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Pulmonary hyaline membrane diseases and its possible relationship to heart failure

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PULMONARY HYALINE MEMBRANE DISEASE AND ITS POSSIBLE RELATIONSHIP TO HEART FAILURE

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Pulmonary hyaline membrane disease is a clinical and pathological entity usually limited in its time of origin to within the first twenty-four hours of life and rarely lasting more than four days.

Hoccheim first described the histological picture of a homogeneous eosinophilic material coating the alveolar ducts, atria and alveoli in 1903.[55] Johnson[38] in 1923, and Meyer in 1925,[18] were the first investigators in this country to describe the disease and following their description and proposed etiology, only Farber and Wilson in 1931,[29] and Rosenthal in 1935,[80] made major contributions to the literature of this disease until the past ten years. The papers mentioned previously, except for that of Rosenthal, regarded the disease as a result of the aspiration of vernix caseosa caused by intra-uterine asphyxia. In 1949, Miller and Hamilton presented the theory that the membrane might be the result of irritation of the pulmonary tract epithelium with resulting injury and sloughing of the epithelium. Miller and his workers presented a large amount of material on the subject in 1950, in which they seriously questioned the importance of the aspiration of amniotic fluid as an etiological factor.[62, 57] This work seemed to stimulate other investigators

and since that time a large amount of work has been done and numerous important articles have been written. Tran Dinh De and Anderson exhaustively reviewed the entire literature of this disease in 1953. In a brief resume of the history of the literature of hyaline membrane disease such as I have attempted to do above, the name of Edith Potter must not be omitted. Since she has devoted so much of her time to the pathology of the fetus and newborn, she has had considerable influence in numerous experimental and clinical investigations of pulmonary hyaline membrane disease.

The topic of hyaline membrane disease is broad, encompassing fifty-two years of experimental and clinical work by many investigators. In spite of the recently intensified search for the etiology of this disease, the clinico-pathological puzzle presented by these infants has remained unsolved. Because of the large number of proposed etiologies and the vast amount of experimental evidence which has been accumulated to support each theoretical pathogenesis, this paper will not present an exhaustive review of the literature of this entity. I shall limit the discussion of all etiologies, except that of heart failure, to a brief review of the literature. The treatment of hyaline mem-

brane will be discussed only as it pertains to the heart failure theory. This is not to say that the present day accepted therapy such as high humidity and low oxygen tension are faulty, but only to admit that a complete discussion is not within the scope of this paper.

Before briefly discussing the various etiologies which have been considered in the past and present, a summary of the developmental anatomy of the lung, the clinical picture of these infants and the pathology found at autopsy should enable us to better understand the problem presented to investigators of this disease.

There are more than 150 papers on the subject of the development of the lung and the way it expands. Since 1923, it has been agreed that alveoli are not present in early fetal life but develop during the intrauterine existence of the fetus. The way in which the alveoli form and their final appearance, prior to and following delivery, have been and still are subjects of debate.

The pulmonary system begins as a local expansion of an entodermal tube which becomes separated from the foregut by a longitudinal constriction. The short cylindrical appendage which is the result of this constriction branches dichotom-

ously and the resulting branches continue to divide and form numerous branching tubes which will give rise to future bronchi. Distal branching continues until large numbers of small bronchi and bronchioles lined by tall columnar cells are formed. Beyond these, the early alveolar ducts are lined by a continuous layer of large cuboidal cells. The mesenchyme into which this entodermal tube grows is also proliferating, and at first this growth is rapid enough to cause the entodermal branches to be widely separated. The relative amount of connective mesenchymal tissue begins to decrease, and by the normal time of birth only a few connective tissue cells remain in the walls of the alveolar ducts and alveoli. Early in lung development, the blood vessels lie in the mesenchyme a distance away from the tubular branches. The capillaries gradually grow out and lie adjacent to the outer surface of the single layer of cells composing the walls of the tubules. When the fetus weighs about 400 grams, the capillaries leave the mesenchyme and penetrate the tubules lining. This ingrowth is associated with elastic fiber elaboration and the tubular cells are pushed aside so that the capillary loop is in contact with the lumen of the tubule. After capillary ingrowth has started it

continues at a rapid rate, and the cells lining the tubules continue to proliferate, forming new branches which are subsequently invaded by capillaries.[9,11,13,66,69] The concept of lung development just presented is that of E. L. Potter and is based on the study of large numbers of autopsies of human fetuses as well as experimental animal studies. Most investigators agree with this concept except to the point where capillary ingrowth begins. Those who dissent with the capillary ingrowth theory feel that the primitive alveoli are lined with cuboidal epithelium which has the capillaries lying on its outer surface. When respirations begin the epithelium is flattened out and the remaining epithelial cells are the lining cells of the alveoli. Windle is one of the chief supporters of this theory.[95] Those who do not agree with him feel that the lobed vesicles formed by capillary ingrowth are unexpanded alveoli and when they are expanded resemble adult alveoli. They feel the role of the epithelium which lines the primitive air passages is solely that of canalization; and except for the size of the lumens of the alveoli and alveolar ducts, there are no differences in the histologic structure of the lung of the fetus before, during, or in the first hours following birth.[9,13]

Much of the dissension about alveolar development has been a direct result of anatomists' inability to agree upon the presence or absence of an alveolar lining epithelium. Controversy on this subject has been extremely bitter since von Kolliker supposedly first saw an epithelial lining of the alveoli in 1881. Since that time he has been supported by W. S. Miller, Bremer, Sprunt, R.D. and S. H. Bensley and others. Among his prominent opponents are Loosli, Adams, Thornton, Palmer, Fried and Potter.[32] In 1952, Low, using an electron microscope demonstrated a pulmonary epithelium in the lung of rats. In 1953, he reported the same situation in the lungs of man. His opinion is that the cytoplasm of the cuboidal epithelial cells becomes attenuated to form a complete lining of the alveolar wall.[32] Other investigators have reported the presence of a definite lining epithelium with a basement membrane, which is distinctly separate from the capillary walls.[32] The question as to a definite epithelial lining is still unanswered, and it will be noted later in this paper that this is one reason for some of the controversy concerning the etiology of pulmonary hyaline membrane disease.

S. B. Rose and W. R. Waddell are the prominent investi-

gators who disagree with the branching entodermal tube theory of lung development. Rose feels that the lung develops in two units; the bronchi forming from the entodermal bud and the alveoli from the capillaries and septal cells which differentiate from the mesoderm of the fetal lung and secondarily join the bronchi.[79] Waddell states that the lung is derived from toti-potent mesoderm whose direction of growth and differentiation is induced by the stimulus rather than the proliferation and migration of previously formed structures.[90] Potter concludes that after examining lungs from over eight thousand human fetuses and infants plus studying one hundred specially prepared lungs and experimental work, the lumens of all portions of the pulmonary tree are continuous at all times with that within the first entodermal bud.[70]

Because some feel that intrauterine respirations are necessary for normal lung development and others have attached great significance to the aspiration of amniotic fluid as a cause of pulmonary hyaline membrane, a few of the investigations regarding these respirations will be discussed. Ahlfield (1905) described rhythmic movements of the abdominal wall of women in the last months of pregnancy and interpreted them as being fetal

respiratory movements. No one agreed with his views until Reifferscheid (1911) confirmed the presence of these movements. The latter investigator considered the fetal respiratory movements to cause the flow of amniotic fluid only as far as the tracheal bifurcation; Ahlfield's opinion being that the amniotic fluid reached the alveoli.[27] Snyder and Rosenfeld (1937) also observed rhythmic movements of the mother's abdominal wall in humans and animals, and demonstrated that the amniotic fluid entered the alveoli since the alveoli and amniotic sac were considered to be in direct continuity.[86] They also examined rabbits in various stages of gestation following hormonal inhibition of labor and sectioning of the mother's spinal cord. They found rhythmical excursions of the chest wall and diaphragm of the fetus. These movements occurred while the fetus was at rest as well as during periods of general body activity.[85] Barron examined the fetuses of sheep and discovered the same type of respiratory movements as described by Snyder and Rosenfeld. He also observed that during these movements the volume of the fetal lung was not altered because the chest was not rigid. Even though the respiratory muscles were contracting they could not cause enlargement of thoracic cavity, the

elasticity of this structure causing it to collapse instead.[8]

Many investigators have attempted to demonstrate the presence or absence of intrauterine respiration by injection of various substances into the amniotic sac prior to delivery. The lungs of the fetuses were examined following delivery to determine if any of the material injected was in the alveoli. Reifferscheid and Schmiemann demonstrated radiopaque material in human fetal lungs following the injection of Umbrathor into the amniotic sac. They also described it as moving rhythmically back and forth in the bronchial tree when the fetus was examined in utero by fluoroscopy.[72,4] Potter injected thorotrast into the amniotic sac of human fetuses immediately prior to Caesarean section and there was no evidence of the material in the lungs following delivery. If the thorotrast was injected twelve to twenty-four hours prior to delivery it was demonstrable in the lungs of the delivered infant. She concluded that sufficient time had to elapse for enough water to be absorbed from the lungs to concentrate the particulate thorotrast and appear on roentgenograms. The material was also demonstrated histologically in those infants that died.[21] Snyder and Rosenfeld injected india ink into the

amniotic sacs of rabbit fetuses which were directly observed to be breathing. After a few minutes the lungs were examined and carbon particles were found in the alveoli. They also pro-duced apneic fetuses by administering sodium pentothal to the mother and injected the ink into the amniotic sacs. Histological examination revealed no carbon particles in these lungs.[86] Those who do not believe the presence of physiological intrauterine respirations point out the ease with which intrauterine respiratory-like movements may be produced by a variety of stimuli. Arey and Dent have also pointed out that the pregnancies which were interrupted in Potter's study should probably be considered ab-normal.[4] Windle is the chief opponent of those who have demon-strated intrauterine respiration. He has done large numbers of experiments on pregnant animals and he cautions: "Under experi-mental conditions it is very easy...to start respiratory move-ments."[95] One of his experiments consisted of injecting thorotrast into the amniotic fluid about the head of the guinea pig late in gestational life by means of a long, fine needle inserted through the abdominal and uterine wall. Under such physiological condi-tions he could demonstrate no aspiration of the material roentgeno-grsphically[96]

He also contends that the fetuses used in Potter's

study were subjected to anoxia during delivery and this was cause of the thorotrast inhalation. Potter points out that if this were the case, thorotrast would have been present in the lungs of all the fetuses, regardless of the time interval between injection and delivery, which was not the case. She also explains Windle's inability to demonstrate thorotrast in the lungs of his experimental animals by pointing out his failure to wait a sufficient length of time before sacrificing the fetuses.[70] The result of these differing viewpoints is that it has definitely been shown that respirations can occur in utero, but agreement can not be reached as to the physiological importance of this phenomenon.

Since no one agrees as to the presence of intrauterine respiration, it is easy to see why there is a difference of opinion as to the significance of amniotic debris in the alveoli of the fetal lung. If intrauterine respirations with a flow of amniotic fluid into the alveoli were normal, then the lungs of all infants dying in the first few days of life should contain amniotic debris. Farber, et al., do not believe that debris can be demonstrated in all of such lungs,[27] but those who believe intrauterine respirations are physiological explain its

apparent absence as being caused by the marked dilution which may be the result of either increased amniotic fluid or the decreased amount of solids in the fluid, or both. They also point out that the distribution of debris in the lungs may be patchy and if enough sections are examined characteristic amniotic fluid contents will be found.[72] Many pathologists have labeled aspiration of sterile amniotic fluid as a cause of death. If intrauterine respiration is physiological, this cannot be done, unless perhaps massive amounts of debris are present in expanded alveoli. The presence of amniotic fluid in the respiratory passages of the lung has also been chosen by some as the etiological agent of hyaline membrane disease. As the question of physiological intrauterine respiration is unanswered so are many of the questions surrounding deaths of premature infants.

Some investigators have attempted to prove the presence of intrauterine respiration by claiming that normal development of the alveoli will not occur without these respirations.[95] Potter and Bohlender examined two fetuses in which lung tissue was not connected to the trachea in one, and the trachea was completely obstructed in the other. Histological examination

revealed normally developed alveoli.[72] Arey also examined an accessory lung which was not connected to the trachea or bronchi and found it to contain bronchi and, "...cystic spaces suggesting alveoli..."[4] In spite of these observations which seem to prove that continuity with the amniotic sac is not necessary for normal alveolar development, Potter reports over thirty cases which tend to refute this. In these cases there was renal agenesis or other urinary anomalies. There was no record of any amniotic fluid being seen by the mother or the attending physician. The lungs almost always showed an extreme inhibition of growth, there being minimal capillary ingrowth and often cuboidal cells lining much of the pulmonary tree. She points out that these "experiments by nature" seem to point out the necessity of fluid within the lumen of the pulmonary tree for normal development.[70]

Since, as will be shown later, pulmonary hyaline membrane occurs most frequently in premature infants, many investigators have considered the possibility of death occurring as the result of prematurity alone. Since statistics show that fetuses weighing about 1000 grams can survive, the question arises whether the lung might show a stage of development less mature than

that of the body as a whole. In order to discount this as a cause of death in the group of infants who die a respiratory death, Norris et al., examined the lungs of 493 fetuses and judged the fetal age from the appearance of the lungs. No disproportionate immaturity was found in this study.[66]

Potter has studied the pathology of fetuses extensively, and she has found that in a fetus which weighs approximately 1000 grams capillary ingrowth in the lungs is sufficient to provide an adequate vascular area to oxygenate the blood and support life.[69] Thus it is seen that the migration of capillaries from the mesenchyme to an exposed portion of the pulmonary tree is probably the most important aspect of development as far as survival of the fetus is concerned. Prior to the age of six lunar months there is a thick layer of mesenchymal tissue between the air containing sacs and the capillaries and respiratory function would be seriously impeded if birth should occur at this time. The capillary bed continues to proliferate throughout gestation and each succeeding week the lung becomes progressively better adapted to adequate oxygenation.[66] Thus, immaturity of the lung can cause death but it will be pointed out later that the highest

incidence of hyaline membrane disease is in infants weighing more than 1000 grams.

In 1955, James Arey made the statement that, "pulmonary hyaline membranes are now the most frequent significant pathologic finding in premature infants dying during the neonatal period."[3] A look at several series reported in the literature reveals the frequency with which hyaline membrane has been seen in neonatal deaths of premature infants has varied from 2.5 per cent reported by MacGregor in 1939, to a high of 50 per cent reported in 1947 by Ahvenainen and in 1949, by Miller and Hamilton.[16] In all of the recent series, such as that of Arey and Dent in 1953, hyaline membranes have been the leading cause of death in liveborn infants.[4, 14, 22, 36] In Chicago between the years 1936 and 1949, there were 10,021 post mortem examinations of infants of age less than one year. As reported by Wallace, abnormal pulmonary ventillation due to either extensive primary atelectasis or secondary atelectasis with hyaline membrane accounted for half of the deaths.[77] Changing these percentages into numbers of deaths per year, we find that in 1950 it was estimated that between ten and twenty thousand premature infants died with a hyaline-like lining in

their lungs.[16] In 1955, this estimate had risen to approximately one in every four hundred live births, or 25,000 infants per year.[94] Some investigators have thought that the disease seems to be becoming more common, others believe this increase is only apparent and is the result of better recognition of the entity as well as an increased number of better qualified examiners of the pathological specimens.[83]

The lesion that seems to be the cause of this large number of deaths is found exclusively in liveborn infants, most often in the premature and those delivered by Caesarean section. Miller and Hamilton apparently reported hyaline membranes in four stillborn infants, but their description of these lungs contained the statement that the hyaline-like material was never in the form of membranes lying against the walls of the air spaces.[61] A series of autopsies by two different groups on 646 stillborn infants revealed no pulmonary hyaline membranes.[16,45] About 90 per cent of hyaline membranes occur in infants weighing less than 2500 grams with the peak incidence occurring in the 1500 to 2000 gram group.[22] Approximately 4 per cent of the cases of hyaline membrane occur in infants weighing less than 1000 grams. The hyaline material

in the lungs is practically non-existent in infants who are delivered vaginally and weigh more than 3000 grams at birth, however, they do occur.[62] Infants who die of this lesion rarely die before four hours of age, never before one hour, and survive less than one week. Most of the babies die in the first forty-eight hours when the cause is uncomplicated pulmonary hyaline membrane.[1, 14, 18, 69] Potter emphasizes the limited time of onset and duration by stating: "If the newborn does not show symptoms of respiratory distress within five hours, and if he does not die within the first thirty-six hours, he will not die of hyaline membrane disease."[77]

In contrast to the specific weight groups of infants stated above, the clinical picture of hyaline membrane disease is found disproportionately often among infants of all weights delivered by Caesarean section. One series has shown the presence of hyaline membranes in 70 per cent of infants dying after Caesarean section compared with 41 per cent of infants dying after pelvic delivery.[14] Although there have been numerous reasons proposed for this difference, some of which will be discussed later, the fact remains that there is no single explanation for the increased frequency of hyaline membranes

in these infants.[4,97]

Since it was shown that there is definitely an increase in the incidence in hyaline membrane formation in infants delivered by Caesarean section, the pregnancies of mothers whose infants died of this disease have been closely examined. Among the complications present when an infant had hyaline membrane disease were toxemia, multiple pregnancy, premature separation of the placenta, placenta previa, cord around the neck, breech delivery and erythroblastosis fetalis.[43] When these cases were examined in large groups rather than individually, it was seen that there was no statistical significance to the correlation of the two diseases. In a number of series of cases of hyaline membrane, the group of infants having the characteristic histological findings were the group delivered by mothers whose pregnancies and deliveries had been without complications.[45,61,62,89]

An increased incidence of hyaline-like membranes in the lungs of infants of diabetic mothers has been pointed out. This is especially true in those delivered by Caesarean section.[45] There appears to be no correlation of the mother's age, parity, race, serology, Rh factor or the type of analgesia used, with the incidence of hyaline membrane formation. The only factors

which have any constant relationship to hyaline membrane disease are prematurity and Caesarean section.[45, 55]

The clinical picture of these premature infants has been described as being so characteristic that a correct diagnosis can be made ante mortem.[4] This feeling is not shared by all and although Miller and Jennison state that there is nothing pathognomonic of the clinical course of these infants to distinguish them from infants who have other serious diseases,[62] most investigators feel that the diagnosis can be suspected but not made with certainity.[22, 74]

It has been stated by many writers that infants dying of hyaline membrane disease usually breathe spontaneously at the time of birth,[4, 39, 62, 69, 71, 73] however, it is often overlooked that these writers say usually. Closer examination of these various papers frequently reveals that the authors describe these infants as either exhibiting signs of asphyxia at the time of birth or breathing normally. Some recent papers have revealed that only 50 - 60 per cent of infants who later died of hyaline membrane disease were in fair to excellent condition at the time of birth.[3, 34, 45]

Those infants who are breathing well at birth usually

do so for a variable period of time, this period extending as long as twelve hours. Usually before twelve hours they begin to have recurrent attacks of respiratory distress which gradually become worse. These are characterized by labored breathing, increased respiratory rate, irregular respirations, cyanosis, costal and sternal retraction, a weak, high pitched cry, and gasping inspiratory efforts. The use of accessory respiratory muscles is usually great and the irregular respiratory efforts are vigorous.[1,28,69,97]

Physical examination of the chest while the infants are having distress reveals diminution in breath sounds and inconstant inspiratory rales at times, but often there are no consistent findings.[3,36,62,69] Miller has recently described a breathing pattern of these infants which is characterized by little or no abdominal or diaphragmatic participation.[60,74] At the present time an insufficient number of infants have been observed to warrant attaching too much significance to this finding.

The picture of respiratory distress described above may be produced by intraventricular or subdural hemorrhage, primary atelectasis, pneumonia, esophago-tracheal fistula, dia-

phragmatic hernia, pulmonary hypoplasia, congenital heart failure and neonatal pneumothorax.[25, 56, 76] This list of pathological entities points out the difficulty of a positive clinical diagnosis by physical examination of the infant.

Because of the difficulty in diagnosis and the presence of the pathological process in the lungs, one would assume that a large amount of time has been spent in the radiographic diagnosis of this disease. If much work has been done, little has been published. In 1945, Caffey noted small opaque areas in the lungs of the premature but dismissed their pathological significance. He called them roentgenographic evidence of physiologic atelectasis and adds that four to six weeks may elapse before the lungs of the premature are fully expanded.[17] Dr. Hardy reported at the fifth M & R conference in 1953, that roentgenographs of an infant with hyaline membrane disease at six to eight hours of age showed miliary foci of atelectasis in the lungs and films at twenty-four hours showed involvement of almost the entire chest.[74] Donald and Lord (1953) reported some cases in which radiological opacities were correlated with hyaline membranes at autopsy.[25] Two months later, Meschan published a case of proved hyaline

membrane disease and presented radiographs of the lungs which showed unusually good aeration. He explains this paradoxical situation of good aeration radiographically and clinical evidence of asphyxia by pointing out that the dilated terminal bronchioles and alveolar ducts obscured the collapsed alveoli.[56] Also in 1943, Donald and Steiner described in detail the radiographic findings in infants who were proved to have hyaline membranes in their lungs.[25] These signs will be presented shortly. In 1954, a group of Cuban investigators reported the same findings shown by Meschan.[87] During the fifteenth M & R conference in 1955, it was reported by Clifford that Pendleton and Peterson described the chest x-ray of infants with hyaline membrane disease as having a homogeneous ground glass appearance.[77] Regarding the physiological atelectasis described by Caffey, radiographs by Donald and Steiner have shown complete radiological pulmonary expansion in normal full-term and premature infants within thirty minutes after birth.[56, 88]

The reason for the few reports of radiographic findings in hyaline membrane disease is probably the result of the traditional "no touch" technique used in the care of infants in respiratory distress. Donald and Steiner have described the ease with

which radiographs may be obtained in such instances, and point out the aid in clinical diagnosis such films provide.[25]

The specific radiographic shadows visible when hyaline membranes are present represent the atelectasis associated with the disease and are not specific for the lesion of hyaline membrane. The findings tend to follow a definite sequence, and this is the reason serial radiographs are essential for the positive clinical diagnosis. Donald and Steiner identify three different stages of hyaline membrane disease radiologically and their description is as follows:

> "1) First there appears a fine miliary mottling throughout the lung fields.
> 2) This is followed in the progressive lesion by a coarser and more coalescent type of opacity. At this stage the bronchial tree is often clearly demarcated.
> 3) Finally the shadows become confluent as a result of lobar or lobular consolidation and collapse."[25]

All of the main types of the above picture may be found at the same time or may follow in succession over a period of hours or days. If the course of the disease is progressive, the mottling coalesces as described above. If the disease improves, the mottling slowly resolves and the lung fields ultimately become clear.[25]

In the clinical differential diagnosis of hyaline membrane disease, radiography is useful in differentiating it from intra-

cranial hemorrhage, esophago-tracheal fistula, diaphragmatic hernia and pneumonia. If hyaline membrane is complicated by pneumonia, however, accurate roentgenographic diagnosis is very difficult.[88, 94] A method of differentiating hyaline membrane disease from primary atelectasis is described by Donald and Steiner.[25]

When the diagnosis is made, if it can be made clinically, in any specific case, what is the prognosis? Although mortality is often stressed when hyaline membrane disease is discussed, Clifford claims "...the vast majority of infants passing through this period of extreme respiratory distress...do recover."[74] Miller and Jennison point out the contrast between the respiratory difficulties seen in infants dying with a large amount of hyaline material in their lungs and those observed in infants who survived. They conclude that infants showing marked distress, with or without sternal retraction, have little chance of recovery. Potter believes the early symptoms fail to progress in about 50 per cent of cases, but also remarks that few infants with severe symptoms recover.[70] The complication of pneumonia also changes the prognosis. It is a rare complication in infants dying in the first twenty-four hours, but in infants living more

than forty-eight hours, Potter states she has never found an uncomplicated case of pulmonary hyaline membrane. Death of these infants is caused by the superimposed pneumonia.[70] In infants living only twenty-four hours or less, death is the result of abnormal pulmonary ventillation with final asphyxia. There is some debate as to whether this decreased ventillatory capacity is caused by the hyaline membrane which forms a barrier to oxygenation of the blood or is due to the atelectasis present, but many pathologists now feel death is caused by the latter.[55,70]

Autopsies of infants dying of pulmonary hyaline membrane disease reveal characteristic findings. Dick and Pund, as recently as 1949, were among the first investigators to emphasize the importance of these findings as a cause of death.[24] The changes are limited to the lungs except for evidence of asphyxia in the other organs (petechia and sometimes ecchymoses). Cardiomegaly has been noted in some cases.[58]

The gross appearance of the lungs is that of well expanded organs which have the consistency of liver. They are a uniform dark red-purple and weigh more than normal. These non-crepitant lungs have sharp, firm edges, and small to moderate amounts of fluid exudes from the cut surfaces.

The whole lung or individual portions sink when placed in water.[4,24,69] If the infants have survived more than forty-eight hours, signs of an inflammatory process is usually superimposed.[69] Since other pulmonary lesions may simulate pulmonary hyaline membrane grossly, microscopic examination must be done for a positive diagnosis to be made.

Although Hoccheim was the first to describe the presence of this peculiar membrane, it was not until 1925 that Johnson and Meyer described the complete histological findings of this disease. Since that time Farber, Potter and Arey are the pathologists who have published the most accurate accounts of the histological findings. Intense capillary engorgement is responsible for the color and the increase in weight, and is one of the most striking microscopic findings. The walls of many alveolar ducts and most of the alveoli are collapsed giving a solid appearance to the lung tissue lying between dilated alveolar ducts. These scattered dilated air spaces are lined by an irregular layer of homogeneous, finely granular eosinophilic material. This material is plastered firmly against the walls in most instances and if polymorphonuclear leucocytes are present, they lie in the lumen of the alveolar ducts. In the

majority of infants surviving less than thirty-six hours there is no evidence of infection but in the lungs of those living longer than this, the evidence of bronchopneumonia is commonly associated with the characteristic membrane. It has also been pointed out that the amount of hyaline material found in these lungs increases with the age of the infant.[4,29,69]

It should be pointed out, that even though hyaline-like membranes are found in the lungs, diagnosing hyaline membrane disease as the cause of death is not always correct. It has recently been pointed out that in many instances the hyaline-like membrane was an incidental finding rather than the primary cause of neonatal death.[58] Because of the difficulty in pathological interpretation in many premature infants, Brims and Shields believe the diagnosis of "hyaline-like membrane disease" should be made only when there is a history of an uncomplicated delivery and progressive respiratory embarrassment with death in one to five days, and the presence of hyaline-like membranes in the lungs as the only significant autopsy finding.[16]

The atelectatic areas of the lung which are a characteristic microscopic finding in hyaline membrane disease has recently become a subject of much debate. Prior to the 1950's the

question had been whether the atelectasis was primary or secondary. Dr. Potter had shown to her satisfaction that the atelectasis was secondary. Support is lended to this theory by the clinical findings of breath sounds which subsequently disappear and the histological absence of the "crumpled sac" appearance which is characteristic of the lung with primary atelectasis.[74] Her explanation of the atelectasis was accepted, and thus most of the arguments concerning hyaline membrane disease were about the origin of the membrane. As will be pointed out later, this hyaline membrane is not only found in premature infants, but also in older infants and adults dying of specific diseases. The microscopic picture of the lungs of these older patients does not show massive atelectasis, and this fact is what has aroused the recent interest in the almost forgotten collapsed alveoli.

In order for secondary atelectasis of the alveoli to occur in a perfectly developed lung, it must be the result of blocking communication of the alveoli to the outside air. If the hyaline membranes are the cause of this obstruction, it must be postulated that they occlude the orifices of the alveoli, which are actually shallow outpouchings of the alveolar ducts, being

almost as wide as they are deep. It is also pointed out that collapsed alveoli and dilated alveolar ducts should never be seen in the absence of hyaline membranes if they are the cause of the atelectasis. Dawson reports that careful examination of his slides has shown the characteristic alveolar ducts and atelectasis without the presence of hyaline membranes, and has never shown membranes present on alveolar ducts prior to atelectasis.[22] This work supports a paper by Ronstrom in 1953, in which he reported finding atelectasis in portions of the lungs containing no membranes.[76] The study of the origin of the atelectasis was prompted by Gruenwald who stated in the Fifth M & R conference that he believes the atelectasis found in the lungs of infants dying of hyaline membrane disease was more important than was the presence of the membrane. His statement, "...I am beginning to feel that perhaps the hyaline membrane is an 'eosinophilic herring'.",[74] was supported by Anderson who revealed that he did not feel that the hyaline membrane was the cause of death and deplored the fact that the important atelectasis was being overlooked.[74] If, then, we question the atelectasis as being secondary to the presence of hyaline membrane, a look at a paper on atelectasis of the

newborn published in 1933 by Farber and Wilson, may help in formulating a cause for the alveolar collapse. These investigators presented several causes for atelectasis in a well developed lung. These included the thought that cohesion of the moist surfaces of the air passages in the fetallung offered resistance to the entrance of air and was the initial resistance to lung expansion. When any complications were present this resistance might prove sufficient to prevent expansion with resulting atelectasis. Of the possible complications, they considered an imperfect or injured respiratory center, a poorly developed muscular and skeletal thorax or bronchial obstruction due to aspiration of amniotic sac contents, mucus or blood.[28] The presence of surface tension offering resistance to the entrance of air into the lungs has recently been shown by Gruenwald.[35] Perhaps the atelectasis is the primary lesion with the spectacular red membrane merely being an interesting but innocent finding. A discussion of the proposed etiologies of this disease may help in deciding.

A large number of theories have been forwarded to explain the pathogenesis of hyaline membrane disease. One of the most important reasons for so many proposals is the relative

ease with which a pink membrane may be produced in the alveolar ducts and alveoli of the lungs of experimental animals. Several of these successful experimental methods are intratracheal injections of amniotic fluid or various irritating substances, bilateral vagotomy, oxygen poisoning, carbon dioxide poisoning and irradiation. Although all of the above produce hyaline membranes few have consistently produced an appreciable amount of atelectasis. Because of this, several investigators have questioned the relationship of the experimental membranes and the pathological picture seen in autopsies of premature infants.[22,23,45] As the significance of the lack of the characteristic anatomic picture in animals has just recently been stressed, many of the "typical" membranes which are discussed in the literature of the experimental investigation of this disease should be re-evaluated.

Recently attention has been focused on the production of atelectasis experimentally. Peck and Levin have enumerated the major requisites for the development of atelectasis. These are mechanical obstruction, sufficient distal circulation to allow gas absorption and the absence of an accessory tract for air entry distal to the obstruction. They also point out

that the normal lung has safeguards against the production of atelectasis, several of which are, an efficient ciliary action, efficient collateral respiration, an efficient cough mechanism and the absence of foreign material in the bronchi.[100] In the immature infant the majority of these safeguards are either absent or underdeveloped. The absence of atelectasis in the adult and the experimental animals whose lungs have the hyaline-like membrane could be explained by the presence of these protective mechanisms. If this were so it would be logical to assume that experimental production of hyaline membrane plus atelectasis could be accomplished by using premature or newborn animals. Tran Dinh De and Anderson subjected nineteen neonatal guinea pigs to high oxygen concentrations (oxygen poisoning) and observed membranes and atelectasis in eleven, or 57.9 per cent, of them.[23] Bruns and Shields produced hyaline membrane with atelectasis in six neonatal guinea pigs using high oxygen concentrations. In two of the six cases a bilateral vagotomy had also been performed, and the most marked atelectasis was seen in these animals.[15] The above discussion would suggest that there is a special predisposition on the part of the newborn lung to the

entity of typical hyaline membrane disease.

Now that some of the problems facing the investigators of this clinical and pathological entity have been presented, some of the etiologies they have postulated will be discussed. The two basic theories for the production of hyaline membranes have existed for almost thirty years and may be designated as the exogenous and the endogenous theories.

The exogenous theory, which implies that the membranes are formed from amniotic fluid or its contents, or are the result of the inhalations of this material, may be subdivided to ease its discussion. Included in this group for ease of presentation will be those theories which indicate the membranes to be the result of other factors in the environment of the fetus.

The first etiology that shall be discussed is aspiration. This was the etiology proposed by Johnson and Meyer in 1925. They thought the membranes might be the result of inhalation of caustic substances used during the delivery, so they attempted to produce the membranes experimentally by injecting lysol and soap intratracheally in animals. When these failed, they instilled egg albumin and observed the formation of membranes. This suggested to them that the membranes

were produced by the aspiration of amniotic fluid prior to labor with the formation of a viscous material from the aspirated cells and fat. As soon as respirations occurred, they believe the air passages became choked with this viscid substance and asphyxia resulted.[39] In 1932, Farber and Wilson instilled india ink, horse serum and fibrinopurulent exudate intratracheally in excised lungs which were then subjected to vigorous artificial respiration. A hyaline membrane which lined the alveolar walls was produced. When they instilled diluted hydrochloric acid in an attempt to reproduce the membranes Winternitz showed with this method, they found edema fluid and hemorrhage in the alveoli. The vascular lesions overshadowed the small amount of alveolar wall necrosis and membrane formation. In this same paper they enumerate the factors they consider necessary for the production of hyaline membrane. These are the presence of material capable of taking the eosin stain, air in the alveoli, partial obstruction to the passage of air, and dyspnea and violent inspiratory efforts which push the inspired air past the obstruction.[30] Ahlstrom (1942) supported the concept of aspiration of amniotic fluid as the etiology and felt that the

condensation of the fluid in the respiratory passages gave rise to the membranes.[16] In 1949, Dick and Pund warmed centrifuged amniotic fluid and placed it in the tracheas of heated lungs of stillborns under positive and negative pressure. They described the presence of typical membranes in these lungs.[24] Miller and Hamilton (1949) used sixty-seven dogs and rabbits as experimental animals and failed to produce membranes with the intratracheal injections of vernix caseosa, meconium and amniotic fluid.[61] In 1951, Blystad and Landing reported the production of hyaline membranes when 15 - 20 cc of amniotic fluid was injected intratracheally in one cc. amounts over a long period of time. Dr. Landing pointed out the sharp inner borders of the membranes, the presence of the hyaline material obstructing a respiratory bronchiole, the intact epithelium underlying the membranes and the presence of squamous cells between the membrane and the epithelium in slides taken from the lungs of infants dying of hyaline membrane disease. He summarizes from these findings and the clinical course of these infants that the hyaline material is present in the lungs at the time of delivery and is derived from the protein of the amniotic fluid by a process of concentration. As a result of

extrauterine respirations of at least one hour in duration this material is plastered against the respiratory epithelium, sealing off the alveoli so that they can not expand; or if they have expanded, cause them to collapse.[14, 74] An English investigator, Claireaux, found on microscopic examination of the hyaline membrane that it was not as homogeneous as it had been described by others. In areas where it was fragmentary he felt that it was in the process of formation and described a cellular structure in which he could sometimes make out a faint nucleus. In his paper, which was published in 1953, he postulates that the membrane is formed of the flat, non-hyalinized, squamous cells of the amniotic fluid, which clump together and lose their cellular outlines. He states that if a sufficient number of microscopic sections are examined, this progressive formation can be identified and traced. In a successful attempt to reproduce these membranes he centrifuged amniotic fluid, suspended it in saline and allowed it to incubate for seven to ten days, recentrifuged the suspension and ground the deposit. This was resuspended in sterile saline, an antibiotic added, and injected intratracheally in six rats. Hyaline membranes were produced in any rat living more than two hours.[18]

Those who believe that amniotic fluid and its contents produce hyaline membranes feel that intrauterine respiration is not a physiological phenomenon, but the result of prenatal anoxia. Schenken summarized their views when he wrote that respiratory movements in utero are variable, but not significant, and it is probably abnormal for the fetus to aspirate large quantities of amniotic fluid.[82] The theory that excessive amounts of amniotic fluid are aspirated as the result of intrauterine anoxia with vigorous respiratory movements is where opponents of the aspiration etiology begin their attack. Pulmonary hyaline membrane rarely occurs in infants who survive for a time after premature placental separation, and frequently when hyaline membrane is present, there is no evidence of preceding anoxia, since Caesarean section and premature delivery should not be accepted as "prima facie" evidence of anoxia.[70] It has been previously pointed out that the pregnancies of the mothers of these infants are uncomplicated and no known reasons for anoxia are present. Dr. Eastman points out that anoxia does not regularly excite the fetus,[74] and experiments done by Snyder and Rosenfeld in 1937, revealed some interesting results of intrauterine anoxia. They caused an oxygen deficiency to occur in fifteen different experiments on fifty-three

animal fetuses still in utero and found that respiration was depressed in all cases. A deficit of CO_2 caused respiratory depression in all thirteen experiments on thirty fetuses and CO_2 excess caused respiratory stimulation in eight of twenty-four experiments using seventy-eight fetuses, there being no effect in sixteen.[85]

In an attempt to produce hyaline membranes by intratracheal injection of amniotic fluid, Potter inserted a cannula into the tracheas of adult rabbits and injected 150 cc. of fluid. The animals were sacrificed immediately and the weight of the lungs of one animal was 35 grams, or normal, thus indicating that the fluid had been absorbed almost as fast as it was injected. Later she instilled amniotic fluid into the tracheas of two anencephalic infants. Autopsy revealed no hyaline membrane in the case on which a post mortem was performed and there were no clinical signs of hyaline membrane disease in the other.[74] Since the lung absorbs fluid so rapidly, Gruenwald has stated that "...it is unreasonable to assume that the fluid found at autopsy in the alveoli of infants who survived for several hours is amniotic fluid in origin."[34]

Another argument against this etiology was pointed out by Miller when he showed how artifidal some of the experiments are which seemingly prove this pathogenesis. An example of this was the relatively large amounts of fluid Blystad injected to form these membranes. If the same relative amounts were aspirated by the fetus, it would have to inhale 100 - 150 cc. of amniotic fluid.[55,74] Finally, the opponents of this theory point out that premature live born infants are not likely to aspirate amniotic sac contents. Wilson and Farber concluded as a result of their experiments, that aspiration was not as an important problem in prematures as it was in full term infants.[28] John Labate, in a review of the causes of neonatal death at Bellevue Hospital, stated that aspiration of amniotic fluid in massive amounts was much more common in the term infants than in the viable prematures.[42] Since "...hyaline-like membranes were almost exclusively observed in premature live-born infants, the group...least likely to aspirate amniotic sac contents,...it seems unlikely that aspiration produced them."[61]

Only a slight deviation from the aspirated amniotic fluid theory, is the theory that the membranes are formed of aspirated vernix caseosa. One of the main reasons for this

theory was the obser ration by some observors that the hyaline membranes stained red with Sudan IV. Blystad and Landing, as well as others, have failed to see positive fat stains in these membranes, and thus this etiology has a very shaky foundation.[14] The main supporters of this theory were Farber, MacGregor and Dick and Paul. All of the arguments against the aspiration of amniotic fluid theory pertain to this one.

Other investigators, who feel, as does Gruenwald, that the fluid in the lungs at autopsy was not present at the time of delivery, have postulated another theory of aspiration. Gellis was the first to propose that infants delivered by Caesarean section swallow a large amount of amniotic fluid and subsequent regurgitation with aspiration and irritation might form the hyaline membranes.[31] He has been supported by Ahvenainen, Ylppo and Ranstrom.[1,75] The latter believes the membrane is formed as a result of the deleterious effect of the gastric juice on the bronchial alveolar epithelium, together with exudation of protein material.[99]

Another exogenous cause of hyaline membranes which has been proposed is infection. In the early literature most of the descriptions of lungs with hyaline membranes were under the

title of aspiration pneumonia. This was the result of the fact that many of these first cases studied also showed bronchopneumonia.[16 55] Miller and Hamilton suggested that an intrauterine inflammatory reaction might injure the epithelium of the air spaces and result in hyaline membrane formation.[61] The resemblance of this membrane to that seen in older individuals dying of acute pulmonary infections of various kinds also suggests the possible role of infection as an etiologic agent. As Potter[70] and also Ranstrom[76] have pointed out, inflammation is absent in many of the cases, especially in the lungs of infants surviving less than thirty-six hours. Thus it seems improbable that pneumonia is responsible for the membrane formation.

Another theory in which the membrane is the result of environmental factors is that of epithelial damage. As early as 1923 the theory of aspiration of an irritative substance was postulated. W. C. Johnson suggested at that time, that the membranes were the result of the aspiration of some irritating substance, probably during labor or birth.[38] In 1949, Miller and Hamilton suggested that the hyaline membrane was due to injuries, probably sustained during fetal life, which involved the epithelium of the terminal air spaces and also the vascular

bed of the lungs. They pointed out that an injury to the terminal air spaces of the fetus would not necessarily be fatal until the organism became dependent on respiration for oxygenation of the blood. They described many of the bronchioles and alveolar ducts of these lungs to be denuded of epithelium, and failed to find hyaline membranes overlying intact epithelium of the respiratory passages. They thought they could correlate the extent of membrane formation with the amount of epithelium lost in the lungs studied by them. They admitted that they did not know the identity of the injurious agent, but suggested an intrauterine infection.[61] In 1951, Miller and Jennison advanced the concept that the agent which injures the lung also precipitates labor. The circumstantial evidence they gave to support this idea was if the agent injured the lung without precipitating labor, hyaline membranes would also be found in the lungs of stillborns.[62] The concept of epithelial irritation by aspirated gastric contents has already been discussed. Bruns and Shields in 1951, postulated that intrauterine anoxia and high oxygen concentration therapy caused epithelial and capillary injury and aided in the formation of hyaline-like membranes.[16] In 1954, these same

investigators reported that microscopic examination of experimentally produced hyaline membranes revealed their epithelial origin. They stated that they coulddemonstrate the progressive stages in the transition of a normal intact epithelium, via cellular degeneration, into a hyaline-like membrane.[16] Tregillus published a paper in 1951 in which he postulated that all infants with hyaline membranes probably suffered from anoxia prior to the formation of the membrane and that this anoxia was the cause of necrosis and hyalinization of the bronchiolar epithelium. He states that the tissues of immature infants are more susceptible to the injurious effects of anoxia than are mature tissues. He describes necrosis and hyalinization of the bronchiolar epithelium with fusion and formation of a membrane.[89]

Opponents of the epithelial damage theory point out that many investigators have observed the hyaline membranes lying against an intact respiratory epithelium.[14, 29] Some have observed squamous cells lying between the hyaline membrane and the respiratory epithelium and others have observed the membranes to be separated from the epithelium by some distance.[14] Landing has suggested that the conclusions of

those who feel epithelial degeneration plays an important part in membrane formation, are due to the fact that the epithelium of the normal alveolar ducts is difficult to demonstrate.[74]

Another etiology which is closely allied to the one just discussed has been called "desquamative anaerosis." This was proposed by Rosenthal in 1935. He described congestion and edema of the submucosa of the respiratory epithelium resulting in cloudy swelling, fatty degeneration and detachment of the bronchial epithelial cells. During respiration he postulated that the detached mucosa folded on itself and obstructed the bronchioles. The pink staining membrane frequently found in these cases was considered by him to be the result of the degenerative process of the epithelial cells. He found "desquamative anaerosis" to be of equal frequency in the lungs of stillborn and liveborn infants who had shown clinical evidence of anoxia in utero.[80] Tregillus reported that he found desquamated fragments of bronchiolar epithelium similar to that described by Rosenthal in twenty-four of thirty-five lungs with a hyaline-like membrane. He also found the same phenomenon in the lungs of 90 per cent of stillborn and 77 per cent of all liveborn infants. After pointing out that similar lesions have

been found in lungs of all ages in routine autopsies, he concluded that "desquamative anaerosis" was an agonal or post mortem change.[89]

Recently another item in the environment of the premature infant has been implicated as causing or helping cause the formation of hyaline membranes. This factor is the rich oxygen atmosphere present in the incubators in which these infants are kept. Pichotka first described hyaline membrane formation as a result of high oxygen concentrations in 1940. He used two groups of guinea pigs, four in each group. He kept the first group in a chamber with an atomosphere of 80 - 96.5 per cent oxygen until they died. Microscopic examination of the lungs of these animals revealed a broad hyaline band-like membrane which stained red with eosin and lay tight against the walls of the alveolar antra and alveoli. In the small bronchi this membrane seemed to be mixed with epithelial cells and he concluded it was a result of swelling and fibrinoid necrosis of the walls of the respiratory bronchioles and the "membranes" of the alveolar antra and alveoli.[68] In 1951, Bruns and Shields duplicated these results in guinea pig lungs using high concentrations of oxygen at sea level pressure.[16] In 1954, they produced hyaline membrane in 75 per cent of guinea pigs by exposure to 98 per cent

oxygen concentrations at sea level pressure. They described the membranes as being similar in specific and non-specific staining reactions to the ones seen in newborns and postulated that the membranes were the result of injury to the alveolar ducts and terminal bronchioles.[15] At the Fifth M & R conference, Anderson reported that the use of CO_2 concentrations of 10 - 15 per cent enabled the production of hyaline membranes in the lungs of experimental animals without raising the oxygen concentration as high as when oxygen was used alone.[74] In 1954, he and Tran Dinh De reported the experiments with neonatal guinea pigs in a high oxygen concentration which have been previously discussed.[23] Potter admits that the infants who develop hyaline membrane disease have been kept in rich oxygen atmospheres but she points out that the air in incubators at Chicago Lying-in Hospital has been kept at 50 per cent oxygen or less for many years and that many infants have the clinical symptoms before being placed in an incubator with a high oxygen concentration.[69]

The endogenous theory implies that the hyaline membranes are formed from the protein exudate within the lungs of the infant. The reason for pursuing this line of thought was the

inability of several investigators to accept the fact that the membranes were formed from material which was in the lungs at the time of birth. Gruenwald points out that the infants that do well immediately after delivery, the infants that live for hours and even days, and the ability of the lung to absorb fluid rapidly, seem to contradict the presence of sufficient amniotic fluid at birth to form a membrane. He also states that the amount of fluid remaining in the lung is probably dependent to a great extent on the circulation of the infant. A defective circulation would not only allow fluid present in the alveoli to remain there, but would also allow more fluid to escape from the vascular bed.[74] Since there is with the first inspiration, a fall in the pulmonary vascular resistance which increases the blood flow, the fluid which may be present in the alveoli could be rapidly absorbed. Ranstrom also believes that if the membranes were formed from aspirated amniotic fluid which was concentrated by fluid absorption, the amount of original fluid must have effectively prevented gaseous exchange. If, however, the fluid is an exudate from the capillaries, it might offer the means of obstruction to gaseous exchange.[76] It has been shown that the protein

content of amniotic fluid is low, especially when compared to the blood protein concentration.[55] Because of these views and others, which conflicted with the exogenous theory, experimental work has been devised to support the theory that the membranes are formed from post-natal edema fluid in the lungs.

Opponents of this theory point out the paucity of precipitated fluid in the alveoli, the sharp inner border of the membranes and the occasional epithelial cell between the membrane and the alveolar wall, and state that it is difficult to explain these findings with the pulmonary edema theory.[14,74] They also remark that if the fluid came from the lung the membranes would be found on the surfaces of the alveoli and alveolar ducts, but are almost exclusively found on the walls of the ducts.[22]

It is generally accepted by the group who support the endogenous theory that the edema fluid comes from the capillaries. The reason it escapes is not agreed upon, there being two main theories to explain this phenomenon.

One group feels that capillary wall damage is the reason fluid escapes into the alveoli. Arey points out the similarity of the hyaline membranes in the lungs of infants and the ones

found in the lungs of adults. He states that he believes the membranes have the same etiology, the common factor being vascular damage or increased capillary fragility.[4] Farber and Wilson describe the membranes found in various types of pneumonia and in newborns as having the same appearance and general staining reactions.[29] In practically all of the twenty-one diseases of childhood and adults in which there has been a hyaline membrane described, there is vascular injury with particular involvement of the alveolar capillaries.[55] Most of these diseases are a type of pneumonia, examples being streptococcal pneumonia, influenza, radiation pneumonitis, and rheumatic pneumonitis. Because Arey assumes the hyaline membrane of newborns to have the same etiology as the membranes found in these diseases, some of the proposed mechanisms of their formation will be noted. Wintermitz and his associates thought the membranes of pneumonia were a result of cellular necrosis caused by the action of some unknown agent. Goodpasture believed they were a result of injury to the pulmonary capillaries which resulted in an exudate entering the alveoli.[33] Wolbach offered the suggestion that the membrane was related to the action of air on some undefined body fluid or exudate. Farber and Wilson were of the

opinion that the membranes found in the lungs of pneumonia were autolyzed exudate which was subsequently plastered against the walls of the respiratory passages by inspired air. They pointed out the absence of exudate in the areas where membranes were prominent and the paucity of membranes in areas where the alveoli were filled with an acute inflammatory exudate.[29] Obendorfer emphasized the degree of vascular damage which is seen in influenzal lungs. According to Wells, inflammation changes the permeability of the vessel walls, so that protein, even fibrinogen, may pass through them.[29] Histologic examination of normal lungs which have been irradiated with large amounts of radiation reveal swelling and distortion of some of the pulmonary tract cells, formation of a hyaline membrane which is adherent to the alveolar walls and edema, congestion and swelling of the arterial walls.[92]

It is known that there is a marked tendency to hemorrhage in the immature fetus and Levine states the chief factor responsible is the increased fragility of the capillaries.[48] This fragility is probably caused by several factors, four of which are the paucity of vascular elastic tissue in the immature fetus, the low level of vitamin C, also perhaps the low level of vitamin P, and anoxia which is known to have a deleterious

effect on capillary wall integrity.[67]

Since the importance of the hyaline membrane without atelectasis has been questioned, perhaps so much dependence on the comparison of the infant and the adult lungs is not logical. There is seldom any atelectasis noted in the lungs of adults dying of the several diseases mentioned above. Capillary damage may be the method in which the protein which subsequently forms the hyaline membranes reaches the alveoli, but it would seem to be necessary to find fault with this etiology as the sole cause for the entire picture found in the lungs of infants dying of hyaline membrane disease.

Another group which supports the endogenous theory feels the accumulation of edema fluid in the lungs is the result of insufficient diaphragmatic activity. This decreased function of the diaphragm has been postulated as being caused by a poorly developed vagal mechanism in the newborn, and especially the premature.

In 1937, Farber, studying the problem of pulmonary edema, did bilateral cervical vagotomies in rabbits. Death resulted in eight to twenty-four hours after increasing dyspnea

and asphyxia occurred. Autopsies of these animals revealed acute pulmonary edema, congestion of the lungs, and the presence of a pale eosinophilic staining material lining the walls of the alveoli and alveolar ducts. In a series of experiments on guinea pigs he excluded alterations in the heart as the etiology of the pulmonary edema, and further experiments revealed the loss of innervation of the lungs was the essential factor in the production of the edema in these animals' lungs. He called this "neuropathic pulmonary edema" and postulated that in man it is probably caused by central or peripheral disturbances to the vasomotor control of the pulmonary vessels.[26] In 1951 Miller, Behrle and Gibson published a paper which compared the hyaline membranes in vagotomized rabbits to those found in the lungs of newborns. They bilaterally severed the vagi in twenty rabbits, and in thirteen of these they found hyaline membranes similar to those seen in infants. The time of appearance of symptoms and death in relation to the operation was reported to approximate the time of hyaline membrane formation in the lungs of newborns following delivery. They also point out that they have always encountered pulmonary edema fluid, usually to a marked degree, in some of the alveoli

of the lungs of infants who died of hyaline membrane disease.[59]

Because of the previous experiments in vagotomized animals, Miller and Behrle decided to study a group of newborn infants in an attempt to answer the question of whether the symptoms and pulmonary lesions of these infants might be the result of a deficient vagal control of respiration. Animal experiments have indicated that the activity of the intercostal muscles and diaphragm are affected by vagal stimuli. The vagus not only helps regulate the rate and rhythm of respiration through the Hering-Breuer reflex, but also has an effect on the tone of large muscle groups concerned with respiration. At the time of birth, Miller and Behrle feel that breathing is a relatively simple action, with the vagi the chief afferent and the phrenics the chief efferent nerves. Because of interruption of this reflex arc, vagotomized animals show diminished and irregular diaphragmatic activity. The extent to which thoracic respiration can compensate for this decreased diaphragmatic activity is not constant, but it was shown by Coombs and Pike in 1930, that vagotomy in young puppies and kittens resulted in dyspnea and death in a few hours. Adult animals on which this procedure was performed survived indefinitely.[60]

Some of the evidence that the newborn has a poorly developed vagal mechanism is papers presented by Wiggers, Hoff and Cutler. The first author pointed out the rapid heart rate in newborns which slows as the infants grow older.[93] Cutler showed that there was a low production of HCl in the stomach of newborns and demonstrated poor peristaltic activity in the stomach and intestines.[20] Miller and Behrle reported that a cough reflex could not be elicited in more than 25 per cent of the newborns in their nursery, but it was present in 90 per cent of the infants older than one month.[60] Another fact suggestive of a poor vagal mechanism in newborns, is the observation of Cross and Roberts that phrenic nerve stimulation failed to inhibit spontaneous respiration in them and did inhibit it in the adult. This is a reflex phenomenon dependent on an intact vagus, since it disappears after division of the vagus in dogs.[19]

Because of the relation of the vagus nerve to respiratory movements, Miller and Behrle recorded the flow of air in and out of the nose and mouth of infants and simultaneously recorded the movements of the upper and lower thorax and the abdomen. They showed that the synchronous movements

of the chest and abdomen present in a large number of infants at birth are replaced in older infants by a pattern in which the lower and sometimes the upper thoracic movements tend to be opposite to those of the abdomen. These discrepancies of movement were formerly thought to be the result of the strength of the ribs, cartilage, and muscular action of thorax in resisting the diaphragmatic pull. Since it is not logical that the thoracic cage would get weaker with age, as would be indicated in the results presented by Miller and Behrle, it is unlikely that this is the answer. It has been suggested by these investigators that the paradoxical movements are caused by the increasing strength and vigor of the diaphragmatic contractions, which are directly related to the maturity of the infant.[60] The less efficient diaphragmatic activity of the newborn has been blamed on a poorly developed respiratory center in the medulla where the arms of the vagus and phrenic reflex arc meet.[60,12]

One infant in Miller and Behrle's series, who died on the second day of life, had hyaline membrane in the lungs at the time of autopsy. The recordings of this infant's respirations showed a marked decrease in the amount of inspired air at

the end of thoracic movement although the abdomen continued to move. This indicated to them that almost all of the air exchange was being made during thoracic movement, and although the abdomen continued to expand it contributed little to actual respiration.[60] This record was comparable to the thoracic records of vagotomized rabbits reported by Kerr in 1950.[41]

Because of this recent interest in a possible deficient vagal mechanism of the premature infant, it is interesting to note some of the respiratory handicaps of the premature as presented by Levine about ten years before these experiments on the respiratory movements of infants. The rapid, shallow, frequently irregular respirations often associated with periods of apnea, which are seen in premature infants who survive, was stated to be the result of an immature respiratory apparatus. The physiologic basis for this respiratory difficulty was noted to be the under-development of the nervous, vascular, pulmonary, muscular, skeletal and hematologic systems. Some of the explanations offered for this concept were the high threshold of the respiratory center due perhaps to incomplete vascularization of the

medulla, the weak gag and cough reflexes, the decreased number of pulmonary capillaries which impedes gas exchange, the decreased muscle tone of the intercostal muscles and diaphragm, and the softness of the bones of the thoracic cage.[48] The deficit with which the premature enters life is well pointed out in his paper and it is easy to see how a relatively small hindrance to the infant's physiological functions could cause death.

Another etiology which proposes that hyaline membranes are endogenous in origin is that presented by Gilmer and Hand in 1955. These authors reported they could identify, with a light microscope, a basement membrane which was distinctly separate from the capillary walls. They accept the presence of epithelial cells lining the alveoli. The hyaline membranes they describe lie beneath the basement membrane and thus it is necessary to postulate an endogenous origin. They present three possibilities as to the origin of these membranes. These are, material from the blood stream as a result of capillary damage, alteration in the basement membrane, or changes occurring in the connective tissue between the basement membrane and the lining epithelium of the alveoli.[32]

Wagner (1954) has proposed the hyaline membranes are formed from endogenous mucus which is derived from the nasopharynx, buccal cavity and bronchial tree of the infant.[91] Lynch and Mellor 1955) postulate the membranes are formed from an uncontrolled secretion of an enzyme system of the bronchial epithelial cells.[50] Both of these theories will be examined further under the discussion of the histochemical composition of hyaline membranes.

Laufe, and Stevenson decided that since both the endogenous and exogenous theories sounded plausible, perhaps both were correct. They repeated and confirmed experiments by Weiner et al., which demonstrated that fresh amniotic fluid would cut the clotting time of plasma in half. Their theory of pathogenesis of hyaline membrane disease is as follows:

> 1) The newborn infant aspirates amniotic fluid.
> 2) The lungs of the infant exude a fluid of high protein content as a result of vagal injury, irritation from amniotic fluid, administered oxygen, anoxia, or some other noxious influence.
> 3) The aspirated amniotic fluid speeds clotting of this exudate which then 'rings' out on the intact walls of the alveoli and alveolar ducts. As fluid is absorbed, the clotted exudate forms a hard membrane...
> 4) Plugs of the clotted material...create extensive atelectasis...

5) As this process slowly progresses, anoxia increases...until asphyxiation occurs.
6) If the changes are minimal...there is... return of areation and recovery."[46]

In an attempt to prove the dynamics outlined above, they injected a one-half amniotic fluid and one-half plasma mixture into the tracheas of guinea pigs. In only three of the twenty-five animals did the classic symptoms and the characteristic membranes, vascular congestion and atelectasis occur. They outlined the faults of their experiments and suggested improvements.[46]

Another concept of the pathogenesis of this disease was presented by Chapple at the Fifth M & R conference. He referred to some experiments by Lurie at the Phipps Institute which were concerned with the regulation of absorption of various materials in the lungs. This work indicated that estrogen causes diminished permeability and progesterone causes the accumulation of fluid. Chapple points out that estrogen also causes muscle tone and progesterone relaxes muscles. He suggests that the absorption of amniotic or edema fluid may be regulated by hormonal levels. Estrogen, which is normally low during the first half of pregnancy, begins to rise at about

four and one-half months and progesterone, which was dominant earlier in pregnancy, follows the estrogen at a lower level until about twenty-four hours before delivery. At this time the progesterone level suddenly falls. When a baby is delivered by Caesarean section, or is premature, an abnormal hormonal situation, as regards the normal time of labor, exists. Since there is a high concentration of progesterone, which causes the accumulation of fluid, at the time of premature delivery, Chapple suggests that experimental work be done on the effect of the hormones on fluid absorption from the alveoli of lungs.[74]

Because of the recent trend to doubt the importance of the hyaline membranes and stress the atelectasis present in the lungs of infants dying of hyaline membrane disease, Dawson feels that the possibility of the alveoli to fail to expand normally should be explored. Since there has been debate about normal lung expansion, and no definite information is available, he speculates about the process. In the expansion of the lung the greatest change occurs in the size of the alveoli, alveolar ducts and respiratory bronchioles. Expansion of the alveolar ducts and the respiratory bronchioles with collapse of the alveoli

might be explained by differences in distensibility of these units. Since each has elastic tissue in its walls, there may be an unequal distribution of this tissue, or even more difficult to prove, there might be differences in the elasticity of the different elastic fibrils. Smooth muscle also resists stretching and this is present in the walls of the alveolar ducts and respiratory bronchioles but not the alveolar walls. A decrease in muscle tone may occur, resulting in dilated ducts which would expand more easily than the alveoli. The resulting dilatation of the ducts would cause the alveoli to be partially collapsed, thus increasing the pressure necessary to expand them, which in turn would cause more dilatation of the ducts. If fluid were present in the respiratory passages, it would be displaced by the air into the alveoli and as it was absorbed more air would be allowed into the dilating alveolar ducts. Once atelectasis occurred, membranes could be deposited from various sources.[22] His views are interesting speculations and recalling that progesterone relaxes muscle and is present in high concentration at the time of premature delivery, perhaps the smooth muscle of the alveolar ducts is under its influence.

In 1950, Landau, Goodrich, Francka and Burns described a clinical syndrome in infants deliverd by Caesarean section which consisted of initial good respirations with cyanosis, dyspnea and costal retraction occurring later. They also noted these infants had a rapid, weak pulse and some of them died in convulsions. Death usually occurred within twenty-four hours of the time of birth. They noted the resemblance of these symptoms to those of hematogenic shock in the adult, i.e. increased heart rate, presence of dyspnea, cyanosis and vomiting. Since it had been shown by Ballentine, DeMarsh, Windle and Alt that immediate clamping of the umbilical cord deprived the infant of 96 to 107 cc. of blood, and a common factor of premature deliveries and Caesarean sections is the immediate clamping of the cord, they devised a procedure by which the placental blood was "transfused" to the infant following Caesarean section. They claimed the previously described syndrome was not observed in any of eighty-seven Caesarean section babies following the institution of this procedure.[44] Since in the majority of infants with this syndrome hyaline membranes were found in the lungs, Landau suggested that hematogenic shock might play a part in their production. His

theory was that all infants inhaled amniotic fluid and normal healthy infants would expel it by coughing. If the newborn was in a state of shock, however, it would use all of its effort for inspiration because of the oxygen lack, and not have the strength to cough. Fluid would then be absorbed leaving the protein membranes to seal off the alveoli.[43]

The last theory of the pathogenesis of hyaline membrane disease which we will discuss was postulated by MacMahon in 1947. He reported progressive cyanosis of the newborn in two cases which was caused by a congenital anomaly he called "congenital alveolar dysplasia."[52] In 1948, he reported three more cases and described the pathological and clinical findings. These infants cried and breathed spontaneously at birth and after a period varying from minutes to hours dyspnea and costal retraction occurred. All died thirty-six to forty-eight hours following birth. The lungs of these infants were well formed, large, firm, dark red, weighed more than normal and sank when placed in water. Microscopic examination revealed an excess of highly vascular mesenchymal tissue containing well formed bronchi and bronchioles. Many of the alveolar ducts were lined by a dense granular eosinophilic

exudate, and the few alveoli present were not uniformly distended. He stated, "at first glance...the lesion suggests a non-specific, proliferative, interstitial pneumonitis...", but he could find no specific signs of inflammatory disease.[53] This lesion has been found in term and premature infants, and is commonly associated with atelectasis. Although the lung superficially resembles an immature lung of four or five months gestation, they are not identical. The pathogenesis of this disease, as postulated by MacMahon, would seem to be retarded alveolar development in spite of normal development of the rest of the lung.[54]

Kaufman and Spiro supported the theory of congenital alveolar dysplasia as the cause of respiratory failure in the neonatal period. They believed the terms congenital atelectasis, fetal atelectasis and atelectasis of the newborn were being used to cover the ignorance of the cause of the respiratory distress of the newborn. They found twenty-three cases of congenital alveolar dysplasia in a study of thirty-seven cases.[40]

In 1949, Miller and Hamilton reported that the picture of alveolar dysplasia was probably more apparent than real because of the presence of pneumonitis, edema and inflammatory

cells which made it difficult to determine the degree of alveolar development.[61] Behrle, Gibson and Miller expanded lungs (resembling those described by MacMahon) by negative pressure and found the areas of highly vascular parenchyma were filled with collapsed alveoli.[11] Potter re-expanded similar lungs with fluid and found normal alveolar development.[69] Martin and More in 1955, reviewed several cases of neonatal death which closely resembled the cases described as congenital alveolar dysplasia and concluded that the histological picture was that of secondary atelectasis with hyaline membranes, rather than a congenital anomaly.[55]

The histochemical nature of the eosinophilic membranes which line the dilated alveolar ducts has not been definitely determined. Most of the investigators who believe the membranes consist of aspirated amniotic fluid or vernix caseosa have shown that fat was a prominent part of them. Potter states that little or no fat can be demonstrated in the membranes.[69] Farber and Wilson[30] demonstrated a positive fat stain in fused necrotic cells, and Blystad and Landing failed to find positive fat stains in the large number of lungs they studied.[14] Miller et al. reported in 1951, that the membranes contained no iron, collagen, amyloid or elastic tissue, but stained positive for a

polysaccharide aldehyde.[11] Blystad, Landing and Smith stated they found no serum proteins, red blood cells or bronchiolar epithelium.[14] Reiner reported a histochemical study of these membranes at the Fifth M & R conference in 1952. His conclusions were that the membranes contained protein, which contained tyrosine and some arginine, a carbohydrate moiety attached to protein and some fatty substance in small amounts.[74] Claireaux (1953) reported the presence of a polysaccharide in these membranes.[18] Laufe and Stevenson found the nucleoprotein stain to be negative and confirmed the negative fibrin staining reaction.[46] In a brief review of the positive staining reactions which had been demonstrated, Bruns and Shields pointed out that a positive fat stain did not mean vernix caseosa and a positive protein test did not limit the origin of these membranes to the protein of edema or amniotic fluid.[15] Wagner, as a result of his histochemical studies, postulates that the membranes consist of either mucoproteins or glycoproteins which probably come from mucus of the upper respiratory passages of the infant.[91] In 1955, Lynch and Miller attempted to demonstrate mucus in the epithelium of the respiratory bronchioles and found the

only mucus secreting glands to be sparse acini below the epithelium. They stained frozen sections of lung, using various methods, and showed the hyaline membrane to stain a uniform royal blue. The epithelium of the respiratory bronchioles and the alveolar ducts also showed a rich royal blue granularity. They decided they were dealing with the cellular respiratory enzyme system (cytochrome-oxidase/cytochrome-C) as the cause of this staining reaction. They did several differential stains which they claim supports this concept, however, they admit any other metallic-porphyrin-protein complex could give similar results. Their theory is that infants suffering from hyaline membrane disease have an uncontrolled secretion of this enzyme system and it is "...probable that the actual hyaline membrane represents a condensed and dried accumulation of this secretion, especially as it is conceded that the only factor known to modify the incidence and severity of this disease is high humidity."[50] Gilmer's studies in 1955, revealed protein was the major constituent of these membranes and confirmed other findings of Laufe and Stevenson.[32] Martin and More (1955) support Reiner's findings and state the membranes give negative reactions for mucus as well as the other substances mentioned

by Miller and his workers in 1951.[55] Gruenwald claims the reason for the different results reported in the histochemical studies of these membranes may be because the membranes do not all consist of the same material. He points out the variety of conditions in which they occur as supporting this assumption.[34]

The large number of theories regarding hyaline membrane disease which have been discussed, emphasizes the need of more careful clinical and laboratory evaluations. A few of the questions raised by the preceding discussion should be presented before proceeding to a discussion of hyaline membrane disease as a manifestation of heart failure. The question of there being different histochemical and morphological types of hyaline membranes was raised. The relation of these eosinophilic membranes to the infant's symptoms was questioned, and the possibility of atelectasis being the primary and most important lesion was presented. The significance of some hyaline membranes as the cause of neonatal death was questioned and the problem of pathological interpretation was presented. Dr. W. E. Nelson summed up many of the problems of this disease in his opening remarks to the Fifth M & R conference.

"Do such membranes actually constitute a valid cause of death, or are they instead merely an alteration occurring secondary to some other lethal process? Do similar membranes occur in infants who do not die, and if so, do they influence the state of well being of such infants? Is it possible to establish a diagnosis of pulmonary hyaline membranes in infants who do not die? What is the nature of the acidophilic material comprising these membranes and what is its source?"[74]

Although we have frequently referred to hyaline membrane and hyaline membrane disease throughout this paper, it has recently been stressed that the eosinophilic precipitate seen in lungs of infants dying a respiratory death is not hyaline, or a membrane.[47] As has been pointed out before, it was only recently that the entire picture of the disease was appreciated and the possibility that the picturesque red membrane might not be the lethal lesion proposed. The recent interest in the relationship of edema fluid in the lungs and the hyaline membrane may have been one of the reasons Lendrum was interested in the relationship of this membrane and left ventricular failure. In 1950, however, he and his associates had already noted a membranous form of exudate plastered

against the wall of alveolar ducts which reminded them of the vernix membrane. They had seen this picture in the lungs of adults with rheumatic myocarditis which had resulted in rapidly fatal left ventricular failure.[101]

As was pointed out by Lendrum, examination of the clinical records of these infants as well as some of the autopsy findings shows a resemblance to the findings in adults who died as a result of acute left ventricular failure. In the adult, acute pulmonary edema occurs when extensive edema of the alveoli complicates congestion of the pulmonary capillaries. The dyspnea caused by the passive congestion (via the vagal reflex) is accentuated by the edema which adds arterial anoxia and causes chemical stimulation of the respiratory center. This extreme increasing respiratory difficulty is associated with cyanosis, which often becomes quite marked.[91] In infants with hyaline membrane disease increasing dyspnea and cyanosis are characteristic findings.

Potter has noted that in addition to the lung findings of marked capillary congestion, hyaline membrane, intra-alveolar pink staining fluid, and atelectasis, the right atrium of the heart in these infants is often greatly distended.[69]

These findings suggest to Lendrum "...heart failure overloading mainly the pulmonary circuit-failure of the left heart."[47]

It will be pointed out by some that although the symptoms are comparable, as are isolated autopsy findings, a hyaline membrane with atelectasis is not characteristically found in the lungs of adults dying of acute pulmonary edema. This is true, but as so many of the earlier investigators seemed to forget, hyaline membrane disease is a disease of newborn infants. There are many physiological and anatomical differences between the newborn and the adult and these must be recognized before the etiology of heart failure can be seriously considered.

The most marked differences between the adult and the newborn are the structural and functional changes which occur in the latter at the time of birth. It has been just recently (1951) that these changes were established. They take place because the fetal circulation which has served its purpose well during intrauterine life must be replaced when life becomes dependent upon ventillation of the lungs. The closure of the ductus arteriosus and foramen ovale are the changes we are interested in at this time. An excellent set of experiments on newborn lambs in 1951, by a group of British

workers showed how these two events take place. Prior to aeration of the lungs the pressure in the ductus arteriosus at its origin from the pulmonary artery was greater than that in the aorta, and the flow of blood through the lungs was slow and small in amount. When ventillation occurred there was a fall in the pulmonary and aortic pressures, which coincides with and is dependent upon the increased blood volume present in the aerated lungs. This change in blood volume causes a decreased flow of blood to the heart which is the cause of the drop in the systemic pressure. The lungs fill with blood in a few minutes and the volume of blood returning to the heart is increased as is the systemic blood pressure. The high resistance to blood flow presented by the collapsed vessels of the fetal lung is absent now and thus the pulmonary pressure (as it is in the adult) remains low. The ductus arteriosus closes within one to two minutes after the aeration of the lungs, at the time when the pressures in both arterial systems are at the lowest points. The hypothetical explanation of this is the ductus is an elastic and muscular tube which is attempting to close at all times, but is kept distended by the high blood pressure within it. When this pressure

diminishes, the ductus closes. The foramen ovale is considered to be closed by the increased blood flow returning from the lungs to the left auricle which forces the membrane over the opening. Prolonged closure of these two structures results in anatomical obliteration.[78] Since the initial closure of these structures is merely a functional one, it is not beyond the realm of possibility that changes in pressures toward those present prior to birth could not reopen them. It must also be pointed out that the muscular wall of the ductus is not as fully developed in the premature as in the full term infant.[47]

The pulmonary vascular system of the newborn, especially the premature, is immature, as has been pointed out by Klemola.[48] At the time of birth the planimetric ratio between the right and left ventricular walls is 1:1, but rapid hypertrophy of the left ventricle normally occurs and by six days after birth the ratio becomes 1:1.35. Other evidence is also present which supports the fact that the right ventricle maintains its fetal dominance at birth and for a short time following birth.[6] As has been previously noted, the volumes of blood passing through the right and left ventricles change rapidly at birth. The large volume of blood entering the left

ventricle has to be pumped through the systemic circulation after birth rather than the placenta which has a relatively low resistance. This increased load is the reason for the rapid hypertrophy which was noted above.[84] The ability of the newborn's heart to function in an extreme state of anoxia is much different from the adult myocardium which must have oxygen or hypoxia and infarction will rapidly occur.[47, 84] The incomplete development of the cardiac muscle in the premature infant must be remembered.[47]

Before we review the series of events in the production of hyaline membrane disease by failure of the left ventricle, let us examine twenty cases of this disease taken from the files of the University of Nebraska College of Medicine. These cases were selected from the autopsies of premature liveborn infants at this hospital between and including the years 1945 and 1955. No attempt was made to find all of the cases of hyaline membrane with resorption atelectasis during this period. The cases to be presented were chosen because the final diagnosis on the autopsy protocol included that of "hyaline membrane" or "vernix membrane." The histological description of the lungs were read, and if the

description did not mention the characteristic microscopic findings, it was not included. Finally, the slides of twenty-one autopsies were examined and the nineteen cases reported here were found to have lung findings of an eosinophilic material plastered against the wall of the alveolar antra, atelectasis, and capillary congestion. Table I summarizes the clinical findings in these infants. Table II is composed of some of the findings at autopsy. The microscopic findings described as being typical of this disease are not included because as was noted before, they were used in selection of the cases (see figures 1 and 2). Figures 3 and 4 are photographs of the lung of a nine month infant who died one day following surgery for a congenital heart lesion. Autopsy showed congestion of the lungs, a calcifying infarct in the tip of the upper lobe of the left lung and pulmonary arteriosclerosis. These hyaline membranes lend support to the theory of their formation from edema fluid and are evidence in favor of the theory of heart failure as the etiology of hyaline membrane disease. Microscopic examination of the hearts revealed normal muscle for the stated age of development in all cases, congestion in the vessels of the myocardium in

nine cases and normal vessels in nine cases. There were no microscopic sections available in the remaining two. Examination of the gross descriptions of the lungs revealed the characteristic findings of dark red-purple lungs, firm in consistency which did not float in water in ten instances. In one instance both lungs were described as being dark red-purple and appearing atelectatic, but the right lung floated in water. In two cases the lungs were described as dark red and firm, but both floated in water. In six the lungs were described as dark purple-red and appearing atelectatic, but no mention is made of an attempt to float the lungs in water. The expected normal weight of the lungs and hearts were calculated by using per cent of body weight. Hess, in his book on premature and congenitally diseased infants, gives the average weight of the heart in prematures as being about 0.7 % of the total body weight. Examination of the figures given by Potter[69] showed that the heart weights stated in her table came very close to being 0.7% of total body weight in all instances. The expected normal weight of the hearts in Table II is 0.7 % of the total body weight. Examination of the average weight of lungs in premature infants as given by Potter,[69] revealed the ratio

lung weight to body weight varied in the different weight groups she gives. The per cent per body weight was calculated for each of these groups and the resulting figures were used in calculating the combined expected normal weight of the lungs.

250 g	to	750 g	= 3%	of total body wgt.	=	comb.	wgt	of	lungs		
750 g	to	1250 g	= 2.5%	"		"		"		"	
1250 g	to	1750 g	= 2.2%	"		"		"		"	
1750 g	to	2250 g	= 2.2%	"		"		"		"	
2250 g	to	2750 g	= 2.0%	"		"		"		"	
2750 g	to	3250 g	= 1.8%	"		"		"		"	

TABLE I

CLINICAL FINDINGS OF NINETEEN INFANTS WITH A PATHOLOGICAL DIAGNOSIS OF HYALINE MEMBRANE OR VERNIX MEMBRANE

Case	Wgt. (gms)	Type of delivery	Cond. at birth*	Onset of symptoms	Symptoms & Physical findings	Age	Clinical diagnosis
#1	1880	vaginal	poor delayed	birth	irreg., shallow, labored, resp., periods of apnea, weak cry, rec. attacks, cyanosis	10 hrs.	Pul. atelectasis.
#2	1695	C. section	poor delayed	3 1/2 hrs.	gasping resp., weak cry, rec. attacks, cyanosis.	8 hrs.	Premature birth.
#3	1500	vaginal	good spont.	3 1/2 hrs.	shallow, gasping resp., soft, grunting cry, rec. attacks, cyanosis.	12 hrs.	Bil. atelectasis of lungs.
#4	1880	C. section	fair sl. delayed	4 hrs.	irreg., weak, labored, resp., resp. grunt, weak cry, rec. attacks, cyanosis, few breath sounds (4 hrs.) bubbling rales (4 1/2 hrs) "state of conscious effort."	8 hrs.	Prematurity

TABLE I (cont'd)

#5	630	vaginal	poor spont.	birth	irreg., labored resp., rec. attacks, cyanosis	5 hrs.	Prematurity.
#6**	1820	C. section	fair spont.	3 hrs.	irreg., grunting resp., weak cry, rec. attacks, cyanosis, costal retraction, x-ray taken.	18 hrs.	Pul. atelectasis.
#7	1965	C. section	fair spont.	9 hrs.	irreg., gasping resp., expiratory crow, rec. attacks, cyanosis.	14 hrs.	Pul. atelectasis.
#8	2960	C. section	good spont.	2hrs.	grunting resp. with marked insp. difficulty, rec. attacks, cyanosis, decreased breath sounds in scattered areas.	40 hrs.	Fetal atelectasis.
#9	1980	vaginal	good spont.	5 hrs.	shallow, irreg., grunting resp., periods of apnea, rec. attacks, cyanosis.	7 hrs.	Prematurity.
#10	1560	vaginal	poor spont.	birth	labored, irreg. resp., marked insp. difficulty, cyanosis, no vesicular sounds over lungs, marked sternal & costal retraction.	13 hrs.	Bil. atelectasis of lung.

TABLE I (cont'd)

#11	1800	vaginal	fair spont.	2 hrs.	irreg., shallow resp. insp. effort, high pitched, grunting cry, rec. attacks, cyanosis asymmetrical thorax, (rt. side not well expanded), breath sounds diminished on rt., sternal & costal retraction.	11 hrs.	Prematurity
#12	1520	vaginal	good spont.	3 1/2 hrs.	rapid, irreg., resp, exp. grunt, rec. attacks, cyanosis, distant breath sounds, sternal retraction.	30 hrs.	Atelectasis
#13	1615	vaginal	born outside hosp. spont.	App. 6 hrs.	irreg., shallow resp., grunting weak cry, rec. attacks, cyanosis, sternal retraction.	15 hrs.	Atelectasis
#14	1100	vaginal	good spont.	1/2 hr.	irreg., gasping, resp., cyanosis, fair breath sounds with deep resp., costal retraction.	7 1/2 hrs.	Prematurity.
#15	1669	vaginal	good spont.	12 hr.	irreg., shallow, resp., labored insp., cyanosis, sternal retraction.	5 hrs.	Prematurity

TABLE I (cont'd)

#16	1930	vaginal	good spont.	12 hrs.	irreg., shallow resp. H.R. = 68, cyanosis, no retraction.	24 hrs.	Hyaline membrane disease.
#17	910	vaginal	born outside hosp.	?	gasping, irreg. resp., rec. attacks, cyanosis, sternal retraction.	21 hrs.	Cong. atelectasis.
#18	1400	vaginal	good spont.	2 hrs.	irreg., grunting, resp., whining cry, rec. attacks, cyanosis, poor lung aeration.	27 hrs.	Fetal atelectasis.
#19	1430	vaginal (breech)	fair spont.	3 hrs.	poor, grunting, resp., weak cry, rec. attacks, cyanosis, "sticky "breath sounds, poor chest excursion, edema of hands and feet.	41 hrs.	Atelectasis.

* Breathing and crying noted as spontaneous or delayed.

** A portable x-ray of the chest was taken in this case. The report described restricted expansion of both lungs, especially the left upper lobe, probably representing a normal physiological pattern and stated that continued increase in lung expansion could be expected.

TABLE II

SOME OF THE PATHOLOGICAL FINDINGS IN NINETEEN INFANTS AUTOPSIED AT THE UNIVERSITY OF NEBRASKA HOSPITAL. OTHER FINDINGS ARE DESCRIBED IN THE BODY OF THE PAPER.

Case	Autopsy	Lung		Heart		Foramen ovale	Ductus arteriosus	Other sign. Path. findings
		wgt. (gms)	exp* normal	wgt. (gms)	exp* normal			
#1	complete	42	41.4	19	13.2	***	***	none
#2	complete	39	37.3	13	11.9	***	patent	none
#3	complete	30	33.7	11	10.5	***	patent 3 mm.	none
#4	complete	29	41.4	10	13.2	guarded	***	none
#5	complete	14.5	18.9	4	4.4	***	***	hem., both lateral vent. (brain)
#6	complete	38	40.0	11	12.7	guarded	patent	none
#7	complete	60	43.2	12	13.8	guarded	patent 0.2cm.	none
#8	no brain	58.0	53.3	21.5	20.7	guarded	***	none
#9	no brain	54	43.6	15	13.9	patent	patent	none

TABLE II (cont'd)

#10	complete	35	34.3	12	10.9	closed	***	none
#11	no brain	39	39.6	12	13.6	***	patent	none
#12	no brain	35	33.4	9	10.6	guarded	patent	none
#13	complete	37	35.6	13	11.3	patent 4 mm.	patent 3 mm.	none
#14	complete	23	27.5	6	7.7	***	***	none
#15	complete	49	36.7	16.5	11.7	***	patent	intratentorial hematoma(2-3cc)
#16	no brain	45	42.5	***	13.5	"large" patent	"dilated" patent	none
#17	no brain	45	23.8	10.2	6.4	guarded	patent	none
#18	complete	32	30.8	10.5	9.8	***	patent	none
#19	no brain	41.5	31.5	9.5	10.0	guarded	***	none

* The method of determing these values is explained on pages 76 and 77.

**

*** No description available.

The series of events proposed by Lendrum which occurs in these infants begins with the birth of a premature infant. In such a newborn, the pulmonary capillaries, the left ventricular wall and the wall of the ductus arteriosus are not fully developed. If the left heart fails to pump out all of the blood which enters it from the lungs, or if there is failure of the ductus arteriosus to close when the aortic pressure is greater than the pressure in the pulmonary artery, congestion of the pulmonary vessels will occur. No respiratory symptoms need occur at this time. The resulting rise in the pulmonary blood pressure causes filtration of the serum into the alveolar spaces. This results in decreased oxygen exchange, and the left ventricle which is receiving less well oxygenated blood, continues to fail. The cycle of increasing pulmonary edema, anoxemia and anoxia of the left ventricle leads to complete failure of the overburdened left heart. As the left heart fails, the pressure rises in the right heart and right to left flow occurs through the foramen ovale and the ductus arteriosus. This return to the pattern of fetal circulation reduces the pressure in the pulmonary vessels. The ability of the newborn lung to absorb water has previously been pointed out. As the decreased

pulmonary vascular pressure occurs, the intra-alveolar fluid begins to be resorbed, the water and electrolytes being absorbed first. The concentrated protein with any remaining fluid is forced toward the respiratory bronchioles and alveolar ducts by contraction of the elastic alveolar walls. Thus the picture of atelectasis as well as the presence of an eosinophilic material pressed against the walls of the alveolar ducts is explained.[47]

A review of the literature of this proposed pathogenesis may help shed some light on its probability. Let us say at the beginning that in the adult dyspnea of cardiac origin is recognized by demonstrating other signs of cardiac disease, particularly by the observation that the heart is enlarged.[37] In 1932, Farber and Wilson listed several conditions in which they observed an eosinophilic membrane in the alveolar spaces. One of these was heart failure, and in these lungs they saw the membranes composed of serum at some distance from the alveolar walls. They pointed out that dyspnea and forceful inspiratory efforts were prominent clinical features in these cases and all had partial respiratory tract obstruction because of fluid.[30] In 1940, Miller and Ross observed three infants of

diabetic mothers who had dyspnea, grunting respirations, feeble cry and cyanosis in the neonatal period. They demonstrated cardiomegaly radiographically and the clinical diagnosis in two of these cases was congestive heart failure with recovery.[63] Miller and Wilson in 1943, found radiographic cardiomegaly in twenty out of twenty-one infants of diabetic mothers in the first ten days of life. The outstanding symptoms in these newborns were dyspnea, tachypnea and cyanosis, and their duration corresponded to the period of cardiomegaly. For this reason these authors felt the symptoms might be the result of cardiac failure. The hearts of the infants who died during their periods of symptomatology showed definite increases in weight and was interpreted as hypertrophy.[64] Miller pointed out that the diagnosis of cardiac hypertrophy in the neonatal period is difficult and a diagnosis of an enlarged heart can best be made by radiological examination.[58] In 1948 Parmelee pointed out the great increase in the pulmonary blood volume and the sudden changes in the pressure relationships intraventricularly at the time of birth. He also noted that the arteriolar and capillary systems of the lungs were being placed under sudden new demands at this time.[54]

In 1949, Lendrum and his associates noted the presence of a "vernix membrane" in the lungs of adults with rheumatic myocarditis.[101] In 1951, Lind and Wegelius noted that during the first few days of life the functional adjustment of the circulation is reversible, the right and left hearts being equally developed. They postulated that some pulmonary complication which increased the pressure in the pulmonary circulation might cause reassumption of the fetal blood flow. They observed this to happen in angiocardiographic examinations of infants with cyanosis during the first few days of life.[49] In 1953, at the fifth M & R conference Hardy reported that Clifford had demonstrated a "...deep space ... visible between the anterior mediastinum and the sternum in the lateral roentgen films..."[74] She felt this might be the result of trapped air but Lendrum interprets this as possibly representing congestion in the dependent (posterior) portions of the lungs.[47] In 1954, Winter and Gellis, in studying infants delivered by Caesarean section who died, concluded that there was a complete lack of correlation between cardiomegaly and the presence of hyaline membranes. They stated that heart failure as an etiology could be dismissed because of the absence of edema, congestion of

systemic veins and an enlarging liver.' It should be pointed out here that the "... restriction of the term congestive heart failure to persons with venous engorgement and edema ... is entirely unjustifiable."[37] It was also noted by these two authors that heart size by roentgen films in the newborn is a "... notoriously ... poor technique ..." and that the weight of the heart at autopsy cannot be used to determine the presence or absence of cardiac failure.[97] Smith also pointed out the difficulties of interpreting a chest roentgen film in the newborn and noted the marked difference in cardiac and mediastinal outlines during the different phases of respiration.[84] In 1955 Arey noted that the time of birth was one of great readjustment and pointed out that if the pulmonary blood flow were to be abnormally increased, as by failure of closure of the ductus arteriosus, the resulting pulmonary congestion might cause the escape of protein and fluid into the alveolar spaces with subsequent hyaline membrane formation.[3]

Before we can interpret the cases we have presented as either supporting or refuting this theory, we must determine what clinical and pathological features should be indicative of heart failure in the newborn infant. The pathological findings

of heart failure in the newborn lungs are obscured by the atelectasis and "hyaline membrane." These are the result of peculiarities of the newborn. The respiratory failure as postulated by Lendrum in these infants is a result of a progressive series of events, each succeeding one partially or completely obliterating the signs of the previous one. At autopsy only the final picture is seen so only those findings which have not been obscured during the formation of this picture have any practical importance. In the lungs of adults dying in acute pulmonary edema there is capillary congestion and alveoli distended with fluid. If the alveoli were collapsed, only the vascular congestion would remain as an indication of heart failure. The physiological and anatomical differences between the adult and the newborn which have been previously pointed out account for the other pathological signs of heart failure in the newborn. A patent ductus arteriosus and foramen ovale are post mortem indications that during life at least part of the blood followed the fetal circulatory pattern. At autopsy the foramen ovale may appear to be guarded by the flap-like septum. If the pressure in the right atrium during life was greater than in the left, it is easy to see how this "flap" could be pushed away from the

foramen. A patent ductus arteriosus can be demonstrated by routine dissection of the aorta and pulmonary arteries at autopsy. It has been shown by Smith that the ductus normally closes within two minutes in the newborn sheep.[84] It is admitted that it is frequently dangerous to interpret human physiology on the basis of animal experiments. The clinical signs of dyspnea and cyanosis as indications of heart failure have already been pointed out. Lendrum has attempted to explain the ineffective inspiratory effort of these infants by noting that the lungs fill the pleural cavities at autopsy and the diaphragm is in an almost horizontal position. This he feels is the result of the marked capillary congestion and edema. The diaphragm, being at its inspiratory position as a result of pressure from the distended lungs, would be ineffective in drawing air into these lungs. Its inefficient contractions would only cause sternal and costal retraction.[47]

I have concluded that the following findings must be present to substantiate the presence of cardiac failure resulting in hyaline membrane disease.

1. Progressive dyspnea and gasping inspiratory efforts.
2. Cyanosis.

3. Heavy red-purple lungs which fill the pleural cavities.

4. Capillary congestion in the lungs.

5. Collapsed alveoli.

6. The presence of an eosinophilic "membrane" lining the alveolar antra.

7. Patent or guarded foramen ovale (this will probably be present in autopsies of all newborns).

8. Patent ductus arteriosus.

9. Cardiomegaly as indicated by increased weight.

Study of Tables I and II reveals that all of these infants showed progressive dyspnea and cyanosis. The column of physical findings is distinctly limited, as in many of these infants no physical examination was reported on the chart. Study of the autopsy findings reveals weight of the lungs greater than the expected normal in thirteen instances, a marked difference being present in only five of these cases. A heart weight greater than the expected normal was found in ten of the eighteen cases in which the heart was weighed (56%). The foramen ovale was described as being patent in three cases, guarded in seven, and closed in one. There was no available description in the remaining eight cases. The ductus arteriosus was patent in all twelve cases in which it was described. The rest

of the information on these charts agrees with previously published facts and figures on the incidence, time of death and physical condition of these infants. It should be noted that in thirteen (76%) of the seventeen cases in which the condition at birth was known, this condition ranged from fair to good. Too few cases have been presented to enable us to draw any definite conclusions, but it must be pointed out that our results, when composed with the findings we have enumerated above, are compatible with the theory of hyaline membrane disease production as postulated by Lendrum. As he has stated if this theory is to be proven, a change in the therapy of premature newborns should be made. This would consist of changing the existing routine in which most of these infants are placed on their backs in an incubator, often with the foot of the bed elevated to 30 degrees. This position and the immobility of these infants causes venous engorgement in the thorax which uses up the already limited space, causes an increased amount of venous blood to enter the right heart and pulmonary capillaries, and predisposes to venous stasis and edema in the dependent portions of the lungs. If the theory of cardiac failure is sound, the position of the baby during the

first two days of life "... should always be such that any excess venous blood would accumulate below the diaphragm..."[47] Only when it has been demonstrated by this technique that the incidence of hyaline membrane disease is reduced, or when experimental left ventricular failure in newborn animals produces this characteristic syndrome, can this proposed pathogenesis be accepted.

SUMMARY AND CONCLUSIONS

The numerous proposed etiologies of pulmonary hyaline membrane disease are examined, and it is shown that none of these explains the pathogenesis adequately. The incidence of this disease, its clinical and pathological features, and its clinical differential diagnosis are presented. The literature of the x-ray diagnosis is reviewed and it is noted that there is dissension as to the signs characteristic of this disease. A brief discussion of the histochemical nature of these membranes reveals their composition is not known at this time. The possible association of heart failure and hyaline membrane disease is explained on the basis of the physiological and anatomical differences in the newborn and adult. Nineteen cases are presented and it is concluded that the clinical and pathological findings in these infants are compatible with the theory of

heart failure as the pathogenesis of hyaline membrane disease. The difficulties in the pathological interpretation of acute left heart failure in the newborn are pointed out. Photographs of the lungs of a nine month infant are shown which tend to support the theory of heart failure as the etiology of this disease. It is proposed that prevention of heart failure by correct handling be included in the management of the newborn premature infant.

In conclusion it should be pointed out that this author does not feel heart failure, or any other isolated etiology, is the cause of pulmonary hyaline membrane disease. This disease is found only in newborns and it is felt that the physiological handicaps of these infants play a great part in the production of this syndrome. The deficient vagal tone in the neonatal period, resulting in pulmonary edema, may cause the increased pulmonary vascular pressure which results in the reassumption of the fetal path of blood flow. The ability of the newborn's lung to rapidly absorb fluid may result in an increased blood volume. The fetal blood flow pattern would cause decreased pulmonary vascular pressure, reabsorption of edema fluid, alveolar collapse and hyaline membrane formation. The

anoxemia resulting from this would be added to an increased systemic pressure (as compared to fetal life) and the result could be left heart failure. This would cause more pulmonary edema and congestion and once more the pulmonary blood pressure would rise. A purely theoretical concept, but it emphasizes my belief that pulmonary hyaline disease is a result of a number of factors in the neonatal period, including and most important, the infant's physiological deficiencies.

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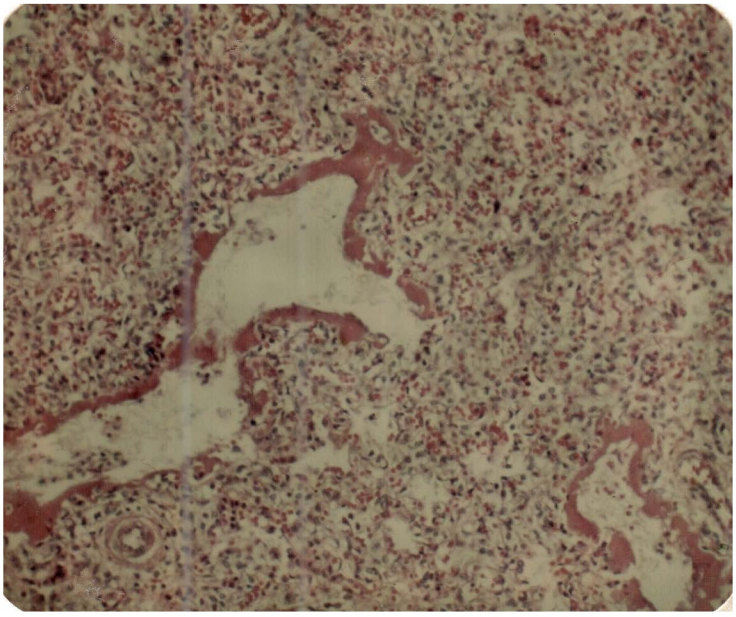
Figure I -- Pulmonary hyaline membrane disease in an infant who died at the age of 18 hours. Note the typical membrane, massive atelectasis and capillary congestion. (37X)

Figure II -- Higher magnification of Figure I. (170X)



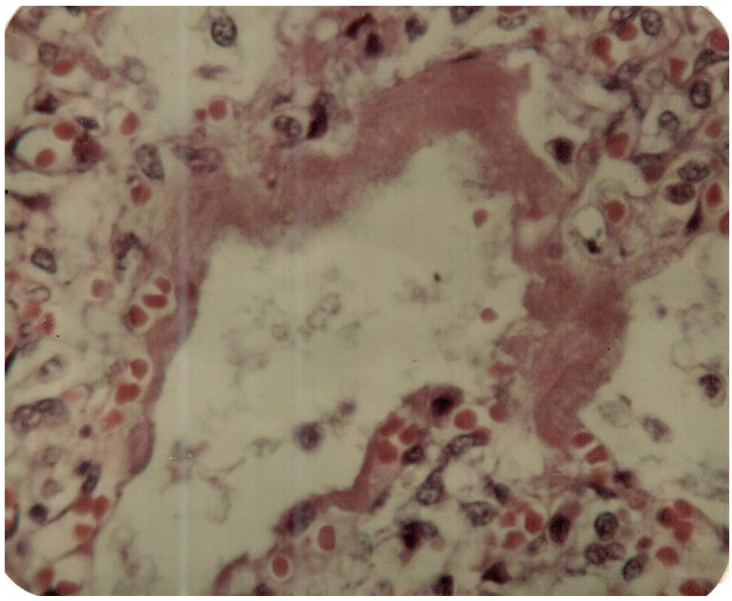
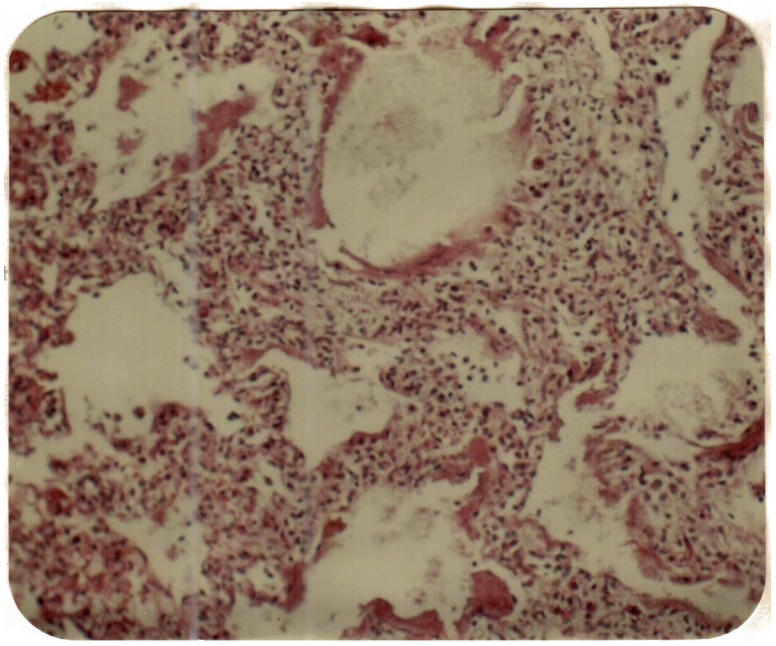
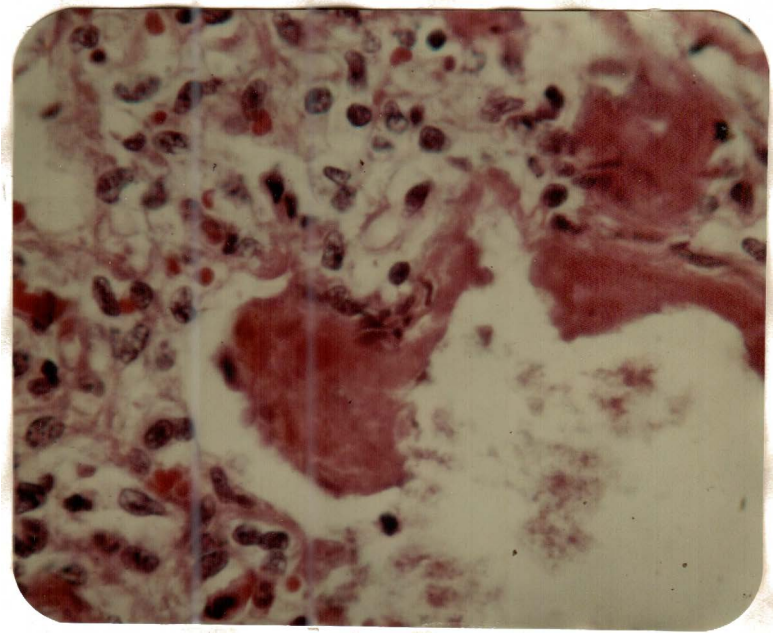


Figure III -- Sections of the lung of a nine month old infant. Atelectasis is not as marked as in Fig. I, but the appearance of the membranes is similar. Note the relationship of the intrautral fluid and the eosinophilic membrane. This case is not included in Tables I and II. (37X)

Figure IV -- Higher magnification of Fig. III which shows capillary congestion and a thick eosinophilic membrane. (170X)





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