity alone.

The possible role of left ventricular failure associated with large left to right ductal shunts should be given serious consideration in attaching the RDS from the circulatory point of view. The use of digitalis has been repeatedly suggested and good result have been claimed. A generalized lack of vasoconstrictor tone could possibly be responsible for systemic and pulmonary arterial hypotension as well as for widely patent ducti arteriosi.

Electocardiographic changes are frequent in the RDS. These changes are not found in infants who die before 12 hours of age even with infants weighing less than 1000 gm. and cannot be the cause of the RDS for it develops only after 12 hours of age. These EKG changes are due or closely related to increased plasma concentrations of potassium; thus resulting in a conduction type disturbance. This EKG change is similar to the one found in an anuric adult with hyperkalemia. There is, however, one major difference; the hyperkalemic infant rarely shows the peaked T waves which characterize the condition in adults.[1]

Recent studies have shown that the systemic arterial pressure of these infants with RDS is lower during the first hour than in comparable normal infants which is not unlike the picture of vasomotor shock. The cause and the significance were not clear.[10, 56, 57]

Oxygen has been advocated as a possible toxic agent in RDS. Although the membranes can be produced in animals by many hours of exposure to pure oxygen, it should be realized that with infants the disease develops quickly while infants are breathing only room air.[3] Another objection to the idea of oxygen as an ideological agent in RDS is the fact that the longer the infant with respiratory distress lives in high oxygen in his incubator the less likely he is to die with hyaline membrane disease.

The studies to date have not shown any "conclusive" evidence of heart failure during the course of the RDS. It is possible,

however, that the terminal incident may be associated with the appearence of acute myocardial failure.[20]

Pulmonary capillary ingorgement in a series of 335 was nearly a universal finding and extreme degrees of this change were interpreted as vascular congestion. A positive relationship was found between pulmonary edema and hyaline membrane. The membrane itself was considered to be the end stage of a progressive development of pulmonary edema fluid concentration and loose adherence to the walls of air spaces.[23]

The presence of small thrombi in the hepatic sinusoids of the newborn have been demonstrated by Wade-Evans. The hypothesis most in accord with the observation made is that thrombi form in the site in which are seen, in the baby as in the adult, as a result of a disturbance of circulation leading to its local reduction with consequent anoxia, a process which when severe may cause in addition focal necrosis. This is of interest for it now seems likely that polymorphonuclear leukocytes arise by the compaction of fibrin containing edema fluid and that a disorder of circulation contributes in the newborn as in certain older patients, to membrane formation. The importance of the occurrence of large numbers of thrombi in infants with hyaline membranes thus lies in their providing further evidence of the presence of circulatory disturbance in such cases.[17]

An examination was made of the prominance of perivascular aggregates of eosinophilic leukocytes in thymic septa of cases

of RDS. Similar examinations were also made in cases of still-birth and perinatal death unassociated with HMD. Moderate or marked thymic eosinophilia was found in more than 90 per cent of 27 cases of HMD. This degree of eosinophilia was encountered in less than 10 per cent of the control group.

Numerous eosinophils were also found in axillary lymph nodes of 4-8 cases of hyaline membrane disease but in only 2 out of 20 control cases.

The exact significance of the observed eosinophilia of the thymus and lymph nodes cannot be precisely defined at this time. But anaphylactic type of reaction in the fetus is highly unlikely as immunological maturity is not usually achieved until some time after birth.

Concentrations of adrenal steroids in the mother are known to undergo progressive elevation in the last trimester and partically during normal delivery, therefore premature and C-section may have lower steroid levels resulting in eosinophilia mentioned.[21]

A method is described for measuring the volume of lower extremity in the neonate in the JAMA. Leg volume and body weight showed proportionate decrease during the first day of life in 9 full-term and premature infants who had no signs of the RDS. In 6 infants with such signs a relative or absolute increase in leg volume occurred at the time when body weight was decreasing.[22]

THE CLINICAL PICTURE AND PROGNOSTIC SIGNS

The first signs usually develop during the first 6 hours of life. One sees labored respiratory distress revealing a lag in the movement of the upper chest as the abdomen rises with contraction of the diaphragm. As the distress becomes more severe this results in the paradoxical "see-saw" sinking of the upper chest with abdominal rising. Sinking of the intercostal spaces varies also with the degree of dyspnea. Retraction of the xiphoid and tugging of the chin with inspiration is a later stage. Expiratory grunting, or occasionally whining, may appear soon after delivery with increasing loudness. If one places a stethoscope on the infant's nose the grunt will be detected earlier.

The normal newborn respiratory rate is approximately 40 per minute, although normal premature and C-section babies may have slightly higher rates.[58, 59] Seventy per cent of distressed infants have a rise in respiratory rate of more than 20 per minute from the first hour of life to the peak rate after 12 hours; such an increase occurs in only 10 per cent of healthy infants. In the distressed infant there is a sustained respiratory distress between 6 and 18 hours, and finally there is either death or gradual improvement during the next 2 days.[1]

Generalized cyanosis may appear at any time, continous or in spells, and it is relieved at first with the administration of additional oxygen. But eventually the cyanosis may persist, even

in the presence of pure oxygen.

Flaring of the alae nasi is a most constant sign of respiratory distress.[3] When the infant begins to breathe through his mouth, the respiratory insufficiency has become severe.

The breath sounds on auscultation are likely to be more bronchial in character than is normally heard in the newborn infant. If the disease is severe, fine, moist rales of pulmonary edema are heard in more than half of the distressed infants between 6 and 48 hours of age.[1] There usually is a dramatic effort put into each breath.

In the there is usually some depression and from birth onward they are flaccid and inactive in varying degrees. This cerebral depression tends to become more pronounced after six hours of age. Most distressed infants show signs of intracranial irritation between 12 and 48 hours of age. Even though they may be limp and spreadeagled, they are excessively overractive to stimuli. The appearance of improved tone and spontaneous stretching activity in a previously depressed infant by about 36 hours of age is the first sign of recovery from the disease.[1]

Later in the RDS as fatigue becomes more marked, the infant becomes flaccid, effort seems to have stopped so that chest retraction is no longer noted, and the respirations become shallow. t this time the infant is gray and appears to die in shock.[3] s noted before at any stage in the progression of the above features listed the infant's condition may begin to improve and recovery takes place without any harmful effects.

Another neurological ma ifestation which occurs for seconds or minutes are spells of apnea. These apneic spells begin before 54 hours of age, the prognosis is always grave, as the usually increase in frequency and severity until death. When these apneic spells begin after 54 hours of age they are prognostically benign, as these occur between the third and seventh days of life in many distressed infants who survive, and although they may be frequent and sometimes require positive pressure ventilation, they do not ordinaril result in death.[1]

The cardiovascular signs consist of tachycardia, a patent ductus arteriosus murmur, hypotension and a liver palpable 2 cm. below the right costal margin, this is slightly larger than that usually found in healthy premature infants. A crescendic late systolic, and sometimes a continous, murmur of patent ductus arterious is heard in one out of four distressed infants who survive. The murmur is usually detected between the third and seventh days of life. It persists for hours to several days, and occasionally up to a month.

Hypotension, as compared to normal infants, is usually present. But the infants having the lowest blood pressure do not necessarily have the highest mortality rate. There is also no tendency for the blood pressure to drop as a herald of death. There could easily be an association between hypotension and RDS, as infants with acute hemorrhagic shock in the same a e group have a respiratory difficulty indistinguishable from RDS. This respiratory distress of neonatal hrmorrhagic shock responds immediately to blood transfusion providing the underlying condition is only blood loss.

dema which is not present at birth on the dorsal surfaces of the hands and feet is an almost universal findin in the first hour of life in the distressed infant who weighs less than 1200 gm. and by 12 to 24 hours of age in most other distressed infants. This pitting edema of RDS always disappears between the second and fifth days of life.[1]

Hardenin of the edematous tissues does produce sclerema, which is not an unfavorable sign occurs in one out of four cases of RDS. The edema in RDS infants occurs during a time of rapid weight loss as the RDS infant loses 12 per cent of the weight found at birth as compared to 6 per cent by the normal newborn in the first 72 hours of life.

Feedings are hampered b abdominal distention, infrequent bowel movements, and regurgitation between the third and seventh days of life. A frequent problem is paralytic ileus manifested by diminished or absent bowel sounds. Relief of the distention is often successful with enemas.

Prognostically severe retraction or grunting during the first 6 hours in RDS indicates a high mortality and a large number with these signs die before the age of 30 hours. Those infants demonstrating these two signs later and less severly when they do die it is usually after 30 hours of age. In infants who do not show improvement in their retractions and air entry after 12 hours the prognosis is usually poor.

The mortality rate is 70 to 90 per cent in those patients who

show severe flaccidity and inactivity between 6 and 12 hours of age, rales during the first 6 hours, definite cyanosis after 12 hours in spite of supplemental oxygen, show liver enlargement after 12 hours of age or have apneic spells before 54 hours of age.

As would be expected there are some differences in the RDS when comparing the large and small premature infants. lso it seems significant that in infants destined for respiratory distress, there is a trend for the rate to increase during the first few hours of life, regardless of the rate established at the time of onset.

Miller et al[58] has classified newborn infants according to respiratory rates for evaluation and prognosis. BY this method, a newborn infant is laced into categories that depend on comparison of respiratory rates shortly after birth and at intervals during the subsequent 48 hours. was mentioned before the normal newborn infant has a respiratory rate of approximately 40 per minute.

Miller's classification consists of three groups: Group I babies are those who have a normal respiratory rate shortly after birth and during frequent checks over the following 48 hours.

Group II infants are characterized by having increased rates during the first hours of life but with a return to normal during the subsequent 36 hours.

Group III infants present with normal respiratory rates shortly after birth but are found to have increased respiratory rates of 60 per minute or greater commencing in the succeeding 48 hours.

With this classification, Miller found that the babies who developed severe respiratory distress and those who died because of respiratory disease were in Group III. About one half of these infants had persistent cyanosis and about 25 per cent died during the first few days. Cyanosis and death were not observed in those infants who had either normal or increased respiratory rates at birth but whose rates were normal after a few days.[60]

Miller also noted that rapid but shallow respirations signified a better prognosis then did a rapid rate associated with deep inspiratory efforts. He noticed that infants who had respiratory rates of 70 per minute but were dyspneic with deep inspiratory movements fared less well than other infants whose rates were 100 per minute who had shallow respirations.

ROENTGENOLOGIC FINDINGS

The radiographic features are usually characteristic and frequently present before respiratory difficulty appears. The most common finding is a reticular, granular pattern with a general increase in lung density, uniform through both lungs or may be especially pronounced in one area.[61] The chest may be well expanded but not emphysematous. The air-filled bronchial tree is clearly deliniated in most instances and produces sharp radiolucent contrast against the overall incompletely aerated lung.

Usher states that there is a typical triad consisting or the generalized reticulogranular pattern of the lung fields, an "air bronchogram" and a widened superior mediastinum. These changes persist until about one week of age in distressed infants.[1]

The chest x-ray is most useful in the larger infants in whom the respiratory distress syndrome is often atypical with little grunting and good air entry. This is to say that infants who show the classic clinical signs of the syndrome, especially the very small babies should be spared the unnecessary trauma, the radiation exposure and should be treated accordingly.[1]

In the atypical syndrome in larger infants mentioned above the chest radiograph can establish or rule out other causes of respiratory distress such as aspiration pneumonia, pneumothorax, lobar atelectasis and diaphragmatic hernia.

The chest cage and the position of the diaphragm show a normal chest volume in RDS as opposed to the hyperexpansion in the aspiration syndrome, radiolucency of pneumothorax, and the poor expansion of primary atelectasis.[3]

An x-ray picture similar to that of HMD has been attributed to incomplete expansion of the lungs at birth but it has been demonstrated that neonatal expansion is usually accomplished during the first few breaths and it is unusual to find areas of atelectasis in chest films made in the first hour of life in normal infants. The diagnosis of HMD in the presence of respiratory distress cannot be made unless there are positive radiographic features.[61]

DIFFERENTIAL DIAGNOSIS

There are many abnormalities that can cause respiratory distress of which a few will be discussed.

Pneumothorax and pneumomediastinum: X-ray examinations are

usually the most helpful for the asymmetric findings on percussion and auscultation and variability of intercostal retraction are always discrete on the thin chest of the newborn.

Aspiration of amniotic fluid and meconium: This syndrome is usually associated with post maturity rather than prematurity and is a relatively rare syndrome. A careful obstetric history may reveal a case of prolonged gestation or pre-existing fetal distress. Remission is usually spontaneous. Rales may be heard and the x-ray film shows hyperexpansion, patchy distribution of densities and areas of emphysema, and increased densities corresponding to the broncho-vascular markings.

Primary atelectasis: Cyanosis and respiratory difficulty are present from birth. Ahistory to suggest and intracranial lesion or depression of the central nervous system is often elicited. The bell-shaped thorax, narrow at the top, is a characteristic finding on inspection, as are steeply sloping ribs on the x-ra film.

Intracranial Hemorrhages: The clinical manifestations, as a rule, are respiratory distress with weak and irregular breathing interrupted by periods of apnea. The normal x-ray of the chest should alert one to the possibility of this entity and a skull film may disclose fractures or separation of the cranial vault sutures but this is not to be relied upon.

Pulmonary Hemmorrhage: This entity may occur in small, clinically insignificant amounts or may be massive resultin in rapid

demise. Fetal anoxia is probably the most probable cause, although this may be complicated by hypothrombinemia or hemorrhagic disease of the newborn. Pulmonary hemorrhage frequently accompanies fatal erythroblastosis fetalis. Clinical findings may be limited to respiratory distress or, in the severe cases, there may be hematemesis or the passage of large amounts of frothy blood from the nose and mouth. Chest x-rays are similar to those infants with the aspiration syndrome, as there are linear and patchy areas of increased density, usually in both lungs, and the prominence of the markings and the distribution depend upon the severity of the intra-alveolar hemorrhages.

Pneumonia: If it is present within the first 12 hours it must have been acquired in utero. Premature rupture of membranes (e.g., 12 hours prior to the onset of labor), pyrexia in the mother, or and unusual amount of obstetrical manipulation makes on more suspicious of pneumonia. Even in the absence of radiographic signs, its presence cannot be excluded either as a cause of the respiratory distress or as an accompaniment of HMD.

Other entities, such as lung cysts, lobar emphysema, congestive failure of diaphragmatic hernia may be detected or excluded with good and repeated physical examination in conjunction with radiographs of good quality.

BIOCHEMICAL CHANGES

In the RDS during the early hours of life infants develop a respiratory acidosis and metabolic acidosis, the tension of CO_2 in

the blood increases and the pH of the blood goes down. Venous pH levels of 7.00 to 7.25 are common. The carbon dioxide tension is usual y 50 to 80 mm. of mercury and the plasma bicarbonate concentration of 15 to 25 mEq. per liter. This is in contrast to healthy premature infants who have a venous pH of 7.30, carbon dioxide of 45 mm. and plasma bicarbonate of 22 mEq.

During the 3 day course of the RDS the plasma bicarbonate tends to decrease during the first 72 hours of life, thereby increasing the metabolic component of the acidosis. Also the carbon dioxide tension remains constant or falls slowly.

There is an accumulation or plasma potassium and nirtogen in distressed infants even though there is no intake of food. Both these substances are excreated in the urine at normal levels. The above may be due to the fact that distressed infants show greater evidence of excessive tissue breakdown associated with their greater weight loss.

The newborn has plasma potassium (4 mEq. per liter) and nonprotein nitrogen (25 mg. per cent) during the first hours after birth which is similar to their mother's values of the above substances. Within 12 to 48 hours these concentrations increase so that plasma potassium concentrations of 9 mEq, and nonprotein nitrogen concentrations of 60 mg. per 100 ml. are common. It is at this time that the hyperkalemic electrocardiographic conduction disturbances ap ear. As the distress process subsides after about 60 hours of age, the

plasma level of potassium and non rotein nitrogen rapidly decreases to normal.

There is a close correlation between the severity of the acidosis and the pro_ osis. Distressed infants with a venous pH below 7.15 (arte rial or capillary pH is usually 0.08 higher than venous), or carbon dioxide tension above 70 mm. of mercury, of plasma bicarbonate of less than 18 mEq. per liter rarely survive without administration of intravenous lucose and sodium bicarbonate solutions.[1]

The most likely reason for the metabolic problems is that the kidney is unable to increase its solute excretion when presented with increased plasma concentrations of potassium and nitrogen, and is unable to compensate for respiratory acidosis by conserving base. Also the failure of the kidney to excrete phosphate deprives the kidney of an effective buffering substrate, as the output is less than one tenth of that excreted after the third day of life. Infants who suffer a respiratory acidosis after the third day of life when the phosphate excretion has increased to normal are able to conserve base and thereby increase their plasma bicarbonate concentration.

Infants put out large amounts of sodium in their urine presumably in an attempt to compensate for the respiratory acidosis. This occurs along with increased adrenal cortical activity, as demonstrated by an increased urinary excretion of 17-hydroxycorticosteroid.[1]

The adrenal cortical hyperactivity associated with potassium retention and sodium excretion, is paradoxical and may be related

to the immaturity of the premature's kidney. An increased catobolic rate due to adrenal cortical hyperactivity results in increased potassium, nitrogen and organic acids from cells.[1]

Mean values of excretion of sodium, potassium and nitrogen in a series of premature infants of diabetic mothers were all increased as compared with those of term infants of mothers without diabetis. These tendencies were especially marked in those premature infants or diabetics who had respiratory distress.

It is beleived that a pattern of metabolism which includes excessive tissue destruction, shift of water from cells to extracellar space, hyperkalemia and excessive excretion of sodium may occur to an even greater degree in extreme prematurity alone.[9]

The plasma protein concentration is lower in distressed infants than in healthy infants or the same weight. Full term infants usually have a plasma protein concentration of 6 gm. per 100 ml., and healthy premature infants of 5.0 to 5.5 gm. per 100 ml. Distressed premature infants usually have only 4.0 to 5.0 gm. per 100 ml., with the sicker infants having even lower values.

The finding of a low plasma protein concentration in infants who are developing edema while losing weight suggests that the mechanism of edema formation is transudation of proteins from plasma into tissue fluid rather than salt and water. The fact that the edema fluid has a higher percentage of albumin (70 per cent) than plasma (60 per cent) suggests a capillary leak with greater loss of smaller molecules. In these infants weak capillary wa ls are demonstrated

by ecchymoses around electrocardiographic suction cup leads on the chest. This does not occur in normal infants without respiratory distress.

Other biochemical disturbances are common in infants with RDS. One third of distressed infants have hypoglycemia with glucose concentrations of 5 to 20 mg. per 100 ml. Plasma concentrations of sodium and of chloride in distressed infants are within the normal ranges for healthy newborn premature infants.

The preceeding description of the biochemical picture of respiratory distress syndrome is true of the infant who is treated conservatively, i.e. not fed for 36 hours after birth. These disturbances can be removed when intravenous glucose and sodium bicarbonate solutions are given at birth until that time when the infant is no longer in distress. This makes it possible to increase the plasma bicarbonate without increasing the carbon dioxide tension and thus to improve the acidosis. lso catabolism is decreased and the plasma concentrations of potassium, nonprotein nitrogen and phosphorus remain stable or rise only slightly after birth even though the urinary excretion of these substances is not increased. The blood sugar concentration is usually maintained above 30 mg. per 100 ml. if the I.V. fluids are given until a time when milk can be given enterally. When the intravenous infusion is discontinued too early, there is danger of sudden and severe hypoglycemic shock manifested clinically b pallor, duskiness, flaccidity and apneic spells.[1]

GENERAL MANAGEMENT

A few prophylactic measures have general acceptance. Cesarean section should be avoided even in the face of certain complications of pregnancy. In the selected group of newborns who are statistically prone to HMD certain prophylactic measures are advocated. Polacek advises early clamping of the cord without stripping to prevent overloading of the circulation.[53] Chapple notes that pre-mature infants are born at a time when maternal progesterone levels are still high and suggests that here the hormone is responsible for fluid accumulation.

Several authors advocate routine catheter drainage of the stomachs of all newborns.[37,38]

The essentials of good management of the distressed premature infant have been elaborately laid down by Usher which will be presented here.[1]

1. For infants of less than 32 weeks a highly experienced obstetrician and pediatrician should be on hand. Every effort should be made to minimize trauma, asphyxia, and exposure to cold during and immediately after delivery.

2. If the infant is apneic or the heart rate is less than 100 per minute and does not respond quickly to pharyngeal suctioning and gentle stimulation a positive pressure mask should be attempted. If this is not sucessful an endotracheal tube should be passed.3. A positive diagnosis of HMD should be established if at all possible by physical and x-ray examination. Ruling out other possiblities must be carefully evaluated.

4. Infants less than 1000 gm. with RDS should be evaluated for blood pH and carbon dioxide content and the necessary intravenous therapy started.

5. Rectal temperature should be maintained at 98 degrees with full humidity in an incubator. This requires about 86 degrees for a 2500 gm. infant and 94 degrees for a 700 gm. infant.

6. Oxygen should be given when cyanosis is present until the baby is pink and decreased hourly until borderline cyanosis appears. This is to avoid the risk of retrolental fibroplasia.

7. Antibiotics when overt signs of infection are present.

8. Close observation of apneic spells so that the infant can be stimulated or given positive pressure to avoid anoxic brain damage.

9. When the baby shows signs of spontaneous activity gastric tube feedings may be started. After two water feedings from 2-10 ml. (depending on infant size) milk may be attempted, and gradually increased. The intravenous fluids are discontinued after the gastric intake is about 65 ml. per kilogram per day. Hypodermoclyses may be necessary to supplement gastric feedins initially. This should be 20 ml. amounts of one third physiologic saline and two-thirds 5 percent glucose and water solution are given with hyaluronidase in the scapular area 1-3 times daily until weight is stable or increasing.[1]

Other methods include: Positioning, Alevaire and an aerosal of ethyl alcohol to decrease hyaline membrane, hypothermia, digit-

alization as indicated by a failing heart,[25] blood transfusion when shock is present;[24] and bilirubin evalutation of the blood, as Miller[58] substantiated a relationship between high levels of indirect serum bilirubin and the administration of oxygen. He found that 20 percent of infants in his group III developed concentrations greater than 14 mg. per cent while those in group I and II did not develop levels this high.[58]

Metabolic management by Usher[1] has decreased the mortality in their nursery to a considerable extent. Since this intravenous therapy has been instituted the mortality rate of distressed infants has fallen from 45 to 25 per cent, and of infants weighing less than 1000 gm. has fallen from 95 to 60 per cent. Deaths in the below 1000 gm. group occurred after the third day of age or as late as the twelfth day.

In Usher's therapy blood pH and carbon dioxide content are measured within 3 hours of birth in all infants who have respiratory distress syndrome or who weigh less than 1000 gm. At the same time an intravenous solution is infused at a rate of 65 ml. per day. This intravenous solution consists of 10 per cent glucose and water with sodium bicarbonate and started in a midline scalp vein. The concentration of the bicarbonate solution depends on the blood pH.

The venous pH and arterial or capillary p. have been correlated with the concentration of sodium bicarbonate that is desirable for various pH values and will be presented in the following table.

Venous pH[1]	Arterial or Capillary pH	Sodium Bicarbonate Concentration Used
Over 7.20	Over 7.30	5 meq. or 0.42 gm. per 100 ml.
7.10-7.20	7.20-7.30	10 mEq. or 0.83 . per 100 ml.
7.00-7.10	7.10-7.20	15 mEq. or 1.25 gm. per 100 ml.
Under 7.00	Under 7.10	25 mEq. or 2.08 gm. per 100 ml.

These determinations of pH and carbon dioxide are repeated at 6 to 24 hour intervals if the original venous pH is belw 7.20 or if the clinical condition worsens. The above table is then used for the proper concentration.

In infants who may already be hyperkalemic and in which there are electrocardiographic changes, emergency treatment with 20 per cent glucose-water and insulin (1 unit per 3 gm. of glucose) for several hours is used to correct the hyperkalemia before maintenance glucose and bicarbonate therapy is started. In those distressed infants first seen after 12 hours one will usually find hyperkalemia.

The initial infusions are given into a midline frontal scalp vein with a No. 23-27 gauge needle. The umbilical vein is reserved for emergencies or where scalp veins are impossible because danger of sepsis.

Fluid retention and cardiac overload is not increased with the above type of therapy. Infants on this intravenous therapy usually lose 5 to 10 per cent of their body weight during the first 3 days of life.[1]

Villavicencio et al[62] carried out studies on the fibinolytic system of 32 healthy prematures and 31 normal childern 1-2 years of age. The prematurs ha an average weight of 1.5 kilograms. No

toxic reactions or undersirable effects were noted in any of these cases after human fibrinolysin activated with streptokinase was used. The fibrinolysin was administered by aerosol and intravenous infusion; the administration of plasmi by aerosolwas followed by an increased lytic activity of the plasma when it was used in conjunction with the intravenous method.

ix patients with line membrane syndrome diagnosed clinically, radiologically, and by laboratory methods as having HM were treated with plasmin areosol. ll recovered completel. Seven patients with hyaline membrane disease were used as controls a treated ith varidase. Four survived and 3 died.[62]

SUMMARY

The term hyaline membrane disease has been replaced by the phrase respir tory distress syndrome when speaking of the disease clinically, as not all cases go to autopsy where the demonstration of a hyaline membrane must be accomplished. In general, this syndrome consists of atelectasis, congestion or pneumo ia and a hyaline membrane although other conditions may be present.

t autopsy the lungs appear purplish and when cut look like liver. They are noncrepitant. The chief microscopic finding is resorption atelectasis with congestion. The feature from which the disease derived its name is a homogenous layer which stains pink on a routine hematoxylin and eosin stain. This layer lines alveolar ducts, terminal bronchioles and some alveoli.

Complications of pregnancy seem to correlate with the RDS. The mortality rate is colsely related to the degree of prematurity and is 10 times greater in 1200 gm. babies as in 2400 gm. babies. Other generally accepted factors increasing RDS are cesarean section, maternal diabetes, fetal distress, placenta previa, and first twins.

The etiology does not seem to be related to the difficulty of the delivery, since these factors which tend to produce trauma, asphyxia or depression, delivery does not seem to affect the incidence of RDS. It is not more common in breech deliveries.

Regarding etiology many theories and experimental findings have been given. In reality the cause of the disease remains obscure. I think that the most likely cause is increased capillary permeablity with transudation or exudation secondary to anoxia with fibrin for-mation with the inability of the lung tissue to activate plasmino en due to certain enzyme deficiencies and a possible placental inhibit-or. These possibilities and others have been discussed in the fore-going material.

The clinical picture of pulmonary hyaline membrane appears to substantiate the presence of anoxia since most babies with the condition have difficulty from the time of birth. Clinical signs and symptoms have been classidied by Silverman and graded from 0-10, the former indicationg no disease and the latter severe distress. This classification is based on five signs and symptoms: 1) retraction of the chin, 2) xiphoid retraction, 3) intercostal retraction, 4) gruntin respiration, and 5) a comparsion of chest and abdominal movement.

Miller's classification consisting of groups I, II, and III which is based on repiratory rate has been helpful in predicting possible outcome. In Group III one half of the infants had persistent cyanosis and about 25 per cent died during the first few days, whereas the other two groups returned to normal.

Clinical findings are, as in Silverman's grading and flaring of the alae, rales of pulmonary edema, edema on the dorsal surfaces of the hands and feet, hypotension, tachycardia, murmur typical of ductus arteriosus, neurological findings, abdominal distention, and a frequent problem is paralytic ileus.

Roentgenologic findings consist of a typical triad: the generalized reticulogranular pattern of the lung fields, an "air bronchgram" and widened mediastinum. Differential diagnosis relies a great deal on x-ray findings.

The differential deagnosis consists of aspiration of amniotic fluid and meconium: (Aspiration syndome), primary atelectasis, intracranial hemorrhages, pulmonary hemorrhage, pneumonia and other lesser entities such as lung cysts, lobar emphysema, congestive failure of diaphragmatic hernia. All this is done on the basis of the clinical findings, x-ray findings and a minimum of labratory work.

The electrocardiographic disturbance is closely related to increased potassium in the plasma. A conduction type distrubance similar to that found in the anuric adult develops, with the hyperkalemia that is present in these infants.

Biochemical findings in the RDS during the early hours of life include a respiratory and metabolic acidosis, hypoproteinemia, hypoglycemia and hyperphosphatemia. After 12 hours of age the metabolic acidosis increases, and hyperkalemia and azotemia develop.

Until the basic physiological observations are more thoroughly understood treatment must be supportive and for the most part emperic and consists of:

1. Minimal trauma, asphyxia and exposure to cold during and immediately after delivery.
2. Early adequate ventilation such as positive pressure or endotracheal intubation if necessary.
3. Feedings withheld to avoid aspiration.
4. Maintainence of temperature and high humidity.
5. Oxygen when cyanosis is present.
6. Digitalization as indicated by a failing heart.
7. Treatment of neonatal metabolic and respiratory acidosis and hyperkalemia with glucose, bicarbonate an insulin as recommended by Usher in regard to pH, CO_2 content, and potassium values.
8. Antibiotics if infection supervenes.
9. positive diagnosis of HMD should be established if at all poss-ible by physical and x-ray examination and ruling out other possibilities must be carefully evaluated.

CONCLUSION

The RDS is still an important cause of neonatal death and has in the past decade roved of growing interest. Experimental studies and detailed examination of human material have only emphasized how far we are from a complete understanding of the pathogenesis of the disease.

In the fore oing pages the pos ible etiologies, clinical diagnosis and differential and the treatment have been discussed.

The fact that positive diagnosis requires the death of the patient is not the only complication of the investigator's problem. The syndrome is limited to a period of normall rapid physiological reorganization and its subjects are not merely newborn but also prematurely born or born to diabetic mother, and, therefor, in many ways resembling premature infants. H aline membrane disease occurs in a wide field of etiologic possibilities.

Beyond the localized morphology and function of the lun itself, the student must pursue etiologic possibilities into the neighboring circulatory system, where general vascular hypotonicity seems to be characteristic, and, perhaps as part of the lack of vasomotor tone, patency of the ductus arteriosus may be a significantly associated feature.

Still more widespread, yet everthless capable of affecting the lungs as parts of all the body, are the changes in acid-base structure and serum protein composition of the blood. This subject is now being widely investigated and an elaborate method of electrolyte therapy by Usher has been out ined.

Many of these abnormalities may as well be secondary to the profoundly disturbing results of inadequate respiration as primary causes of the respiratory difficulty. Indentification of etiology is not easy in a two-pound patient whose clinical process begins at or immediately after birth, its degree rapidly increasing so that within three hours the infant may be in profound distress and in another hour dead.

It is extremely important to rule out or treat any of the other causes of respiratory embarrassment which are amenable to correction. For the most part, the general support of the infant with this syndrome of unknown cause represents the present limit of our method of management. Certain additional measures which have recently been advocated have been mentioned.

It seems likely that the incidence and severity of the hyline membrane syndrome will diminish in the future as obstetricians are more careful in safeguarding the infant against anoxia, trauma, and difficulty during the birth proceedure. The anesthestist, pediatrician, and pediatric cardiologist all have a part to play in successfully tiding these infants over the dangerous first three to four days of life.

In the preceding pages the literature has been reviewed on a controversial subject and the various possibilities discussed. Also the accepted medical procedures at present have been given.

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