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Pulmonary hyaline membrane disease : a challenge to research

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PULMONARY HYALINE MEMBRANE DISEASE - A CHALLENGE TO RESEARCH

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INTRODUCTION

Each year in the United States, approximately twenty-five thousand babies die within a few days of their birth of a disease which cannot be definitely diagnosed until after their death. This is pulmonary hyaline membrane disease, one of medicine's most extensively studied, most disputed entities, yet still one of the least understood processes known. In this paper, some of the more important results of past studies will be presented with the intention of clarifying the basic problems and with the hope that it will not add to the confusion which already fills the literature.

Hyaline membrane disease will be presented from the clinical, pathological, radiological, and etiological aspects and some of the recent promising experimental work in the field of definitive therapy will be discussed.

THE PROBLEM

More newborns who survive the initial hazards of birth die from respiratory failure than from any other cause. Atelectasis (after initial expansion) is the most common cause of death in this group and a hyaline membrane is often associated with this secondary atelectasis. More than thirty percent (30.5%) of live births who came to autopsy at Johns Hopkins Hospital from 1937 to 1949 showed evidence of hyaline membrane disease, although no membrane was demonstrable in stillborns or in liveborns living less than one hour or more than three days. (1) These findings are typical of those reported throughout the nation. In Boston in 1951, 509 consecutive autopsies of 187 stillborns and 322 liveborns were reported and no hyaline membrane was found in any of the stillborns or in any liveborn less than one hour old. Forty-four percent of prematures had evidences of hyaline membranes while only 22% of term babies demonstrated the same. A history of cesarean section, fetal distress or placenta previa was elicited in 43% of those with hyaline membrane but in only 8% of those without it. (2) A study at Johns Hopkins revealed the following association: (3)

Complication of Pregnancy	No. of Times More Than Expected Incidence that H.M.D. was found
Maternal diabetes	18
Cesarean section	8
Prematurity	7
Breech delivery	6
Multiple pregnancy	4
Maternal toxemia	3

Autopsy reports of neonatal deaths at Glascow Royal Maternity Hospital in 1956 showed the following causes of deaths in 99 consecutive cases: (4)

Asphyxia, atelectasis, prematurity	42
Intraventricular hemorrhage	23
Tentorial tear	8
Fetal abnormality	14
Hemolytic disease	5
Infection	3
Pneumothorax	3
Pulmonary hemorrhage	1

The increased incidence of pulmonary hyaline membranes in prematurity is demonstrated in an interesting study by Landing in 1955. (5)

Weight in Grams	% With Hyaline Membrane Disease P.M.
2,500 and over	17
2,000 to 2,499	47
1,500 to 1,999	38
1,000 to 1,499	33
400 to 999	25
Total prematures	38%

Therefore it can be stated that pulmonary hyaline membrane disease is seen in the neonatal period, never earlier than one hour after birth and seldom after the third day. It is not seen in stillborns and is more prevalent in prematures, in infants born through cesarean section, in infants born of diabetic mothers, and associated with such conditions as breech delivery, multiple pregnancy and maternal toxemia, although it may be also seen in conjunction with a full term, uncomplicated pregnancy and a normal delivery as well.

THE CLINICAL PICTURE AND DIFFERENTIAL DIAGNOSIS

It has been generally accepted that the infant dying with hyaline membrane disease always looks the picture of health at birth; at least there is no evidence of respiratory embarrassment. A recent study by Latham (3) suggests that this is most likely a result of retrospection and comparing the infant in distress with his earlier picture at which time the disease was not anticipated. He recorded the birth condition of a series of newborns and later reviewed the recordings of those infants who died with hyaline membrane disease. The results were as follows:

Condition at Birth	Percent
Excellent	26
Fair, poor respirations, good heart	36
Poor, apneic, fair heart	31
Poor, apneic, irregular heart	5
Poor, fair respirations, poor heart	2
	100%

Pulmonary hyaline membrane disease manifests itself within the first few hours after birth, usually within the first twelve hours. The first signs of respiratory distress are sub-costal retraction with forceful inspiratory movements. These are followed by intercostal and supra-sternal notch retraction and eventually by retraction of the lower thorax with inspiration. Terminally, the thorax collapses and the abdomen expands with inspiration. Retraction is a much more onimous sign in the full term infant than

in the premature since in the latter, the very flexible rib cage lends itself to retraction very easily. Later in the disease, flaring of the alae nasi is seen and an expiratory grunt is audible. Auscultation reveals generalized fine moist rales and a decrease in breath sounds throughout the lung fields. The respiratory rate is in the neighborhood of sixty per minute but slows markedly near the end with periods of apnea. At first the infant is usually pink and has short outbursts of crying. He will usually take a supine position with knees flexed and thighs abducted. The arms will be flexed at the elbows with the hands fully supinated alongside the head which is turned to one side. Within a few hours from the onset of symptoms, the infant becomes exhausted and stops breathing for a few minutes. Due to the resulting gray pallor, this is commonly referred to as a "gray attack." The infant may succumb at this time but most often will soon resume the above pattern of breathing and eventually have another attack. More than five such attacks is generally considered a very grave prognostic sign, the infant usually dying within the first thirty-six to forty-eight hours of life. (4) Occasionally an infant may recover from a series of "gray attacks" and thus survive hyaline membrane disease. There are those who question the presence of a true hyaline membrane in these cases and since there is no autopsy to offer proof, who can deny either premise? (6)

The differential diagnosis is a most important aspect of this

disease since, although there is no known definitive treatment for hyaline membrane disease, some of the other entities which have a similar clinical picture can be effectively treated. These entities are: central nervous system hemorrhage, pneumonia, other infections, spontaneous pneumothorax (by no means rare), diaphragmatic hernia, cardiac abnormalities, intrapulmonary hemorrhage, and aspiration of foreign material.

THE PHYSIOLOGY OF INITIAL RESPIRATION AND PATHOPHYSIOLOGY OF PRIMARY ATELECTASIS

The first breath and the resulting initial expansion of the newborn's lungs is dependent upon many complex factors. The causes of early respiratory distress may be divided into five main categories. The first possible cause is failure to establish respirations, due to such things as an incompetent respiratory center because of antecedent anoxia, increased intracranial pressure and/or immaturity. The second is absence of a patent airway due to aspiration, mucous plugs in the tracheo-bronchial tree, etc. Thirdly is some defect in peripheral circulation such as fetal shock seen with an imbalance in vascular dynamics during the sudden shift from fetal to infant circulation. Fourthly is some obstruction to respiratory movement such as a diaphragmatic hernia, soft thorax or muscular weakness. Lastly is the quality of the atmosphere breathed, which is actually the least important of all the factors. (4)

The mature infant usually expands his lungs rapidly and attains complete expansion within a matter of minutes while the premature is usually completely expanded within a few hours. Normally it takes considerable effort to initially expand the lungs since there is a powerful surface tension to overcome. Once the alveoli are expanded, it takes much less effort to keep them open. The initial intrathoracic pressures were measured in newborns while they were in varied degrees of passage through the birth canal. The pressures were indirectly measured by means of an intraesophageal

manometer. Initial pressures were in the range of 40 cm. of water and the pressure exerted upon crying was in the range of 90 cm. of water which is about the same pressure which would result as a response to clasping the hand over the mouth and nose of an adult. The periods of extremely elevated pressure are maintained for a very short time, however, less than 0.15 second, so this must be kept in mind when attempting manual inflation of the newborn's lungs. (4) The weak premature or the sedated term infant is at a decided disadvantage from this point of view because he does not have the necessary reserve to initiate respirations. This disadvantage is compounded when there is aspiration of amniotic fluid, as has been suggested as a possible etiology of pulmonary hyaline membrane disease.

Physiologic changes attendant with neonatal respiratory distress have been fairly extensively studied and the following report should demonstrate the extent of the burden placed upon the newborn with hyaline membrane disease. (7, 8)

Minute volume	increased 75%
Respiratory rate	increased 90%
Tidal volume	normal (15 cc)
Crying vital capacity . . .	decreased 50%
Alveolar ventilation . . .	decreased 30%
Arterial 002 tension . . .	increased 30%
Functional dead air space .	increased 70%
Functional residual capacity	decreased 45%
Negative pressure change .	increased300%
Lung compliance	decreased 80%
Pulmonary work per minute .	increased400%

THE X-RAY DIAGNOSIS OF HYALINE MEMBRANE DISEASE

The pulmonary hyaline membrane per se cannot be visualized by x-ray but the radiographic evidence of the pathology is consistent enough to be of use diagnostically. The most important factor which makes the x-ray useful is the fact that this disease is a generalized one and the pathology is not limited to specific portions of the lung field but is seen throughout. A generalized marked increase in pulmonary density is seen with punctate and linear images. This phenomenon is known as the reticular granular pattern. In contrast to the normal lung findings, the bronchial air shadows can be seen extending far out into the periphery of the lung field. Peripheral radiolucencies up to 2 cm. in diameter are also seen. Early, the picture is one of fine mottling throughout, which later changes to a coarser, more coalescent opacity with clear demarcations of the bronchial tree as described above. Terminally, the shadows become confluent and the picture is one of a lobular or lobar pattern of consolidation and collapse. The pattern of fetal aspiration is somewhat similar but it is more irregular. Some of the other entities in the differential diagnosis can be picked up by x-ray, including diaphragmatic hernia, pneumonia, cardiac abnormalities, and spontaneous pneumothorax. (9)

THE PATHOLOGY OF THE PULMONARY HYALINE MEMBRANE

Grossly, the lungs are the size of normal, well expanded lungs but have the consistency of liver. They are uniformly dark red-purple in color and are much heavier than normal. The lungs will sink when placed in water, in contrast to a normal lung.

Histologically, there is widespread resorption of air and the walls of many alveoli and alveolar ducts are collapsed, giving a solid appearance to the parenchyma between the few remaining open alveolar spaces. There is evidence of marked capillary engorgement (hence the color and increased weight). The inner surface of the alveolar ducts and alveoli which remain open are covered with an irregular layer of homogenous eosinophilic membrane. (1)

Mellor, in biochemical studies of the membrane itself, found among other things, iron in the form of iron-porphyrin compounds thought to be either from hemolyzed red blood cells or from disintegrated peroxidase type enzymes. (10)

Study of the membrane through electron microscopy revealed that the membrane is composed of cell debris, (nuclei, nucleoli, vacuoles, mitochondria, endoplasmic reticulum, etc.) plasma protein, and fibrin particles in various stages of polymerization. The membrane was located within the air spaces, overlying the alveolar, ductal and bronchiolar epithelium and not under the epithelium or between basement membranes as was previously proposed before the time of the electron microscope. (11)

By using fibrin antibody, labeled with fluorescein, the membrane was found to abundant in fibrin. (12) It is not certain whether the fibrin comes from an exudate, a transudate or is totally exogenous, although many investigators have used the above information as "conclusive" proof of one or the other theory.

THE ETIOLOGY OF PULMONARY HYALINE MEMBRANE DISEASE

Most investigators are able to arrive at somewhat the same conclusions regarding the clinical signs and symptoms, the radiographic picture and the pathology involved in hyaline membrane disease, but the etiology of the disease has been the subject of more investigations and studies than have all the other aspects of the disease. Nearly every possible factor involved in the complex physiology and anatomy of the newborn's respiratory system has been investigated, and likewise nearly every factor has been implicated by one investigator or another as being the source of fault or pathology in the pathogenesis of the disease. Some of these theories will be presented at this time in an attempt to demonstrate the confusion which presently exists in the literature. No attempt will be made to prove or disprove any of the theories but merely to present them for what they may be worth.

For convenience, the various theories will be divided into the endogenous and the exogenous groups. This by no means implies that there are only two camps, for each of the two groups may be subdivided ad infinitum with a staunch supporter of each sub-theory. This particular area of investigation is a prime example of the maxim, "The less man knows about a subject, the more he writes about it."

The Exogenous Theories.

Aspirated amniotic fluid has been cited as the initial agent by many investigators but this is the only fact they have in common.

One investigator reports that, "Through special staining techniques, the hyaline membrane was found to be composed of fat, polysaccharides and flat squames from amniotic fluid." And from these findings, he proposed that, "two factors are necessary to produce a hyaline membrane; a large amount of amniotic fluid and a period of air breathing. The membrane being formed by resorption of amniotic fluid leaving a sediment which is then compressed against the walls by respiratory movements." (13)

Another report states that the membrane consists of "fused, resolving exudate made up of necrotic mononuclear cells, leukocytes, red blood cells, and altered fibrin or amniotic sac contents." The mechanism of membrane formation is explained thus: "These materials are forced into distal alveoli by violently inspired air." (14) A study of hyaline membranes at autopsy revealed that, "all had some, and most had large amounts of vernix caseosa, probably due to fetal aspiration initiated by excess respiration with fetal anoxia." (15)

The mechanism by which amniotic sac contents were aspirated has been the subject of many investigations. For example: "Amniotic fluid is aspirated due to a weak cough and gag reflex in some newborns." (16) Thorotrast radio-opaque dye was injected into the amniotic sacs of normal guinea pig fetuses late in pregnancy and x-ray studies failed to demonstrate fetal aspiration. When the fetuses were induced to execute rhythms of respiratory-like motion during experimental anoxemic periods, some fetuses did aspirate the

dye. These studies seemed to show that difficulty during labor or late pregnancy leading to fetal anoxia could feasibly cause aspiration of amniotic fluid. (17)

The same sort of experiments were performed with similar results on human fetuses in utero in early pregnancies about to be terminated by a therapeutic abortion. (18)

Some investigators were not able to prove what the primary etiologic agent was but they were able to theorize as to what it was not. For example, after examining hyaline membranes, one reporter states that "the membranes do not consist of vernix caseosa." and, in answer to a suggestion that meconium might be the initiating agent; "if meconium were aspirated, one would find amniotic sac contents plus intestinal secretions plus mucous, and since there is no mucous in the hyaline membrane, the membrane must not be due to meconium." (2)

The above theories concerning amniotic fluid have long been the source of controversy. The low count of squamous cells in the respiratory tract secretions of newborns with hyaline membrane disease was offered as proof that the membrane was not due to amniotic fluid since amniotic fluid contains many squamous cells. (16)

Another investigator promptly attempted to disprove the last assumption by performing squamous cell counts on amniotic fluid samples from different periods in pregnancy and found that the count was very low early in pregnancy but rose sharply near the end. This

seemed to explain the disparity in squamous cell counts of hyaline membranes since the infants may have been born during different periods of the last trimester of pregnancy. (2)

A study intended to point away from anmiotic fluid in hyaline membrane disease was reported in which 80 cc. of amniotic fluid was introduced into the lungs of an anencephalic monster per tracheal catheter. The monster died a few hours later and autopsy and microscopic studies showed no evidence of a membrane. (19)

The action of gastric juice on swallowed amniotic fluid which was later vomited and aspirated was proposed to be a necessary factor in the production of a membrane. (20) Oxygen given for respiratory distress, causing pulmonary irritation, pulmonary edema and the end result of expanding gas bubbles plastering respiratory secretions against the alveolar walls was presented as the pathogenesis of hyaline membrane disease. (21)

The fact that the membrane is not demonstrable in stillborns or in liveborns who do not live more than one hour has been investigated and such theories as "an unknown factor needing oxygen for membrane production" (16) have been presented. The membrane "as a response to infection" (16) has also been suggested.

The Endogenous Theories.

A decrease in vagal chemoreceptor activity due to a decrease in blood pH and an increase in serum potassium attendent with early perinatal physiological changes have been suggested as the basis for

membrane formation. The decreased vagal chemoreceptor activity leads to relaxation of bronchi which then results in acute emphysema. The capillary dilatation and sudden change in pulmonary vascular dynamics which follow this may lead to left heart failure and pulmonary edema with formation of a membrane in conjunction with pulmonary edema. (16)

For a time the estrogen:progesterone balance in pregnancy was considered as a possible mechanism for membrane formation. Estrogen, which generally dominates pregnancy, is known to cause body cells in general to be less permeable; while progesterone, the level of which falls terminally but is quite high early in pregnancy, seems to cause cells to be more or less permeable. From these observations, it was suggested that in premature births, early induced deliveries, and cesarean sections the progesterone level might still be relatively elevated and thus be in some way related to the production of a pulmonary transudate. The fetal lung resorbs fluid at a very rapid rate and since water is absorbed more rapidly than solids, the residue might form a membrane. (22)

The sudden vascular dynamic changes associated with birth and the initial respirations have been studied. These changes are namely, discontinued placental flow and resulting decreased venous blood flow, a decrease in right atrial pressure, an increase in the volume of the pulmonary capillary bed and a decreased right ventricular pressure, and an increased left atrial and ventricular pressure.

These changes cause severe demands on the cardiovascular systems of all newborns but especially on those of premature infants since their pulmonary vascular bed, left ventricle and ductus arteriosus are not yet ready for the stress of sudden change. If the demands cannot be met, there is an early state of pulmonary congestion leading to an increase in pulmonary blood pressure. Edema fluid from this pulmonary hypertension infiltrates into the alveolar spaces and acts as an incomplete barrier to air exchange. The resulting decrease in blood oxygenation adds to the imminent left heart failure on the basis of myocardial anoxia. The pressure in the right ventricle becomes greater than that in the left ventricle and there is resumption of fetal blood flow through the still patent foramen ovale which results in a decreased pulmonary pressure. Since the newborn lung has marked powers of resorption, water is resorbed faster than the protein and terminally the resorption is proposed to lead to atelectasis and consolidation, the formation of a membrane questioned as possibly merely an artefact. (23)

A truly different point of view is presented by Gruenwald (6) who states that very little that is presently known about the disease is actually verified. He claims that the very name "Hyaline Membrane" disease is a misnomer and for years has alluded to the name as an "eosinophilic red herring." His basis for this particular point is that the membrane is an inconstant finding in the clinically diagnosed disease and that it is a secondary manifestation

of many forms of respiratory diseases including such entities as atelectasis of prematures, aspiration of vernix caseosa, cesarean section and maternal diabetes in the newborn, viral pneumonias in older infants, and a host of adult diseases. Some adult diseases in which a hyaline membrane has been reported include varicella, poliomyelitis, sulfadiazine hypersensitivity reactions, subacute bacterial endocarditis, metastatic carcinoma of the lung, Hodgkin's disease, uremia, milk aspiration, radiation pneumonitis, influenza pneumonia, rheumatic pneumonia, war-gas pneumonitis and plague. (24) Gruenwald suggests the following pathogenesis: the lungs of the premature infant are predisposed to poor expansion. With initial expansion, the bronchioles distend and the alveoli collapse due to high surface tension. There is a low ratio of capacity of the alveoli to that of the bronchioles and with a moderate loss of air with expiration, the alveoli collapse before the bronchioles. In this manner an atelectasis at birth is overcome only to recur with mild apneic periods. The additional burden of a pulmonary transudate initiates a vicious circle once aeration has become inadequate, the dyspnea being even greater since the premature is easily exhausted. Since it takes less effort to expand the bronchioles than it does to expand the alveoli, as the infant tires and respirations become weaker, they also become much less effective. With anoxia, there is a certain degree of capillary dilatation and resultant transudation of fluid into the air spaces. Gruenwald believes that the presence or absence of a membrane depends solely upon the amount

of transudate present.

Some of the above views were experimentally backed up when an investigator attempted to expand the lungs of dead newborns with air. Microscopic examination of these lungs revealed distention of proximal air spaces and an exaggeration of the distal collapse already present. (25)

A RECENT PROMISING ETIOLOGICAL CONCEPT

In 1955, Stevenson and Laufe (26) reported a method by which they were able to fairly consistently reproduce hyaline membrane disease in live guinea pigs which would satisfy all three criteria of the "classic triad" of atelectasis, pulmonary vascular engorgement and an eosinophilic, hyaline membrane lining the alveoli and alveolar ducts. They found that amniotic fluid would cut the clotting time of plasma in half (possibly due to the high thromboplastin content), and injected plasma and amniotic fluid into the tracheas of live guinea pigs under local anesthesia. The amniotic fluid was aspirated prior to elective amniotomies under sterile conditions and was then administered fresh or was deep-frozen and then quick-thawed before use. The pigs were covered with Penicillin and Streptomycin to avoid any infection complicating the experiments. Four groups of pigs were studied as follows:

Group I - 65 pigs - given 1.0-1.5 cc. each of amniotic fluid and plasma.

26 died of pulmonary edema within 30 minutes.
5 died within 5 hours, cause (?).
6 died within 5-72 hours with the triad of atelectasis, engorgement and hyaline membrane.

Group II - 15 pigs - given 1.0-1.5 cc. each of plasma and amniotic fluid, repeated in 3-72 hours.

3 pigs had atelectasis, engorgement and hyaline membrane.

Group III - 7 pigs - given 2 cc. of one part sediment from amniotic fluid and four parts plasma.

3 pigs died early.
4 pigs died later, one of which had hyaline membrane, etc.

Group IV (Control) - Saline alone - no membrane
Amniotic fluid alone - no membrane
Plasma alone - no membrane
Plasma and saline - no membrane

These authors' theory was that plasma caused pulmonary irritation and exudation. The amniotic fluid, besides causing a certain degree of mechanical atelectasis, also acted as a source of thromboplastin to catalyze the clotting action in the exudate formed by the action of the plasma and thereby resulted in the formation of a membrane. This theory was then theoretically applied to the newborn. The newborn aspirated amniotic fluid is high in thromboplastin content. The lungs exude a high protein exudate as a reaction to vagal injury, high oxygen concentration, anoxia, etc. The amniotic fluid clots the exudate and as the serum from the clot is resorbed, a hyaline membrane is formed. The clotted exudate plugs alveolar ducts and bronchioles leading to atelectasis. The anoxia ends terminally in asphyxia unless the amount of exudate and membrane formation is minimal and/or unless there is an extremely active phagocytic process.

In 1959, Lieberman (27) proposed a new concept in the etiology of hyaline membrane disease based on an absence of a fibrinolytic enzyme system in infants who succumbed to the disease. An assay for presence of tissue plasminogen (fibrinolysin) activity was carried out on 41 fetuses and infants who were stillborn or died in the neonatal period of causes other than proven hyaline membrane disease. Activity was found as early as the third fetal month and

of the 41 cases, 10 demonstrated no activity. These ten were scattered throughout the range of weight and age and thus immaturity was considered not to be an essential factor governing the presence or absence of the activity. Eight newborns who died with proven hyaline membranes were also assayed for plasminogen activator activity and none of the eight showed any evidence of activity.

The fact that certain species of laboratory animals were much more susceptible to the experimental production of hyaline membranes suggested that these animals (guinea pigs and rabbits) might also display a lack of plasminogen activity. Guinea pigs, rabbits, mice and rats were assayed for presence of activity and none was found in the guinea pigs or rabbits while activity was demonstrable in rats and mice. Hyaline membrane disease was then experimentally given to two groups of guinea pigs; the first group was exposed only to high concentrations of oxygen and membranes were successfully produced but were very scanty. The second group received high concentrations of oxygen but also received a fine spray of filtered amniotic fluid and the hyaline membrane formed was very dense. This lent support to the theory that the amniotic fluid seemed to have a catalyzing effect upon the formation of a membrane.

From these studies, Lieberman concluded that the mechanism of production of a hyaline membrane was probably similar to that of an intravascular fibrin deposition which is seen with amniotic fluid embolism. Under normal conditions, the body is able to lyse the

fibrin, presumably through activation of an enzyme system. If the fibrin found in pulmonary hyaline membrane disease had the same etiology, namely through the action of thromboplastin in amniotic fluid upon the normal constituents of the plasma clotting mechanism (alveolar effusion), it was believed that the normal newborn would be able to liquify the fibrin through activation of the intact fibrinolytic system. Therefore, if certain infants either are lacking in the enzyme or activator system or have a decrease in the activity of either, or have some excessive inhibitory process, a hyaline membrane might feasibly be formed. This formation would depend not only on the absence of fibrinolytic activation but also on the aspiration of amniotic fluid, the alveolar effusion being explained as a reaction to the anoxia of birth.

The fact that activity was variably present (or absent) at all fetal ages after three months seems to direct attention toward the possibility of a congenital factor rather than a question of an immature enzyme system. The increased frequency of hyaline membrane disease in cesarean sections and in infants born of diabetic mothers was not explainable with the working theory but the suggestion was offered that, in the case of cesarean section, perhaps this is a reflection of greater susceptibility to amniotic fluid aspiration.

As an additional investigation, the question of a possible genetic factor was studied. The maternal histories of three groups of infants who died with hyaline membrane disease and absence of plasminogen activator activity were reviewed. In the first group

of 18 mothers, 5 had histories of having delivered live premature infants that died within 48 hours of birth. A second group of 5 mothers whose infants did not have membranes but were without fibrinolytic activity revealed one mother who had delivered a premature infant that lived only 15 hours. The last group consisted of 19 mothers whose infants died perinatally and who also had no fibrinolytic activity. In this group, no previous peri-natal deaths were reported. This study was by no means conclusive but offered a promise of significant findings in further, more extensive study.

If Lieberman's findings can be duplicated and the exact deficiency can eventually be found, there is a distinct possibility of finally finding a definitive treatment for the disease through replacement therapy.

RECENT DEVELOPMENTS IN THE THERAPEUTIC FIELD

In November of 1959, Usher reported on an interesting correlation of electrocardiographic tracings and serum electrolyte levels with a hint a prognostication in newborns with respiratory distress.(28)

The infants under study were limited to those weighing from 500 to 2,500 Gm. who for hours or days after birth have chest retraction, expiratory grunting, and auscultory evidence of a decreasing entry of air without any evidence of other disease. Fatal cases in this group revealed atelectasis, hyaline membrane formation and congestion. One-hundred and seventeen infants were studied, fifty-nine prematures with respiratory distress,

of whom 38 died (55% mortality), 45 prematures without respiratory distress, of whom 3 died of bronchopneumonia, and 13 normal term infants. All the prematures had a high humidity environment and oxygen if cyanotic. Serial physical examinations, x-rays, electrocardiograms and blood studies revealed the following information:

Electrocardiogram. Abnormalities appeared after 12 hours in infants with respiratory distress but not in those without it. Of the "controls" who expired, none showed any ECG changes. Those with respiratory distress began having abnormal ECG patterns at from 12 to 60 hours, being normal (like those of controls) during the first 12 hours.

Abnormal changes consisted of:

1. A prolonged PR interval over 0.11 sec.
2. A prolonged QRS interval over 0.04 sec.
3. Decreased QRS voltage in standard leads
4. A prolonged QT interval
5. Broadening and flattening of T waves
6. Left axis deviation and left ventricular preponderance.
7. Absence of P waves
8. Peaking of T waves
9. A two-to-one A-V block

Of these changes, the first six were most commonly observed, the abnormalities increasing in number and severity until death or disappearance with recovery. The prolongation of the PR and the QRS intervals was the most constant finding and this was not related to the heart rate. The mean heart rate in the infants with respiratory distress was 138/min. and the control was 144/min.

Serum potassium concentration. The levels found in the control

infants ranged from 4.2 to 7.0 mEq/L. and from 5.1 to 6.8 mEq/L. for prematures and for full term infants respectively. Infants with respiratory distress were found to have normal ECG conduction times when the K concentration was below 7.0 mEq/L. but prolonged times with levels above 7.0 mEq/L. The mean K rose from 5.1 in the first 6 hours to 9.0 at 18-24 hours and fell after 48 hours. Changes in K concentration compared quite closely with ECG changes.

Eighteen of 29 infants with respiratory distress had K levels of more than 8.0 mEq/L. and a close correlation was established between K levels and mortality; e.g. none of the 8 with K levels of over 10.0 mEq/L. survived, 1 of 4 with levels of 9-10 mEq/L. survived, 3 of 8 with levels of 8-9 mEq/L survived, and 6 of 11 with levels of less than 8.0 mEq/L. survived. A progressive rise in K concentration was closely correlated with a deteriorating electrocardiograph.

The Effects of Treatment. Solutions of glucose, insulin and bicarbonate were given to infants with respiratory distress when they appeared to be dying and within 10 minutes the serum K had decreased, the ECG pattern had improved and the infants showed clinical improvement. Eighteen of 24 such infants went on to die and 6 lived, but it was not possible to say with any certainty that their change of course was due to the treatment. The mean age at death of those who were treated was 58 hours while that of the untreated infants was 37 hours. The solution consisted of 15 Gm. glucose, 5 mEq. sodium bicarbonate, 7.5 Units regular insulin per 100 cc. of

water at the rate of 60 cc/Kg/day until adequate oral intake could be established.

From this data the following conclusions were derived:

Premature infants with respiratory distress develop hyperkalemia with resulting abnormal electrocardiographic changes. Those without respiratory distress do not develop these changes of potassium levels. A high serum potassium might then be of assistance in differentiating respiratory distress from some other entity.

Hyperkalemia may be a direct cause of death, since there was a good correlation between potassium levels and mortality, and since life appeared to be somewhat prolonged after treatment and subsequent lowering of the potassium level.

Since most of the infants die even after treatment of the hyperkalemia, it has not been proved that such treatment is actually effective, although most of the infants were nearly terminal before treatment was initiated.

Parenteral treatment may very well be more effective if begun earlier, perhaps even as a routine sort of prophylaxis.

The exact cause of the hyperkalemia in respiratory distress is uncertain. Among the most likely possibilities are respiratory acidosis, dehydration, starvation, shock, adreno-cortical exhaustion, and inability of the neonatal kidney to handle heavy solute loads.

The evidence suggests that premature infants with respiratory distress develop a toxic degree of hyperkalemia which is reversible.

SUMMARY

Pulmonary hyaline membrane disease has been considered from the clinical, pathological, radiological, and etiological aspects and some of the recent experimental work in the field of definitive therapy has been presented.

CONCLUSIONS

The exact etiology of pulmonary hyaline membrane disease is as yet unknown, but recent work, such as that of Stevenson, Laufe, and Lieberman seems to indicate that the answer may be near at hand. In spite of the apparent complete disparity of views by the many workers in this field, it is altogether possible that they are all partly correct since this disease is most likely no different than most other diseases, in that the final pathology is a reflection of the entire body's response to a stimulus and is not just the response of a single organ system. Lieberman's work certainly justifies further investigation in the same direction, and even if it does not eventually result in solution of the problem, it will have opened up new pathways for the study of enzyme systems and perhaps added something to the field of genetics. This is just another example of apparent failure in one field of scientific endeavor leading to important discoveries in another. The very recent contribution by Usher regarding serum potassium levels, ECG changes and the empirical treatment of hyperkalemia with a significant degree of reversibility is a most heartening addition to the field.

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