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Respiratory distress syndrome

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THE RESPIRATORY DISTRESS SYNDROME

by

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RESPIRATORY DISTRESS SYNDROME

Respiratory distress syndrome is at this time an imperfectly understood entity. There is not even a universal definition that all investigators use. This paper will review some of the current thinking on the respiratory distress syndrome or hyaline membrane disease.

A currently used definition of the respiratory distress syndrome is any type of respiratory distress that develops shortly after birth, that is not due to any presently known condition which may cause such respiratory distress as respiratory infection, central nervous system depression, congenital anomaly or aspiration of meconium.[1] Thus, with this broad definition, it is necessary that one have a working definition to aid in the diagnosis of this syndrome.

In order that the reader of the literature on this subject has a means of evaluating the work, it is essential that objective criteria be used to define the respiratory distress syndrome. Various men working in this field have different signs and symtoms in making the diagnosis of the respiratory distress syndrome and evaluating the severity.

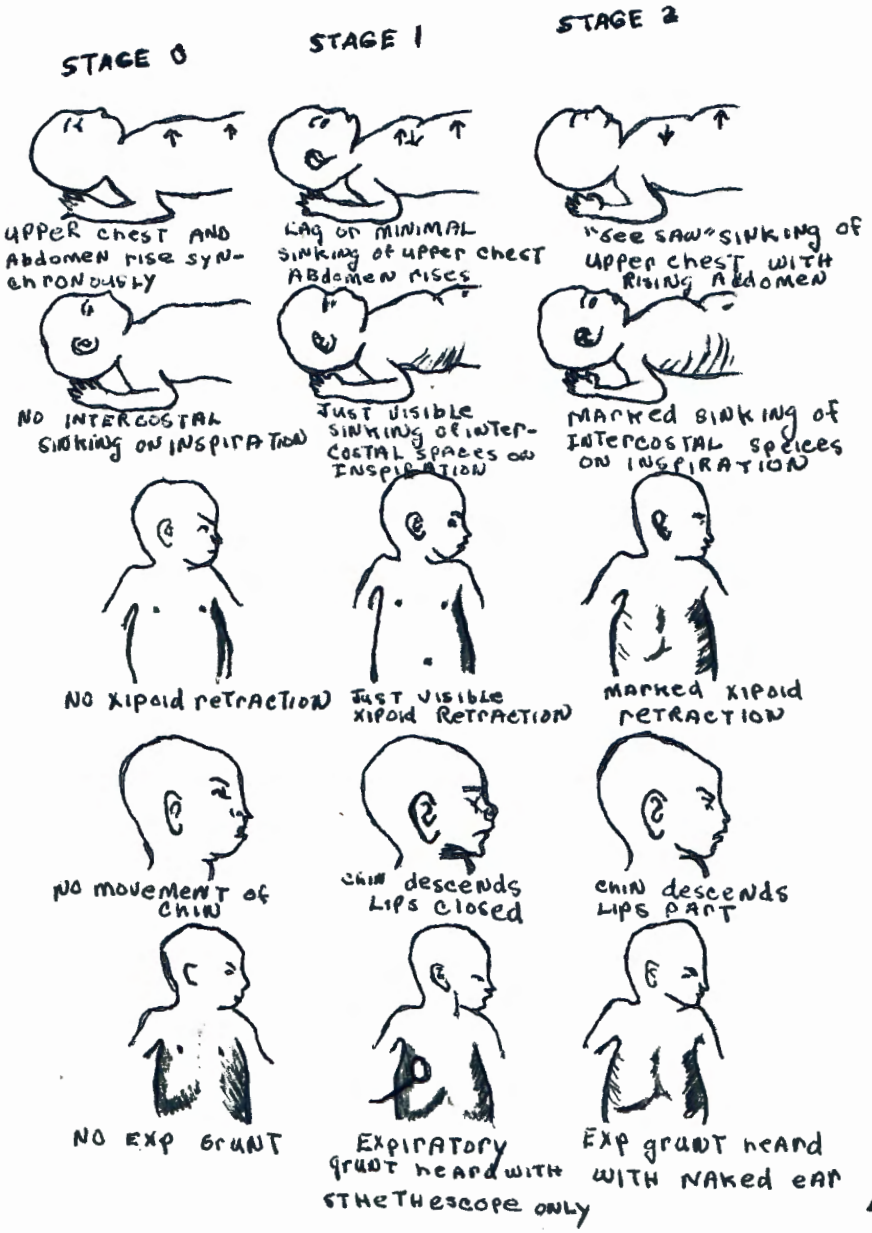
The different methods of diagnosing this syndrome will be presented. One set of criteria was proposed by Usher. He stated:

> The diagnostic signs of respiratory distress syndrome are chest retraction, expiratory grunting and decreased air entry on auscultation, present during and persisting beyond the first three hours of life in the absence of co-existing disease.[2]

The above definition is not entirely objective. From one of the other studies of Miller, the following is presented as being objective, reliable and easily recognized signs of the respiratory distress syndrome. The first was expiratory grunt present after one hour of age. Next was a resting respiratory rate above sixty-five per minute between one and thirty hours of age persisting for more than one observation. If there was an increase in resting rate between one and thirty hours of age of more than fifteen per minute over the highest rate recorded during the first hour after birth, this was considered to be indicative of respiratory distress. Infants who had any one of the above criteria were considered to have the respiratory distress syndrome. Chest retraction was not included among the criteria used in the diagnosis of the respiratory distress syndrome because of its high incidence in infants who were considered not to have this syndrome. This study proposed that chest retraction is practically universal among infants with the respiratory distress syndrome. Also, the respiratory distress syndrome must be differentiated from transitory initial res-

piratory distress often seen at birth. This is a delay in spontaneous respiration for less than one minute.[3]

In the literature frequent reference is made to the Silverman score. The method used is retraction scoring. This scoring system is based on the following observations. A score of zero is given if there is a synchronous use of the upper chest and abdomen. A one is given if there is a lag or minimal sinking of upper chest as the abdomen rises. A two, if there is a see-saw sinking of the upper chest with rising of the abdomen. The next major consideration if the intercostal spaces. If there is no intercostal sinking on inspiration, the score is zero. One is scored, if there is just visible sinking of the intercostal spaces on inspiration. Marked sinking of the intercostal spaces on inspiration is scored as two. Scores of zero, one or two are given if there is no xiphoid retraction just visible xiphoid retraction, or marked retraction. The fourth observation is based on movement of the chin. Zero is scored if there is no movement of the chin. If chin descends but lips are closed and chin descends but lips are opened are scored one and two respectively. In the final category, no expiratory grunts when one listens with a stethescope is zero. Expiratory grunt heard only with the stethescope is one. Expiratory grunt heard without stethescope is two. In this system the maximum score is ten.[4] This can be summarized with this drawing:


STAGE 0
STAGE 1
STAGE 2
UPPER CHEST AND ABDOMEN RISE SYNCHRONOUSLY
LAG OR MINIMAL SINKING OF UPPER CHEST ABDOMEN RISES
"SEE SAW" SINKING OF UPPER CHEST WITH RISING ABDOMEN
NO INTERCOSTAL SINKING ON INSPIRATION
JUST VISIBLE SINKING OF INTERCOSTAL SPACES ON INSPIRATION
MARKED SINKING OF INTERCOSTAL SPACES ON INSPIRATION
NO XIPOID RETRACTION
JUST VISIBLE XIPOID RETRACTION
MARKED XIPOID RETRACTION
NO MOVEMENT OF CHIN
CHIN DESCENDS LIPS CLOSED
CHIN DESCENDS LIPS PART
NO EXP GRUNT
EXPIRATORY GRUNT HEARD WITH STETHESCOPE ONLY
EXP GRUNT HEARD WITH NAKED EAR

The studies of Bauman point out the value of this system. Scores of less than two indicated no signs of distress and of the babies studied only one had pulmonary hyaline membrane. Of those babies whose autopsy findings disclosed hyaline membrane disease, twenty of twenty-one had had significant retractions at the first scoring period. This is compared to twenty-two who died without hyaline membrane findings at autopsy, few babies had distress when they were observed for retractions. Therefore, a frequent forerunner of death with pulmonary hyaline membrane disease was respiratory distress. There were babies who had distress and died but did not have hyaline membrane. This indicates that the often fatal respiratory distress syndrome not only includes babies with hyaline membrane but also those with other lethal conditions. That is why such factors as pulmonary vascular engorgement, metabolic and enzymatic disturbances, muscular underdevelopment and anatomic interference with respiration are considered in the study of the respiratory distress syndrome.

The majority of those infants whose score was less than 2 at each of the scoring intervals (that is, at 6, 12, 18, 24 hours) survived more than one week regardless of birth weight group. The dyspneic premature infants had a larger proportion of deaths. The number of babies of less than 1,001 grams who died and had distress at 6, 12, 18, 24 hours was greater than the number surviving. Deaths in the 1,001

to 1,500 grams showing retraction at 6 and 12 hours also outnumbered survivals, whereas, among the infants with dyspnea at 18 and 24 hours there were more survivals than deaths. In the weight group of more than 1,500 grams, there were more survivals than deaths.

In summary, roughly, three-fifths of the infants with respiratory embarrassment died before 8 days of age. Of those with no retractions, about one-tenth died. The dyspneic newborn prematures had a case fatality rate about six times as great as the ones without distress. Of those who died about one-half who had retractions had pulmonary hyaline membrane, whereas, a much smaller proportion of those without distress during life had hyaline membrane at autopsy. Disregarding birth weight, the 19 of 48 infants studied had significant retractions at the 6 hour scoring period, pulmonary hyaline membrane at autopsy had a median age at death of 25 hours, whereas, 14 with distress but no membrane at autopsy had a median age at death of 78 hours. The nine with neither respiratory distress nor pulmonary hyaline membrane at autopsy had a median age at death of 78 hours.[5] From the preceding data, it can be observed that the Silverman's score can be of value in assessing the severity of respiratory involvement.

The respiratory rate is perhaps the most important observation. Infants with a persistant respiratory rate of 100 to 110 rarely die. Inability to increase the respiratory rate in face of severe disease is a poor prognosis. Decrease

in respirations during the first twelve hours after birth may reflect the severity of cerebral insult. This may be caused by several things, such as, cerebral insult associated with intrauterine or birth asphyxia, may result from cerebral hemorrhage, may accompany hypothermia and in small infants may reflect extreme immaturity of the babies enzyme system and consequently decreased ability to detoxify sedative drugs given to the mother and transferred across the placenta to the fetus. Perhaps the five most important parameters available to clinician in assessing the severity of the respiratory distress syndrome are arterial pO2, arterial pH, serum potassium, birth weight, and respiratory rate. The arterial pO2 and pH serum potassium may be of value in the research situation but in the practical situation obtaining these studies is difficult. Some authors have devised a mathematic assessment of severity of involvement on the basis of the above parameters. This is complex but worthy of further evaluation.[6]

In reviewing the definitions presented, all are of value to the practicing clinician. The first definition is an overall view of what is considered to be the respiratory distress syndrome. The criteria of Usher, although not entirely objective and specific for the respiratory distress syndrome, are easily recognized and can alert the

physician to the possibility that the infant is in difficulty. The observations presented by Miller require more constant observation of the newborn but tend to be more specific for the respiratory distress syndrome. These signs would be of value in a research setting so that all the examiners would be talking about the same thing. The Silverman score is of value in assessing the severity of the disease and evaluating the prognosis.

Data will be presented so as to provide an assessment as to the magnitude of this problem. The studies of Miller demonstrated that the incidence of respiratory syndrome in premature infants weighing between 1,000-1,500 grams was about 80%. The infants between 1,501-1,000 grams was about 50%. In the weight range of 2,000-2,500 grams it was 25%. In this study severe respiratory distress was determined clinically by observing cyanosis in infants with the criteria for the respiratory distress syndrome previously summarized. The laboratory measurement of the oxygen saturation of arterial blood and of the pH of venous blood can be used to differentiate infants with mild respiratory distress syndrome from those with the severe form.

In the study of Miller, all the normal infants had an oxygen saturation of the peripheral blood of ninety per cent or greater at one-half hour of age. pH of venous blood was 7.3 or greater at two hours of age. Carbon dioxide tension ranged from twenty-seven to forty-two millimeters of mercury in all normal newborn tested. In those with mild respiratory

distress and peripheral blood oxygen saturation was between eighty-nine and ninety-nine per cent saturated. Only one-third had a venous pH less than 7.3. This is compared to those with severe respiratory distress syndrome. In this category none of the infants had greater than ninety-three per cent oxygen saturation of the peripheral blood. Seventy per cent had less than eighty-seven per cent saturation of the first six hours. Two thirds of the severely affected infants had a venous pH of less than 7.3 at two hours.

The incidence of severe respiratory distress in the same three weight categories was 67%, 23% and 7% of the total number of infants in each age group. In the full term in- infants born vaginally, the incidence was 8.8%. Of those born by Caesarian section, the incidence was 21.3%. But a severe respiratory distress syndrome was observed in only 0.6% of full term infants born vaginally and 5.5% of the group born by Caesarian section.[7]

As a comparison to the study of Miller as to the incidence of this disease, a study based on four years of observation and one hundred fifty infants is presented. Fifty per cent of the premature deaths occurred in the first three days of life. Of the total number of premature births, fourteen per cent were considered to have the respiratory distress syndrome. Fifty per cent of the infants weighing from 1,000 grams to 1,500 grams had respiratory distress syndrome as compared to 5% weighing from 2,000-2,500 grams. Four of five of those who die of the respiratory distress syndrome do so

in the first twelve to seventy-two hours. Observed mortality rate if the infant would live forty-eight hours was 25% and 11% if the infant would live seventy-two hours. The incidence for the same weight ranges was doubled if infant was delivered by Caesarian section. Infants greater than thirty-seven weeks gestation or 13,000 grams delivered either vaginally or by Caesarian section, not a single case of respiratory distress syndrome was observed.[8] Another interesting observation is that there seems to be an increased incidence in male infants. One author cited three hundred thirty-eight cases of premature infants and one hundred thirty-six cases of hyaline membrane disease. There was found to be a four-fold increase in males delivered per vagina. In the 1,000-1,500 gram infants, there was a similar incidence in male and females. The frequency continued to rise in male toward maturity while falling off in the female.[9] From these various incidence figures, it can be noted that similar figures are obtained. This syndrome seems to be infrequent in term infants.

To make a diagnosis of the respiratory distress syndrome, the newborn infant must be under careful observation. Frequently, the experienced nurse can make meaningful observations in the newborn nursery about the condition of the baby. The observations should begin immediately after birth. The incidence in term babies is so low that it would not be practical to observe all babies for respiratory distress with

the care used in institutions where intensive research is carried out on the respiratory distress syndrome. Because with the criteria proposed, it would take trained help and constant observation. This type of observation would be of value for all premature infants and many full term infants who by reason of the type of birth or maternal illness particularly diabetes mellitus or failure to initiate respiration within the first minute after birth. Because, these are the infants who are the most likely to develop the respiratory distress syndrome.

In reviewing the pathogensis of this disease, many interesting theories are proposed; but as yet, they are merely theories. Many factors have been considered and it is possibly a combination of several factors that are involved in this syndrome. A major factor may be a substance known as surfactant. Electron microscopists have by the study of the anatomy of the alveoli of the lung proposed a cell that is thought to produce surfactant. Recent studies with the electron microscope have demonstrated that the alveolar epithelium lining consists of continuous squamous epithelium. A great portion of the lining membrane being too thin, 0.2 micron and less to be distinguished by the electron microscope.[10] The alveolar cells are of two types. Type one is vacuolated with lipoidal material. Type two is non-vacuolated, and these cells have the appearance of connective tissue cells. They also have lamellar inclusions. It is suggested that the lamellar inclusions contain surfactant or its pre-

cursors.[11] It is thought that these cells appear in the human fetus at about the fifth to sixth month gestation.[12]

Surface tension reducing substance, surfactant, has been identified as a lipoprotein. It has a choline base plus saturated fatty acids. This is thought to be essential to the surface active property. Also, in the crude material derived from the lungs, surface behavior depends upon the protein fraction as well. In 1947 Gruenwald proposed an explanation of the classical X-ray appearance of the lung in hyaline membrane disease with the surface tension factor as a basis. By this is meant that the diffuse reticulogramular appearance found in the chest X-ray of a patient with hyaline membrane disease is the result of a lack of a surface tension which counteracts the entrance of air but has no effect on the aspiration of fluid. This then leads to the characteristic diffuse atelectasis that is the classical X-ray appearance of the lung in hyaline membrane disease.[13] Surface active substances reduce the pressure necessary for aeration. This is why it has been considered that the administration of surface active substances to air or oxygen which is taken in by the newborn infant might aid in relieving the initial atelectasis of newborn infants. Avery and Mead have found that the surface tension of extracts from lungs of infants weighing less than 1,000 grams or dying with hyaline membrane disease is higher than expected.[14] These observations indicate that the respiratory distress syndrome

is associated with an absence or decrease in the amount of surface active material. Whether the absence of the lipoprotein film in hyaline membrane disease is due to its failure to appear or its inactivation is uncertain. The argument that the process is one of developmental immaturity depends on the observation that an alveolar lining substance with characteristic surface active property is not present in most infants of less than 1,000 grams at birth. In these infants atelectasis is prominent. Hyaline membranes may be found but are not as common as in slightly heavier infants.[15] This absence or deficiency of the surface active material is probably secondary to some other process. For example, in the lung of a patient dying after a cardio-pulmonary bypass, there is an increase of the minimal surface tension of lung extract.[16] This suggests that an adequate pulmonary circulation is necessary if the integrity of the alveolar cells which produce the surface active material is to be maintained.

The fetal lung is not an inert organ. During the later half of gestation, considerable amount of fluid is produced.[17] This study was done by Adams and co-workers using fetal lambs. It was found that the osmolality was equal to that of plasma. The pH of this secretion in the lung was 6.43 as opposed to 7.34 of plasma or 7.07 of amniotic fluid. The chloride content was 144 milliequivalents. While that of plasma is 105 milliequivalent and amniotic fluid is 94

milliequivalent. The above suggest that this fluid produced by the fetal lung is an ultrafiltrate of plasma with selective reabsorption of secretion. Now, this intra-alveolar fluid, with such a chemical composition, is thought to be of prime importance during initial lung expansion. Its low protein concentration together with the fall in pulmonary pressure that occurs when the lung expands with the rising arterial oxygen tension, all would facilitate the reabsorption of this fluid. This fluid is rapidly absorbed. Avery and Cook, studying fetal goats, have estimated that the volume of fluid in the fetal lung is about sixty per cent of total weight of the organ.[18] Any change in the electrolyte composition or protein composition could be a detriment to the reabsorption of the fluid and initial lung expansion. The composition of this fluid is interesting because it illustrates that normally all factors involved in initiation of respiration are directed toward this end. Thus, the slightest change in this fluid whatever the cause, could lead to the respiratory distress that can be observed at birth.

It is proposed that abnormal shunting is involved in the respiratory distress of the respiratory distress syndrome. The ductus arteriosus is widely patent in these babies, and, in the severely ill infant, there is usually a right to left shunt through the ductus. There is also a right to left shunt at the foramen ovale. Recovery is ac-

companied by rising systemic pressure and a resulting left to right shunt that diminishes as the ductus closes. Deterioration is accompanied by a fall in systemic pressure and large right to left shunting. Such shunting at the foramen ovale and ductus arteriosus, if large, result in decreased cardiac output. The increasing right to left shunt in these infants in distress, together with the impaired pulmonary diffusion and atelectasis, will make oxygenation increasingly more difficult. It is unlikely that pulmonary edema or failure of left ventricle, if present, can be explained solely on the basis of large left to right shunts since they are observed during recovery in both lambs and babies. In the healthy infant, the right to left shunt can amount to twenty-five per cent of the cardiac output.[19]

In respiratory distress syndrome Nelson and co-workers have found that underperfusion of the ventillated alveoli and underventillation of the perfused alveoli occur. They have calculated that in the respiratory distress syndrome more than sixty per cent of the alveoli are underperfused.[20] There is also a significant arterial gradient for carbon dioxide. Since carbon dioxide is so highly diffused through the alveolar membrane and excreted if the arterial carbon dioxide is high, this indicates a mixture of blood that has not been in contact with the alveolar gas. It is possible for disturbances in the so-called ventillation to perfusion ratio, to arise from a by-pass at the level of the alveolar

capillary. But, it is more likely that they result secondarily from right to left shunts through the ductus arteriosus or foramen ovale. Therefore, the immature anatomy of premature infant may be one reason for the higher incidence of the respiratory distress syndrome in these infants.

There seems to be two main areas of investigation regarding the factors that are involved in this syndrome. One is the study of surface tension. Some of the basic ideas of this have been presented. The other is the study of the relation of fibrinolytic activity and hyaline membrane formation. Since the hyaline membranes found in the respiratory distress syndrome are composed of fibrin, the relationship of fibrinolytic enzymes to the development and ~~or~~progression of the disease in premature infants has been under investigation. A recent study is that of Markarian and co-workers. Eighty-two premature infants weighing between 750-1750 grams, nineteen full term babies and their mothers in labor, and thirty-five normal adult controls were studied for fibrinolytic activity with the euglobulin fibrinolysis method.[21] Before the results are reviewed, a scheme of the fibrinolytic system is presented:

Streptokinase

Proactivator - - activator

Tissue activator - - plasminogen
(Profibrinolysin)
(This is found in Beta Profibrinolysis globulin of blood)

Urokinase

antiplasmin

Plasmin - Antiplasmin complex inhibits

Plasmin
(Fibrinolysin)

Hydrolyzes fibrin clot and other plasma proteins

Protein fragments.[22]

The following general observations can be made: Pregnant women have less fibrinolytic activity than normal adult controls. Pregnant women who delivered premature infants with the respiratory distress syndrome have less fibrinolytic activity than those who delivered normal premature or full term infants. A changing pattern of fibrinolytic activity with age has been noted in all newborn infants. This pattern is evident in the first few hours of life. The low birth weight infants had less fibrinolytic activity than full term infants from birth to fifty-five hours of age. Now premature infants with the respiratory distress syndrome had less activity than those who were unaffected. Those with the respiratory distress syndrome who died had the least fibrinolytic activity from six to fifty-five hours of age.

The work of Arustowicz indicates similar findings. His studies suggest a lower fibrinolytic activity as well as a greater lability of the fibrinolytic system in newborn than in adults. The greater the body weight, the shorter the time of fibrinolysis. A comparison with the very low fibrinolytic activity always found in the newborn during fully developed hyaline membrane disease indicates that this activity is fully depleted by activation and utilization by the fibrinolytic enzymes or that there is an increased amount of antiactivator present. The above allows one to

assume that the administration of fibrinolytic enzymes to the newborn with respiratory distress syndrome may be a symptomatic cure but not a casual one. This article pointed out that a longer lysis time is not pathognomonic for this disease.[23]

Markarian's article and data showed that there was no difference in fibrinolytic activity between the women in labor who delivered full term or premature infants without respiratory distress syndrome. Likewise, there was no difference in the fibrinolytic activity of the women who delivered premature infants with respiratory distress syndrome whether the baby lived or died. But women who delivered premature infants with the respiratory distress syndrome had less fibrinolytic activity (that is, a longer fibrinolysis time) than those who delivered full term or premature infants without the respiratory distress syndrome. There is, as previously indicated, a changing pattern of fibrinolytic activity with age apparent in all newborn infants. There is an increasing fibrinolytic activity from birth to one and one-half hours of age and a decreasing activity from one and one half hours to twenty-five hours of age and a slight increase from twenty-five to fifty-five hours of age. Premature infants with respiratory distress syndrome had less fibrinolytic activity from birth to fifty-five hours than those who were unaffected. Birth weight of this group was 750-1750 grams and those with respiratory distress syndrome

who died had a longer fibrinolysis time - decreased fibrinolytic activity, from six to fifty-five hours of age as compared with those with respiratory distress syndrome who lived. This initial deficiency of plasminogen in premature infants may make them more susceptible to fibrin membrane formation in the lung. There was a diverging pattern of fibrinolytic activity at the six to twenty-five hour age in the respiratory disease syndrome died group as compared to those with respiratory distress syndrome lived group. This would indicate a more severe deficiency in the former group. This may be related to more severe disease and or greater use of the fibrinolytic enzymes.

It can be emphasized that plasminogen levels have been measured by several investigators with reasonably good agreement. There is a decreased plasminogen level in the neonatal period, premature infants being more deficient than full term. The work of Berglund has demonstrated no correlation between the fibrinolytic activity of the blood of pregnant women and cord samples of their babies.[24] At this time, there is no evidence that it is passibely transferred from mother to fetus. Therefore, the fibrinolytic activity must arise in the fetus.

Studies have been made comparing the fibrinolytic activity in the blood of the umbilical vessels and peripheral blood. The studies show that there is more fibrinolytic activity in the umbilical vessel blood than there is in the

peripheral venous blood. There is marked activity in the blood of umbilical artery as compared to that of the umbilical vein at the time of birth.[25] These data indicate that the infant produces fibrinolysin, but it is either inactivated or utilized in the placenta. Another possibility is that the intravillous thrombi of the placenta in the later months of pregnancy release an activator into fetal circulation.

Many theories have been proposed regarding the production and release of endogenous fibrinolytic activity. Some have proposed shock, stress, thromboses, hyperventillation and a number of drugs. Perhaps a common factor is histamine. Holeman and Langdell have shown that intravenous histamine does increase fibrinolytic activity in the dog. They suggest that the development of hypotension may be the mechanism by which histamine is released resulting in an increase of the fibrinolytic activity.[26] Vascular tissues, particularly small veins, contain abundant fibrinolytic activators. Since histamine has direct injurious effect on the endothelium of vessels, activators could be released into the general circulation. There is some evidence available to indicate that the increased levels of histamine in pregnant women are related to increased production by the fetus. Babies with hyaline membrane disease may have increased histamine levels.[27] Adding to the importance of a consideration of histamine is the work of Cho and Choy.

They have reported that drugs which increase fibrinolytic activity have the ability to release histamine.[28] This also demonstrates the relation of histamine and increased fibrinolytic activity. From all of the above, one may conclude that hypotension, hypoxia, and possibly elevated histamine levels in infants with the respiratory distress syndrome may be related to increased levels of pulmonary plasminogen activator. There has been no apparent correlation of fibrinolytic activity with major prenatal complications such as placenta previa, eclampsia, preclampsia and hypertension.

Preceding information can be summarized in the following manner: Since infants who died of the respiratory distress syndrome had lower levels of plasminogen than normal premature infants, it is possible that this is due to a utilization of fibrinolysin in the lungs of the affected infants as the disease progresses or due to an antiactivator. There is an increased incidence of hyaline membrane formation in premature infants. Or, there is an inability to dissolve the formed membrane which may be related to a more immature enzyme system. Although the significance of hyaline membranes is controversial, there does seem to be a relation between them and the fibrinolytic enzyme system.

The significance of the above, in terms of therapy, is still being worked out. Urokinase activated human plasmin

has been used in treating infants with the respiratory distress syndrome. Ambrus had a survival rate of 86% but only fourteen infants were treated.[29] Active plasmin would not tax immature enzyme system of the newborn. But if it were used in excessive quantities and not rapidly neutralized by antiplasmin, it could hydrolyze other proteins including fibrinolysin and other coagulating factor. Further studies are needed to determine whether the development of the respiratory distress syndrome can be altered by increasing the fibrinolytic activity in high risk premature infants.

Before treating this disease, it is of value to review some of the findings at autopsy. In the respiratory distress syndrome, chief pathologic findings are reviewed from the data of Miller.[30] Infants in the study were born at the University of Kansas Medical Center between 1954 to 1961. The infants were classified in the following manner: Infants who were alive at seven days were considered to have survived. Infants were considered apneic at birth, if spontaneous self-sustaining respirations began later than one minute after birth. These were, in turn, classified as either mild or severe. The mild required no oxygen therapy. The severe were cyanotic in room air and did receive continuous oxygen therapy, after the first hour of birth. About one-third of all neonatal deaths are associated with some major congenital anomaly. These deaths were not considered in this study.

Deaths of premature infants weighing less than 1,251 grams at birth was most often associated with pulmonary atelectasis. Sometimes a few polymorphonuclear cells were seen in the alveolar spaces, but atelectasis was prominent. Pulmonary hyaline membranes were the chief finds at autopsy of premature infants weighing over 1,240 grams at birth. Hemorrhages into ventricles of the brain was restricted to infants weighing less than 1,500 grams at birth. Hemorrhages into the alveoli of the lungs were observed in larger premature infants. Aspiration of amniotic sac contents with pneumonia was characteristic of full term infants who died of the respiratory distress syndrome. With the different birth weights, there was an associated primary autopsy finding. In this study, the chief cause of death did not differ significa ntly between apneic and non apneic infants. But infants apneic at birth were more likely to develop severe respiratory distress syndrome than the non apneic infants.

A table of deaths among apneic and non apneic premature infants with severe respiratory distress syndrome according to birth weight is presented to emphasize the importance of apnea.

Condition of Infant	Number of Infants	Died Number	Per cent
1,000-1,250 gm.			
non apneic	15	6	40
apneic	17	13	76.5
1,251-1,000 gm			
non apneic	25	4	11.4
apneic	37	17	51.4

Incidence of apnea at birth that lasted more than one minute varied from fifty per cent in infants weighing less than 1,000 to 1,500 grams at birth to 1.6% in full term infants.[32] There was observed a marked drop in neonatal deaths when signs of respiratory distress were first observed after thirty minutes of age. The incidence of certain complications of pregnancy such as dystocia, vaginal bleeding was about three times as high in mothers of apneic infants in all birth weight categories. Thus, as would be expected, subh complications seem to be related to the apnea of the newborn. Auld et al. have shown that unresponsiveness of infants at birth was positively correlated with certain kinds of anesthesia, cord about the neck, fetal tachycardia, meconium stained amniotic fluid, prematurity and long labor.[33]

Past studies have concluded that intrauterine asphyxia of moderate proportions would be capable of producing apnea at birth. The difficulty comes in accounting for apnea at birth in instances in which there is no obvious maternal complication. This present study of Miller suggests that whatever produces apnea at birth is related in some way to the development of the respiratory distress syndrome in some infants. Therefore, the chief cause of death of infants with the respiratory distress syndrome, as demonstrated from the data obtained by Miller, was more closely associated with

the degree of the infant's maturity at birth than with the presence or absence of apnea at birth or the type of maternal complication.

After considering some of the basic aspects of the disease, a means of treatment will be presented. Since this syndrome is apt to occur in subsequent pregnancies, particular care should be given. It has been suggested that the disease may be prevented by delayed ligation of the umbilical cord. Early clamping of the umbilical cord means that the cord is clamped before the second breath. Late clamping of the cord means that the cord is clamped after the second breath. The reason that late clamping of the umbilical cord is advocated is that early clamping may be involved in the pathogenesis of the respiratory distress syndrome. The placenta is an organ of low vascular resistance and, therefore, receives the major portion of the total fetal cardiac output. With the onset of respirations, pulmonary vascular resistance is reduced and increasing quantities of blood circulate through the lungs. Pulsations of the cord become progressively weaker and finally cease after the transition from placental to pulmonary oxygenation is complete. This gradual change over is probably accomplished with only minor alterations in systemic blood flow, pressure and resistance. If the umbilical cord is occluded prior to expansion of the pulmonary vascular bed, the systemic vascular resistance would rise sharply. With ventricular stroke volume

remaining unchanged (for at least one or two beats) the arterial pressure must rise. The sudden high head of pressure transmitted through the ductus arteriosus to the pulmonary vascular bed may cause transudation through or even rupture of the capillary alveolar membrane as well as the capillaries of the brain, adrenals and other organs.[34]

This is an interesting hypothesis. There is data available to support the chain of events proposed. Many investigators have demonstrated that clamping of the umbilical cord prior to onset of respirations can be associated with a sharp rise in systemic arterial pressure.[35, 36] Hemorrhage is frequently found in association with the respiratory distress syndrome of the newborn.[37] Although this hypothesis does have some objective support, at this time, this observation remains to be confirmed. At the present time, there seems to be no specific therapy. Introduction of surface active material has not proved effective. The use of fibrinolytic substances has been recently studied. As to date, streptokinase activated plasmin has been of no significant value. The use of urokinase activated human plasmin has been more promising.[38] Thus, at this time, the clinician is left with supportive therapy. Since most of these babies are premature, general care of the premature infant is given. The following general mode of treatment can be followed: First, one must establish a diagnosis. The criteria previously

previously stated can be used. Ancillary aids such as X-ray may suggest the diagnosis when the typical diffuse reticulogranular pattern is present. X-rays are of value because it helps to rule out other serious conditions which are amenable to specific therapy. This would include such things as disphragmatic hernia and pneumothorax.[39] Sometimes one must do a lumbar puncture to rule out a central nervous system cause for the respiratory failure. If the infant has been borne prematurely, if amniotic fluid is clear, and if X-ray films of the chest or serial studies show no abnormalities, other than the characteristic findings, the diagnosis of respiratory distress syndrome is probably correct.

The ambient air should be kept between 32° and 34° (89-93° F) because the oxygen consumption of the infant will be lowest at this temperature range. At room temperature, the newborn human infant loses about 600 calories per minute. The chance of survival of the infant is increased if his axillary temperature is maintained between 35 and 36°C (95-97° F). This is accomplished most easily if the environmental humidity is between 80-100%.[40] Oxygen is of value in the cyanotic infant, particularly when the hypoxia is so severe that responsiveness of the respiratory center is impaired. One must be aware that supplemental oxygen levels of 30-40% adds the risk of retrolental fibroplasia if the

blood oxygen tension rises above normal values. Reid indicates that prolonged respiratory therapy is a serious undertaking, but the earlier it is started, the more likely it is to be effective. He also emphasizes the need for adequate humidification of inspired gases. A gastrostomy may be advantageous in the maintenance of the severely ill newborn infant.[41] Pressures of 2-2½ atmospheres have been tried to increase O2 tension. Blood oxygen tension may be temporarily improved. All other biochemical abnormalities are unchanged.[42]

If reasonable suspicion of infection exists, antibiotics should be given. In any event, if the infant is moderately or severely ill at thirty-six hours, antibiotics should probably be given because of increasing possibility of superinfection. An article by Cook points out that the commonest treatable complication is pneumothorax. Sudden deterioration in an infant's condition possibly accompanied by distant breath sounds should alert the clinician to the diagnosis and order a chest X-ray to confirm it. Thoracentesis may be lifesaving. Another complication is hyperkalemia. It is seen less frequently if glucose has been given. This is diagnosed by following serial EKG's, proper electrolytes. Additional glucose will help to restore serum potassium toward normal. Guiding principle proposed by Cook is:

Avoid doing anything more than necessary but do enough - and not add to the infant's trouble. Many of these patients with respiratory distress syndrome require only the routine care given to all prematures.[43]

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