1954

The Problem of the pulmonary hyaline membrane in newborn infants with emphasis on its pathogenesis

William J. Chleborad
University of Nebraska Medical Center

THE PROBLEM OF THE PULMONARY HYALINE MEMBRANE IN NEWBORN INFANTS WITH EMPHASIS ON ITS PATHOGENESIS: A Review of the Literature

William John Chleborad

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

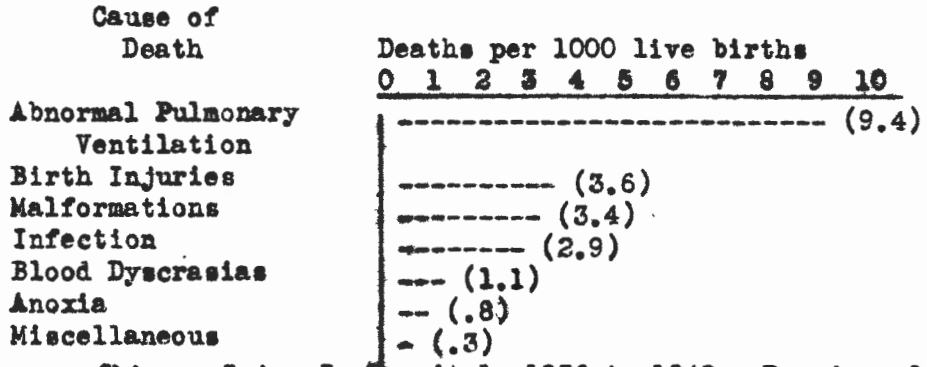
March 1, 1954

Omaha, Nebraska

OUTLINE

Much renewed interest has arisen in the recent literature regarding the high incidence of mortality in infants, especially of those in the newborn period. Prematurity is by far the most important cause of death in this early period of life, but too often, this diagnosis is made merely because of inability to ascribe a more specific process resulting in death. Causes of neonatal death are obscure. Dunham, in 1948 said, "Even if clinical and postmortem examinations...on prematures...are made carefully, there will still be a large proportion of cases in which no specific cause of death is determined". (23) Data in her book show that prematurity alone was the chief cause of death found in 121 autopsies out of 348 done on prematures by Edith Potter at the Chicago Lying-In Hospital. Approximately 5-6% of all infants born alive weigh less than 2500 gms., (ie) are premature, and more than 50% of infants who die within one month of birth are in this group. (54) In another study, made in 1951, nearly one-half (46%) of neonatal mortality is ascribed to prematurity, and the incidence of premature live births in the U. S. is 7-11%. (58) This incidence is slightly higher than that previously reported by Potter. In 35% of these cases, it was said, a cause of death could not be determined. Another observation, from 1941 to 1950, at the Evanston Hospital, reported that prematurity accounted for 54% of the deaths in their series. (80) At the Southern Baptist Hospital in New Orleans, of 266 infant deaths, 134 were neonatal. 56% of these deaths were ascribed to prematurity. (19) At the University of Nebraska Hospital, from 1940 to 1950, prematur-

ity was also the major factor in causing fetal death. (65) An analysis of the caused of death at the Bellevue Hospital by Labate, based on 868 autopsies, listed prematurity as the highest cause of death (27.6%), with pulmonary lesions (22.5%) second, and birth trauma (16.9%) next. (36) At Chicago, from 1936 to 1949, an analysis of 8,905 postmortems on premature neonatal deaths revealed 43.7% of the deaths were due to abnormal pulmonary ventilation (16.6% birth injury, 15.8% malformations. 13.4% infection). (67)

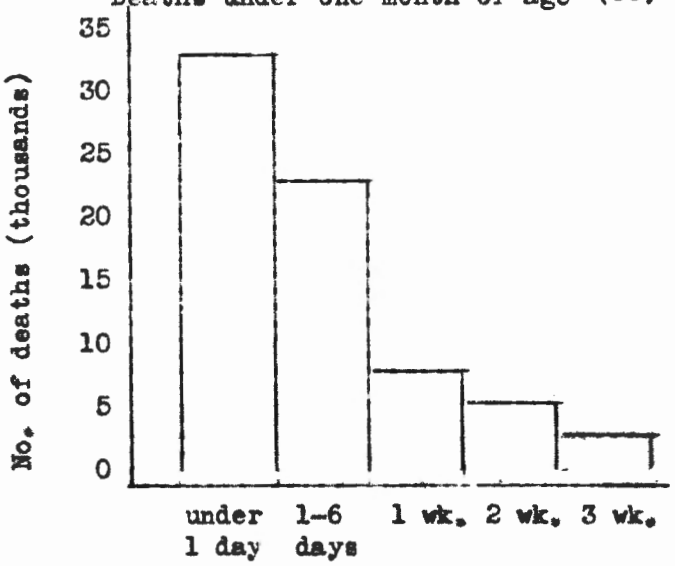


Chicago Lying-In Hospital, 1936 to 1949. Based on 8,905 neonatal deaths and 873,310 births. (17)

From the few random records just presented from various hospitals throughout the country, it is obvious that the problem of neonatal mortality, especially concerning prematures, is, as yet, a large and unsolved one. In order to expand on the problem further, it has been shown that 97% of the deaths, or almost all of those attributed to premature birth, occur during the first month of life. Of these, 57% occur during the first 24 hours. (58) At the Evanston, Ill. Hospital, of 86 premature deaths occurring in the first ten days of life, 54, or 62% occurred under 12 hours. (80)

At the Chicago Lying-In Hospital, the percentage of deaths in the first day was over one-third of those occurring in the first year of life. (17) It was said by these authors that over 50% of these neonatal deaths occurring in the first day of life are due to abnormal pulmonary ventilation. It is obviously of special concern.

Deaths under one month of age (58)



During the past ten years especially, much attention has been given to pathologic conditions found in the lungs of premature, and even mature infants. Most deaths that are related to the fact that an infant is premature are caused by pulmonary disturbances. (54) In 1938, Farber, in an article on Unexpected Death in Early Life, said that even in some closely observed hospital cases, the cause of death was unexpectedly found in the lungs. (25) It is obvious that neonatal death may result from an interference with aeration of the lung.

Pulmonary lesions are greatest in incidence among infants

between 1000 and 2000 gms. according to material studied by Miller and Jennison at the University of Kansas. (45) Helen Reardon (58), in 1951, gave three explanations for the respiratory failure of premature infants who are free from infection or congenital anomalies. These include:

"(1) Injury associated with trauma of birth to centers responsible for the nervous control of respiration.

(2) Ineffective action of feeble respiratory muscles...

(3) The state usually diagnosed as 'atelectasis' when either the lung is (a) not capable of expansion, or (b) anatomically perfect and expansible, but not expanded for some physiological reason."

Tucker, from Chicago, in Sept. 1953,
pulmonary ventilation includes deaths, exclusive of those from anoxia, where no specific pathology was present outside the lung. (78) This is a very interesting statement, and readily applicable to an entity found in newborn lungs causing abnormal pulmonary ventilation with which I shall deal in this paper, for, often times, an erroneous diagnosis for the cause of death is made when no pathology is found outside the lungs, and the term 'atelectasis' is written on the death certificate.

Abnormal pulmonary ventilation can, itself, be broken down into a number of conditions related not only to lung pathology, but to heart and brain pathology as well, such as anoxia of the respiratory center. This paper is not concerned with these conditions

although, it will be necessary to discuss anoxia and respiration of the fetus, both intra- and extrauterine. Of those entities found in the lung, the terms 'atelectasis' and 'asphyxia' are loosely used. Atelectasis, whether primary or secondary is frequently encountered in prematures and is the most important of death among them.

Of the pulmonary abnormalities found atelectasis of the newborn, the most striking is the presence of a hyaline membrane. It has caused widespread discussion and controversy among pathologists, pediatricians and obstetricians alike. Much has appeared in the literature, and numerous studies have been made in the past fifty years concerning this condition, its relation to fetal and neonatal mortality, and its pathogenesis, in an attempt to reduce the incidence of the disproportionately high occurrence of abnormal pulmonary ventilation in an altogether too great a neonatal death rate. This subject is obviously an important one such membranes are the single , most constant finding to which the death of premature infants are attributed." (59) In 1952, Potter estimated that annually, 10,000 to 20,000 premature infants who die within the first two weeks of life have a hyaline like lining in their lungs. (55) This striking figure is obviously cause for concern.

Considerable confusion and disagreement has existed concerning the incidence, etiology, pathology and treatment of this condition. Because of its importance in reducing neonatal death,

and because of the controversial nature of the subject, a review of the literature concerning the pulmonary hyaline-like membranes in newborn infants was made, with special reference to its pathogenesis. Since the presence of such a membrane, and possibly its etiology is presently thought by some to be closely associated with the presence or abscence of intrauterine respiration, it is deemed necessary also to carry on a discussion of such respirations.

Various names have appeared in the literature, all of which are related to the same entity, which, in this paper, I shall refer to as the pulmonary hyaline membrane of the newborn. Titles of some of these articles related to this subject depict either the type of membrane, the pathological process undergone as a result of the membrane, or, in the authors opinion, the etiology of the membrane. These synonyms include: Aspiration of Amniotic Fluid; Aspiration Pneumonia; Congenital Aspirational Pneumonia; Asphyxia Membrane; Hyaline Membrane; Vernix Membrane; Eosinophilic Membrane; Necrotic or Exudative Membrane; Resorptive Atelectasis; Congenital Alveolar Dysplasia; Desquamative Anaerosis; Oxygen Poisoning.

Regardless of the name applied to the phenomenon, certain features brought out by each advocate are in common. The clinical findings of these newborns found to be dying with atelectasis and the presence of the pulmonary hyaline membrane are characteristic. Certain predisposing factors seem to be present. It occurs much more frequently in viable premature infants (1,000 to 2,500 gms.) and less in full terms, over 2,500 gms. Reports on percentages of viable prematures found with the membrane rage from about 6% reported by Miller & Jennison (45) to 100% reported by

Johnson (32) in 1923. There is still much controversy as to whether or not it is found in stillborns. Miller & associates (45) reported three cases. The problem, however, is one involving primarily the premature infant. Since it has reportedly been found so rarely in stillborn infants, the condition seems to be associated directly with extrauterine breathing.

Another predisposing factor is thought to be intrauterine distress resulting from a state of anoxia and causing the aspiration of amniotic fluid in utero. This also is controversial, and arguments will be presented.

Delivery by Cesarian section may also be predisposing. For some as yet unknown reason, the relative percentage of infants having hyaline membranes following delivery by Cesarian section is greater than in those delivered vaginally.

Clinical Signs And Symptoms

The clinical signs and symptoms of this condition are characteristic, although it is frequently misdiagnosed as intracranial hemorrhage, or even congenital heart disease. According to J. R. Schenken (67), cyanosis is the primary symptom, having occurred in 65% of the cases at Childrens and Methodist Hospital. Sidney Farber in 1938 (25) said, "The most frequent cause of pulmonary cyanosis is aspiration of amniotic sac contents, demonstrable by the presence of...hyaline membrane...". Characteristically, the onset of respiration is spontaneous following an uncomplicated delivery in most cases.

Respirations, and other activies, continue normally for an hour or two following delivery, but after this short period, breathing becomes difficult. There is increasing dyspnea and cyanosis which becomes progressively worse. If placed in oxygen, the baby may breath normally for awhile, but soon becomes cyanotic again and respirations become shallow. The sternum and lower ribs may be retracted from respiratory effort. Death frequently occurs in 24 hours following delivery, but may be prolonged to four or five days. Cause of the death is abnormal pulmonary ventilation as a result of atelectasis and a hyaline membrane lining alveoli and alveolar ducts, acting as a barrier to gaseous exchange between alveoli and capillaries. X-ray findings are usually of progressive atelectasis with areas of emphysema. Cardiac dilatation may be present.

The following is a typical case report taken from the files of J. R. Schenken (67) at the Nebraska Mathodist Hospital:

> Full term W.M., one day old. Normal, spontaneous delivery with somewhat difficult resuscitation. Appeared normal after short period of cyanosis. Cyanosis again appeared several hours later. It was easily corrected, and remained so except when placed in oxygen.
> Physical Examination: No evidence of cyanosis while in oxygen. Fontanels 2 x 2 cms. - no bulging or depression. No murmurs. Lungs clear. No other findings.
> Laboratory Work: Hgb. 17 gms. R.B.C. 5.07. W.B.C. 24,100. Segs. 37, Staffs 39, Lymphs 21, Monos. 3.
> X-rays: Cardiac dilatation, chiefly right ventricle. Increased expansion of right upper lobe of lung. Small lobular areas of density in the lungs, indicating neonatal atelectasis.
> Course: Downhill. Respirations grunting. Difficulty swallowing. Death 48 hrs. following birth.

Pathology

Pathologically, the picture is again characteristic. E. L. Potter, (57) has described the gross appearance of the lungs as being a uniform dark red-purple color, of the consistency of liver. This is the appearance of an atelectatic lung, but areas of emphysema are also seen. She said the aletectasis is more complete, and the hyaline material greater in amount in those infants who die in the first few postnatal hours. Microscopically, there are areas of collapsed alveoli, giving a solid, atelectatic appearance. Other areas have dilated alveoli lined by irregular layers of a dense, homogeneous, granular, eosinophilic staining material. Desquamated squamous epithelial cells are oftentimes found imbedded in th s hyaline-like membrane. Rosenthal, (61) said, "The most reliable and constant evidence of aspiration of amniotic sac contents was the presence of desquamated epithelial cells". Lanugo hairs and meconium may also be present.

Histochemically, much remains to be done before conclusions can be drawn regarding the material comprising the membrane. The exact nature of the chemical composition is not fully understood. Many investigators have based their opinion concerning the pathogenesis on the fact that the membrane contained fat which could be stained with Sudan III. Hence, they arrived at the theory of a 'vernix membrane' resulting from the aspiration of vernix caseosa. Since fat stains have not been positive in every case, considerable suspicion has been cast on

the vernix theory. Johnson, (33) in 1925, noted that staining showed the membrane to be loaded with fat droplets. Farber & Sweet (26), in 1931, recognized fat droplets of various sizes dispersed in the membrane. They said it represented vernix. Miller & Hamilton (44), however, say that fat is derived from the fetal circulation as a result of injury to the capillary bed of the lungs. Rosenthal (61) attributes the fat droplets the accumulation of cellular debris. Dick & Pund (22) have reported that some membranes take a fat stain while others contain little or no lipid. Arey (5) objects to the vernix theory because of equivocal results obtained in sections for fat. Claireaux (18) found that often, but not always, neonatal fat is present. All authors agree that no fibrin is present. Several men have said that chemical elements found to be negative by various methods include: iron, mucin, elastic tissue, serum proteins, red blood cells, and bronchial epithelial cells. Polysaccharides, however, are reported as being present. (76) Potter (59) has found protein (tyrosine and arginine) to be present.

Association With Pneumonia

A few words must be said about the association of the hyaline membrane with pneumonia in the newborn, whether or not such an association exists. Certain of the earlier investigators said an association does exist. Johnson (33) described the hyaline membrane as "pneumonia in the newborn with lesions resembling influenza". Helwig (31) reported all stages of pneumonic

consolidation were observed in microscopic sections of lungs containing large amounts of amniotic fluid. Agnes MacGregor (38), in 1939, in a pathological examination of 541 ncropsies of infants, found that 177 of them showed inflammatory changes in the lung with aspiration of amniotic sac contents. Some foreign authors as Hook & Katz, and Steinharter (76) also emphasize the association. Mitchell & Nelson (46), in their Textbook of Pediatrics, have a section on Aspiration Pneumonia in which they say it may result from the aspiration of amniotic fluid. In some instances, they describe the formation of a membrane. More recent investigations, however, de-emphasize the association of pneumonia in the newborn with the formation of a membrane, at least, in so far as the etiology is concerned. In a report by Schneider & Sellers (69), 8.4% of the autopsies in their series showed evidence of pneumonia. They said it develops in the fetal lung during intrauterine fetal life as the result of aspiration of infected amniotic fluid. Others as Blystad, Landing & Smith (13), Schenken (68) and Potter (56), stated that inflammation usually is evident if symptoms persist more than 48 hours. Delee (29), in his Textbook of Obstetrics, also said that if the infant with a hyaline membrane lives longer than 48 hours, a leukocytic infiltration may occur and an infectious process may be superimposed. Potter (56) stated she has never seen an uncomplicated case of 'resorption atelectasis' in infants surviving 48 hours. Death subsequent to this is caused by superimposed pneumonia. Schenken's series (68) of 35 cases having

hyaline membrane, also showed evidenc e of pneumonia in sy of these. However, the duration of life with no pneumonia was 2I hours. While those infants with superimposed pneumonia lived 36 hours. (Ave.) It evidently, "required the addition of pneumonitis to cause death."

Complications of Pregnancy

Some controversy is also found in the literature concerning the relationship of the complications of pregnancy and labor with the finding of a hyaline membrane in the newborn lung. Helwig (31) said the incidence of hyaline membrane is higher when there are complications of pregnancy. MacGregor (40) said the liquor amnii is inhaled because the fetus is asphyxiated in utero. Russ & Strong (64) have shown in their series that Cesarian section, for whatever complication of pregnancy, has relatively increased the incidence of hyaline membrane. Labate (36), and others, said the aspiration of large quantities of amniotic fluid occurs as the result of fetal intrauterine anoxia. Schenken (68) showed the second of twins is more likely to aspirate amniotic fluid. Miller (45) suggested the pulmonary lesion might be related to deficiencies in protein of the maternal diet, though he did not stree this aspect. In the series of Tregillus (77), in 9 of the 35 cases of hyaline membrane, there were complications of pregnancy, "which might have caused anoxia to the fetus". Blystad, Landing & Smith (I3) said that Cesarian section, fetal distress and placenta praevia accounted for 43% of cases of membrane formation compared with 8% who did not have complications. Baty (9), in 1952, showed that

maternal diabetes increased the incidence of respiratory complications in the newborn. In a detailed report by Claireaux (18), of 22 infants having hyaline membrane and delivered by Cesarian section, complications of pregnancy were present in all but one. Thirteen had pre-eclampsia, three had placenta praevia, three diabetes, and two had ante-partum hemorrhage.

No correlation concerning the incidence of membrane formation could be made by Potter (54) in relation to any particular type of delivery except for its higher incidence following Cesarian section. She said that it may be found following any type of delivery. She further said there is no relationship to maternal complications, type or degree of anaesthesia, time of rupture of membranes, or to any other known condition.

Work by Bruns & Shields (16) confirm reports by Miller & Jennison (45) that parity, age, race, serology, Rh factor, analgesia, anaesthesia, maternal and obstetrical complications, or type of delivery bear any direct relationship to the formation of the hyaline membrane. "One-third of the mothers delivered prematurely without apparent cause, while maternal complications which predispose to or are associated with prematurity occurred in two-thirds of the cases." Most recent authors emphasize the fact of increased incidence of the membrane formation following Cesarian section. Contrary to those delivered vaginally, the majority of these are full term infants. No plausible theory has been advanced to give reason to these findings. Potter (57)

recently pointed out an associated finding in death following Cesarian section. Th s is the observance of meningeal edema and an increase in sub-arachnoid fluid which were prevalent along with the hyaline membrane.

Pathogenesis

The biggest diversity of opinion concerning the pulmonary hyaline membrane of the newborn is still centered around the pathogenesis. In reviewing the literature, this aspect was found to be most interesting, and for this reason, as well as, in an attempt to afford the reader a knowledge of the work which has been done on this subject, I will present in chronological order the thoughts of various investigators who have attempted to derive an etiology for this rather mysterious phenomenon. As was tabulated previously, the terminology of the subject is somewhat confusing, and various names have been applied to what apparently is the same entity, indicating the diversity of opinion concerning the pathogenesis of the membrane. The literature goes back a half century, but it has only been n the past ten years that renewed interest has been taken in the subject. Table I is a brief composite of the incidence of hyaline membranosis, as well as each authors theory of etiology which I found reported in the literature. It is seen that of 6,659 autopsies done on newborn infants, 892 cases of hyaline membranosis are reported. Of those reported, 3,133 were liveborn infants, of which a membrane was demonstrable in 619. From these figures, it is seen that 19.7% of liveborn infants have a hyaline membrane.

TABLE I

Summary of cases in the literature (1903-1953) of Hyaline-Like Membranes in the Newborn Lungs.

Yr.	Author	No. Autopsies	No. cases with Memb.	% age	Pneumonia	No. Liveborn	% live. with Memb.	C. sections Auto.	C. sections Cases	C. sections %	Pathogenesis
1903	Hoccheim	43	2	4.7	0						Asp. Amn. Fluid
1923	Johnson	4	4	100.	0	(case histories)					Asp. Irritating Matl.
1925	Johnson & Myer	500	8	1.6	97 (19.4%)	97	7.2				Asp. Am. Fl. and Vernix.
1928	Hook & Katz	73	1	1.4	0						Aspiration, Irritation.
1931	Farber & Sweet	124	18	14.5	0	124	14.5		3		Asp. Am. Fl. and Vernix.
1932	Farber & Wilson	50	50		0	(Experiments on rabbits)					Asp. & Mech. Dispersion.
1932	Hunt	118	11	9.4	0	118	9.4				Asp. Amn. Fluid.
1933	Rutledge	43	2	4.7	0						"
1933	Helwig	159	2	1.3	66	159	1.3				"
1935	Rosenthal	100	31	31.0	0	62	50.				Desquamative Anaerosis.
1937	Steinharter	2	2		0	(case histories)					Asp. & Mech. Dispersion.
1939	Patterson & Farr	25	1	4.0	0	12	8.3				Asp. Amn. Fluid.
1939	MacGregor	541	11	2.0	177	448	2.4				Asp. & Mech. Dispersion.
1940	Benner	70	2	2.9	0						Asp. and Infection.
1942	Ahlstrom	27	5	18.5	0						Aspiration, Condensation
1946	Russ & Strong	12	9	75.0	0			12	9	75.	Aspiration Pneumonia.
1947	Ahvenainen	108	42	38.8	0	81	50.				Asp. Am. Fl. Desquamation

TABLE I (Cont't.)

Yr.	Author	No. Autopsies	No. cases with Memb.	% age	Pneumonia	No. Liveborn	% live. with Memb.	C. sections Auto.	Cases	%	Pathogenesis
1947	Arey	22	4	18.2	0						Asphyxial Membrane.
1947	Labate	868	4	.46	(27%)	319	1.3				Asp.Amn.Fl. Absorption.
1947	McMahon	2	2	100.	0						Develop. Anomaly.
1947	Schenken	80	32	40.	17			80	6 (5 full term)	7.5	Asp. Amn. Fluid.
1948	McMahon	3	3	(case histories)		3		3	1	33.	Develop. Anomaly.
1949	Arey	50	8	16.	0	45	17.7				Asp. Amn. Fluid.
1949	Dick & Pund	119	7	5.9	0	60	11.6				Asp.Amn.Fl., Dispersion, Resorption.
1949	Gellis et al										Ingestion & Regurg. Am.Fl.
1949	Miller & Hamilton	79	26	32.9	0	47	55.3				Epithelial Injury.
1949	Tesseraux	1	1	(case histories)							Asp. & possible oxygen poisoning.
1950	Arey & Dent	20	15	75.0	0			20	3	15.	Asp. Vernix.
1950	Miller & Jennison	93	31	33.3	0	71	43.6				Intrauterine Injury.
1950	Potter	125	40	32.0	0	125	32.0				Resorption Atelectasis
1951	Behrle	55	13	23.6	0						Membrane preventing lung expan.
1951	Blystad	509	97	19.0	0	322	30.1			27.	Aspiration, Condensation.

TABLE I (Con't.)

Yr.	Author	No. Autopsies	No. cases with Memb.	% age	Pneumonia	No. Liveborn	% live. with Memb.	C. sections Auto. Cases		%	Pathogenesis
1951	Bovet & Dubois	36	29	80.5	0						Asp. Am. Fl. Oxygen poisoning.
1951	Bruns & Shields	703	114	16.2	0	439	26.9				Intrauterine Anoxia & O_2 Poison.
1951	Kaufman & Spiro	37	23	62.1	0						Congenital Anomaly.
1951	Simpson & Geppert	268	22	8.2	0	114	19.3				(None given)
1951	Tregillus	244	35	14.3	3	122	28.7	35	5	14.3	Necrosis & hyalinization bronch. epith.
1952	Benitz	100	12	12.0	0						Asp. Vernix, Contact with air.
1952	Schneider	266	54	24.1	13 (8.4%)						(None given)
1952	Schoenvogel	109	1	0.9	0						Congenital Malformation
1953	Claireaux	810	108	13.6	0	376	29.0	108	22	20.	Hyalinization of squames & dispersion.
1953	Jones	46	1	2.2	0				1		(None given)
1953	Potter	(No new cases reported)					3/1000 live births.				Resorption Atelectasis
1953	Uni. Nebr. Hosp.	15	8	53.3	0			12	8	66.6	Asp. Amn. Fluid.

It is impossible to draw any specific conclusions from these figures because of several variable factors not reported by each author, such as the total number of cases studied, whether or not the autopsies include stillborns, and the viability of the infants.

A German pathologist, Hoccheim, in 1903, first reported seeing a peculiar membrane in two newborn infants. The term 'myelin' was applied to the substance which he saw in the lungs, and he believed it was formed from desquamating cells of the alveolar epithelium. (76)

An interesting sidelight is that in 1919, Goodpasture believed a pulmonary hyaline membrane to be peculiar ot the inflammatory reaction of influenza. The etiological factor predominating in this condition, (as well as inhalation of war gases producing a similar lesion) was thought to be exposure to some agent exerting a strong irritative and destructive on the walls of the air passages. (32)

In 1923, Johnson (32) reported four cases at the Sloan Hospital, New York, in which he found lesions resembling influenza in these newborns. All were premature and had the hyaline membrane with no other findings. There were no maternal complications, but one was delivered by Cesarian section. He said that it was produced by condensation of a granular precipitate, probably derived from an inflammatory edema, but possibly also from the aspiration of some irritative substance either during labor or birth.

Two years later, a report was given by Johnson & Meyer (33) on their investigations of 500 autopsies at the Sloan Hospital in which they found 8 cases of pneumonia associated with a hyaline membrane. They gave the probability that the coating of walls of smaller air passages with a layer of viscous material was derived from aspirated epidermal cells and fat of vernix caseosa. Asphyxia and atelectasis results when the air passages become choked by this material.

In 1928, Hook & Katz, from Germany, reported one case of hyaline membrane found in 73 autopsies. They regarded it as aspiration of amniotic sac contents and resultant irritation. (76)

Farber & Sweet, in 1931, (26) said the term 'hyaline membrane' is a misnomer, as the membrane is formed of vernix. Hence, they gave the name 'vernix membrane' to the entity. They studied 124 unselected cases of neonatal death occurring in five weeks or less and found that 18 had aspirated large quantities of vernix and epithelial cells, a number of which also had evidence of membrane formation. They also believed the aspiration of vernix is precipitated by intrauterine asphyxia, and state, "the greater and more prolonged the intrauterine asphyxia...the larger is the size, and the greater the number of membranes in the lung".

A year later, Farber & Wilson (25, 27, 83) said the bulk of the membrane is composed of vernix caseosa, but there is no evidence of necrosis in association with it. They consider the masses of eosin staining material found free in alveolar spaces

in the newborns as early stages in the formation of the membrane before it has been dispersed toward the periphery and ultimately applied closely to the alveolar wall in membrane formation.

In 1933, Helwig (31) reported on 159 necropsies at St. Lukes Hospital in Kansas City, Missouri. He found the frequent occurrence of amniotic sac contents in pulmonary alveoli of newborns and reported two cases of membrane formation. He described all stages of pneumonic consolidation but did not get the impression that the aspirated fluid acted as an irritant to the alveolar lining. According to his report, "in some cases, birth trauma might have been a factor in producing brain hemorrhage which in turn could then, by pressure on the respiratory center, stimulate premature respiratory efforts with resultant filling of the lungs with amniotic fluid. This theory is not plausible in the majority of cases since no other pathology can be found.

Rosenthal (61), in 1935, afforded a new term to the phenomena - 'desquamative anaerosis'. This author found that the membrane was not present with pneumonia, but was usually associated with marked fatty and granular degeneration and desquamation of bronchial epithelial cells. The term he uses is descriptive of pulmonary lesions in asphyxia in which large amounts of desquamated bronchial epithelial cells are found lining the small bronchioles and alveolar ducts. Thirty-one cases also had a pink staining membrane. In these cases, there is intense congestion and edema of the submucosa with cloudy swelling and fatty degeneration and

even detachment of bronchial epithelial cells.

In 1937, another German, Steinharter, reported on two case histories of the hyaline membrane. He said it was due to aspiration of amniotic sac contents with subsequent dispersion to alveolar walls. (76)

Benner (12), in 1940, tried to correlate infection in sinuses and middle ear with lung infection. He concluded that aspirated vernix appeared to have been forced against the alveolar walls where it lies as a barrier to gaseous exchange.

Ahlstrom, also a German, in 1942, described 5 cases of hyaline membranosis in 27 autopsies, and thought it resulted from the aspiration of amniotic fluid with resultant condensation in the respiratory passages. (76)

In the Edinburgh Medical Journal, in 1943, MacGregor (39) reported on "the remarkable effect produced when inhaled liquor amnii contains any large amount of vernix". In the bronchi and alveoli are masses of structureless, acidophilic material, which, when air enters, is spread out and plastered upon the walls of the air spaces as a membrane, acting as an obstuction to the passage of air. This she terms a 'vernix membrane'.

A great deal more work has been done on this subject from the year 1946 to the present time than had been done in all the years previous to that. Among the most noteable and outstanding papers in this group are those of Russ & Strong, Arey & Dent, Labate, Schenken, Miller, Hamilton & Jennison, Bruns & Shields,

Blystad and colleagues, Tregillus, Claireaux, and Edith Potter of Chicago. Although there is great diversity of opinion among them concerning the pathogenesis, they have done much toward arousing new interest in the entity, and impressing on the medical profession the notoriety of the peculiar phenomenon.

As will be emphasized later, a significantly high percentage of babies exhibiting this membrane have been delivered by Cesarian section. In 1946, Russ & Strong (62, 63, 64) dealt a great deal with the problem of infant deaths following Cesarian section. Of 12 deaths following Cesarian section, 9 were found to have died from what he terms 'aspiration pneumonia' (ie) pneumonia due to the aspiration of amniotic fluid containing lanugo, blood, meconium and other detritus. He found that the average Cesarian baby will not breathe within 30 seconds, and suggested that routine intratracheal catheterization be done. About 3.7 cc. of a thick mucoid material can be aspirated, whereas in those babies delivered through the normal birth channel, only 1.2 cc. is found. In their large series, death rate following Cesarian section after which intratracheal catheterization had been done was 2%. This incidence was 9-10% in the group on which the procedure had not been done.

Arey (2), in 1947, described four cases of asphyxia in 22 premature deaths to which he ascribed a pink staining membrane lining the alveoli. He called it an 'asphyxial membrane' due to aspiration of large amounts of amniotic sac contents as a result of fetal asphyxia. A later series by Arey (3), in 1949, reported

a series of 50 autopsies in which 8 cases of hyaline membrane were found.

Also in 1947, there were two proponents of the term 'hyaline membrane'. Labate (36) at the Bellevue Hospital in New York admitted the etiology of the condition was unknown, but said it may represent a late effect of intrauterine aspiration of amniotic fluid. The fluid is absorbed following birth and the solid elements of the amniotic fluid remain and become altered to form a hyalinized gummy substance. J. R. Schenken (66, 67, 68), at Nebraska Methodist Hospital says the basic pathology is aspiration of amniotic fluid following which a membrane is formed when extrauterine respiration is established and air enters the lung. He also calls it a 'Hyaline membrane'.

Ahvenainen (76) had written extensively on this subject in 1947 and 1948, reporting on a series of 108 autopsies of which 42 cases of hyaline membrane were seen. He was of the opinion that it resulted from aspiration of amniotic fluid and desquamation of alveolar cells. According to him, it "had no specific relation to an inflammation, but was a consequence of interstitial emphysema and pneumothorax".

In a series of articles in 1947 and 1948, McMahon (41, 42) offered an interesting theory in 3 case histories in which he found an eosinophilic material varying from hyaline to granular. He suggested a morphologic anomaly in the lungs of newborn infants and called it a 'diffuse congenital alveolar dysplasia'. He further

suggested it represents a retardation and disturbance in the normal developement of the lungs in which there were, "too few alveoli and too much interstitial tissue". It is commonly associated with atelectasis and gives a pathological and clinical picture very similar to that described by other authors as 'hyaline membrane'.

In 1948, Zuelzer (87), although presenting no cases, offered that amniotic fluid in the lungs is recognized by the prescence of vernix caseosa and keratinized epithelial cells from fetal skin. The aspirated vernix is pushed against the walls of alveoli and bronchioles as air enters the lung, and is compressed into dense membranes.

Anderson's Textbook of Pathology (1) describes a common cause of failure of lungs to expand completely after respiration is established as obstruction of bronchioles by vernix aspirated with amniotic fluid during untrauterine respiratory movements or during the first inspiratory effort following birth. Hyaline membranes are then formed by flattening of the lipid substance (vernix) against the walls of the respiratory bronchioles.

Miller & Hamilton (44), at Kansas University, in 1949, expressed two main theories for what they called a 'vernix membrane'. One theory is the aspiriration of infected amniotic material or vaginal secretions. The other is chemical irritation of the lungs by meconium, vernix and amniotic fluid, and, therefor, epithelial injury. They believed that aspiration of vernix is the cause of the membrane but also suggested that failure to find it in stillborns

indicates the aspiration theory might not be correct.

Gellis, White & Pfeffer (28) became interested in the work by Russ & Strong on Cesarian babies in which they pointed out that fluid in the upper respiratory tract is inhaled with the first breath. Their paper attempted to add another cause of delayed respiratory distress following which each successive breath packs debris against alveolar walls forming a membrane. They believed amniotic fluid is ingest, subsequently regurgitated and then aspirated. In babies delivered by Cesarian section, the gastric content of amniotic fluid is greater than those delivered through the pelvis.

Dick & Pund (22), in 1949, did much work concerning asphyxia neonatorum and the vernix membrane. They found 7 cases of pulmonary hyaline membrane in 119 autopsies and said the presence of a membrane may repreeent only a more serious manifestation of the aspiration of amniotic sac contents. The vernix may have been concentrated in the lungs either because of absorption of the fluid or because only small amounts of amniotic fluid were present. Like other authors, they say that following the first extrauterine breath, this material is forced against the walls of alveoli while that material in the upper respiratory tract lodges in bronchioles.

Tesseraux (76), a Frenchman, was the first to suggest possible 'oxygen poisoning' as a cause of the membrane formation.

Arey & Dent (4), in 1950, also considered the membrane to be the result of aspirated vernix compressed against the walls

of air spaces as a result of the inhalation of air. The membrane lines bronchioles and alveoli and the intervening lung parenchyma is collapsed, giving an apparent thickening of intra-alveolar septa.

Further work by Miller & associates (43, 45), in 1950, still considered these pulmonary lesions to be the result of injury to epithelium of terminal air spaces by some unknown agent, contrary to previous thoughts that it is the result of aspirated amniotic sac contents. They state, "Facts suggest the fetuses lung is susceptible to some type of injury at a certain stage of development, and possibly the agent causing the injury also precipitates premature labor and birth". They described 3 cases in stillborns and so suggested the injury probably occurs 'in utero'. They could describe no etiologic agent, but said a wide search for the irritative material would be necessary in view of the many different agents already shown to be associated with the presence of a hyaline like membrane in the lungs of adults and older children.

Behrle & Gibson along with Miller (10), the following year, reported 13 cases of hyaline membranosis and showed that expansibility of the lung is impeded in these babies though the cause of it is not clear to them.

Simpson & Geppert (72), also in 1951, reported 14.5% of neonatal deaths had hyaline atelectasis. They suggested the etiology may be related to our methods of resuscitation. This possibility may have been prompted by the work of Behrle in which

they used negative pressures to test the lung expansibility. They also noted the membrane was especially common after Cesarian section and in infants of diabetic mothers.

Kaufman & Spiro (35) uses McMahon's theory of 'Congenital Alveolar Dysplasia' and suggest the entity may represent a retardation or disturbance of the normal developement of pulmonary alveoli. They said the condition is frequently accompanied with bronchial pneumonia, true atelectasis, fetal atelectasis, congestion, edema, aspiration pneumonia, and intra-alveolar hemorrhage, "each, or all of which, may mask the underlying alveolar disorder".

Blystad et al (13) did extensive work on a series of 509 autopsies and experimental studies on guinea pigs and mice. They discounted the work of Miller who suggested epithelial damage by demonstrating the frequency with which the membrane overlies the intact bronchiolar lining. They also discounted the theory of a vernix membrane by demonstrating color reactions of the membrane to be consistent with that of concentrated amniotic fluid proteins and not fat. Consequently, they tried to demonstrate that the membrane was a concentrated protein derived from aspirated amniotic fluid.

Bruns & Shields (16) demonstrated the membrane in 16.2% of neonatal deaths at the Colorado General Hospital. They said the etiology was probably not related to the aspiration of amniotic sac contents, but factors in the formation of the

membrane "may be intrauterine epithelial capillary injury" from anoxia and "extrauterine high concentration of oxygen therapy". They endorse the suggestion of Miller, Hamilton & Jennison that the etiology represents a reaction to pulmonary epithelial injury. The premature tissue is a likely candidate for the insult of injury by intrauterine anoxia and high concentrations of oxygen given therapeutically may further injure the tissue and produce disease.

Tregillus (77), also in 1951, reported an incidence of 14.3% of hyaline membranes in newborns. He termed it an 'asphyxial membrane'. He recorded his results because they show that vernix plays little or no role in the formation of the hyaline membrane in the lung. Thirty-three of the 35 cases reported were immature; complications of pregnancy were found in 9; and 5 were delivered by Cesarian section. All of these factors may have been responsible for anoxia of the fetus. A hyaline membrane was not seen in any lung having amniotic fluid unless there was also evidence of necrosis of bronchiolar epithelium. Tregillus believes:

"1. The asphyxial membrane found in lungs of liveborn infants is formed by necrosis and hyalinization of bronchiolar epithelium.

2. Necrosis of bronchiolar epithelium is due to anoxia and its higher incidence in immatures is due to incomplete development of lungs.

3. The formation of the membrane increases the degree of anoxia."

Therefor, a viscious cycle is set up. Intrauterine anoxia leads to tissue damage and necrosis forming a membrane which causes further anoxia.

Schoenvogel & Higgenbotham (70), in 1952, reported one case of hyaline membranosis. They, like McMahon and Kaufman, called it a 'Congenital Alveolar Dysplasia'. Schneider & Sellers (69) reported 24 cases with hyaline membrane, but gave no theory concerning its pathogenesis. Baty et al (9), following work by Gellis & White, proposed the trouble might arise from swallowing large amount of amniotic fluid following which regurgitation and aspiration occur. Benitz (11) tends to support the theory that the membrane develops from aspirated vernix after contact with air under tension.

In the past year, various men have noted the higher incidence of hyaline membrane following Cesarian section. Wile (82) said these infants are particularly susceptible to respiratory difficulty and exhibit a hyaline membrane. Though the cause is not clear, he said it may be a mechanical consequence of aspiration. O. Hunter Jones (34), at the Charlotte, N. C. Memorial Hospital, could give no pathogenesis but said the membranes occur seemingly more often in Cesarian section babies. Neuhouser & Wittenborg (49) are not certain the only cause of the formation of a membrane is aspiration of amniotic fluid. They suggest the possibility that pulmonary edema and excess fluid in the bronchi from an intrinsic origin may also be responsible.

Further reports were made by Arey & Dent in 1953. (5) They concluded at that time that there is insufficient evidence to support the view that these membranes are composed of amniotic sac contents and vernix. They gave evidence to support the concept that vascular damage and increased capillary fragility may play a role in the origin of the membrane. They further observe the almost exclusive appearance in liveborns, presumeably due to the fact that mechanical dispersion of the material to the periphery of the lungs is brought about only following inhalation of air. Some inherent defect may be present in prematures, such as increased capillary fragility, since the premature suffers from certain physiological handicaps. They could give no single explanation to account for the relative frequency following Cesarian section. However, Landau (37), in 1950, noted that immediate clamping of the cord deprived the infant of 90 cc. of blood, and it conceivable that this loss, permitting decreased oxygen carfying capacity of the blood , may play some part in the pathogenesis of the membrane.

Claireaux (18), at London, England, became interested in hyaline membranosis, and reported 108 cases in a series of 376 liveborn infants - an incidence of 29%. He also did much experimental work which will be reviewed later. This author believes a progressive change can be traced in nearly every lung containing a membrane whereby the squames become more acidophilic and hyaline-like in the air spaces. The flat squames, derived from liquor amnii, fuse together, lose their cellular outline

and identification, and form a syncitial membrane. He believes it occurs more frequently in prematures because of their high sensitivity to changes in oxygen tension with resultant intrauterine respiration and aspiration of amniotic fluid. Furthermore, absorption of this fluid in the lung is less likely to occur since the circulatory function is poor, and the squames "incubate" in the fluid medium, allowing hyalinization to proceed. Claireaux recognizes Blystad's theory of protein concentration, but states that it merely adds to the thickness of the membrane already formed by hyalinization of the squames.

Edith Potter, (17, 52, 53, 54, 55, 56, 57), at the Chicago Lying-In Hospital, has probably done more work on this phenomenon than anyone else in recent times. Her mortality reports have carried hyaline membranosis as a seperate entity of a cause of death in newborns since 1950. She describes it as the most important condition causing death in which prematurity is directly related to the pathologic process. "Among infants normal at birth, it was responsible for almost all the deaths of premature infants at the Chicago Lying-In Hospital from 1940 to 1950." In a series of articles since 1943, she has termed the entity 'hyaline membrane with resorption atelectasis'. The solid material seems to be definitely extrinsic in origin, and it appears when condensation of the foreign substance occurs, respiratory distress develops. She describes the atelectasis produced as a secondary atelectasis caused by the membrane surrounding and lining the air spaces.

producing an active block to oxygenation. Resorption of air in the alveoli then occurs, and the atelectasis is produced. The atelectasis is more complete, and the hyaline material greater in amount in infants who survive 24-36 hours than in those who die sooner. She therefor ascribes the etiology to the aspiration of amniotic fluid, chiefly vernix, with condensation and subsequent resorption of air. There is also the suggestion that high concentrations of oxygen at low humidity pressure may have something to do with causing dryness. At Chicago Lying-In, they never use over 50% oxygen, and keep the humidity at 85-90% if it is necessary to put the newborn in an incubator. She has recently noted the meningeal edema prevalent along with the hyaline membrane in death following Cesarian section. Clifford (19), in 1940, also described this. She rejected the idea of inflammation or congenital malformation as having any etiological significance.

Experimental Work

Ever since Johnson & Meyer, in 1925, first described the occurrence of a membrane in the lungs of newborn infants, experimental work has been undertaken in an effort to determine cause and composition of the membrane. Since the majority of men believe the basic pathology is the aspiration of amniotic sac contents, most investigators have attempted intratracheal instillation of a variety of foreign materials in an effort to reproduce a membrane of similar characteristics. However, with but few exceptions, this method has proven unsuccessful. Winternitz (86), in 1920,

experimentally produced a pulmonary membrane in rabbits by intratracheal insufflation of weak hydrochloric acid. It was also known at this time that war gases produce a membrane. In these conditions, a strong irritative and destructive action on alveolar walls seems to be the predominant etiological factor, and, evidently, this had a strong influence on the beliefs of the earlier workers. Johnson & Meyer (33) tried to determine if lesions were produced by such irritative substances as lysol and soap used to wash the vagina. However, lesions produced by intratracheal injections in rabbits were not typical. A hyaline membrane of resemblance was produced with small quantities of egg albumin, suggesting the membranes are produced by a viscous material adhering along walls of air passages. Farber & Sweet (26) concluded a membrane could be produced on a purely mechanical basis and found it to be identical in staining properties with that found in influenza. Later, Farber & Wilson (27), working with rabbits, cats, dogs, and rats, forced the animals to breathe low oxygen and high carbon dioxide concentrations until dyspnea and death occurred. The alveolar spaces were then filled with varying amounts of serum frequently pressed by the inspired air against alveolar walls. Small areas of hyaline membrane were found when foreign substances, as horse serum, india ink, or fibrinopurulent exudate were instilled into the trachea and vigorous artificial respirations instituted. Various other investigators tried toxic and non-toxic materials, but were unable to produce such a membrane. Dick & Pund (22), in 1949,

used lungs of stillborn infants and introduced intratracheally, warm, centrifuged amniotic fluid and were able to produce a pseudo-membrane which covered bronchioles, but not alveoli. Miller & co-workers (44,45), in a series of experiments, introduced such substances as amniotic fluid, vernix, meconium, saline, and water in dogs and rabbits. They were unable to produce a hyaline membrane, but discovered a leukocytic reaction with edema, congestion, and serum proteins in the alveoli. Cruickshank (20) also was able to elicit an inflammatory reaction, but no membrane. Blystad et al (13), in 1951, used excised adult guinea pig and mouse lungs and injected intratracheally 15-20 cc of human amniotic fluid in 1 cc amounts, and then artificially expanded and contracted the lungs for one hour at one pound pressure. A thin hyaline membrane was seen in some alveoli and the authors concluded that considerable amounts of the fluid must be present, as well as extrauterine respirations before a membrane can be produced. Claireaux (18), in London last year, attempted to prove his theory of hyalinization of squames by reproducing a membrane 'in utero' in six albino rats. He took the solid material from amniotic fluid, resuspended it in saline, and incubated it at 37 degrees centigrade. After 7-10 days, the squames were seen to lose their nuclei, become acidophilic, and hyalinize. To .5 cc of this material, .5 cc of sterile saline was added as well as 65 micrograms per cc of chloramphenicol. This was then injected intratracheally into the six rats which were then killed at 1, 2, 3, 5, 24, & 29 hours later.

In all but one, (in which the injection was unsatisfactory), hyaline material was found, and in those rats killed after two hours, a membrane was found to be exactly comparable to that found in lungs of newborn infants.

Some experimenters have been interested in the role of the vagus nerve on respirations of the newborn and its relation to the membrane. Farber (25) and Miller (44, 59) attempted bilateral vagotomy on rabbits and were able to produce these membranes in nearly all rabbits. Miller believes the activity of the thorax and diaphragm are altered after birth. The mature type of breathing is that in which the diaphragm plays a major role, while in the immature type, the chest does most of the work. Observing immature infants with respiratory distress, it was seen that the chest heaves tremendously, and there is minimal diaphragmatic activity. At autopsy, these infants had extensive hyaline membranes in their lungs. In 1951, Miller, Behrle, and Gibson (10) vagotomized 20 rabbit lungs and found hyaline membranes in 13. Histochemical reactions were similar to those membranes described in human beings.

Another factor which has been considered in the formation of these membranes as the role of 'oxygen poisoning'. Bruns and Shields (16), in 1951, following the work of two German pathologists, Kuhns & Pichotka, attempted to produce a membrane by means of oxygen inhalation. Three adult and nine infant guinea pigs were subjected to concentrations of 90-98% oxygen for 36 hours or more.

It was possible to produce a hyaline-like membrane in six out of nine animals whose lungs were directly exposed. These membranes were very similar to the ones found in lungs of prematures dying in the neonatal period. More recently, they produced changes in the lungs with only 70% oxygen, consisting of edema and desquamation. They feel that newborns are more resistant to oxygen poisoning than are adults. In 1953, Tran-Dinh-De and George Anderson (76) have repeated these experiments and have been able to duplicate previous work in producing hyaline membranes. They were impressed with the edema produced and evident vascular factors involved as a possible explanation for the production of capillary injury and resultant membrane formation. These membranes, however, are not associated with atelectasis. Edith Potter has evidently given consideration and concern to high oxygen concentrations, as was mentioned previously, she recommends using oxygen concentrations of no more than 50-60% when it is necessary to give the newborn resuscitation.

Respiratory Activity

Since a great many of the theories regarding the pathogenesis of the hyaline membrane in the newborn are based upon the aspiration of amniotic fluid by the fetus, a discussion of the presence or absence of intrauterine fetal respiration must of necessity be carried on. According to some authors previously mentioned, the occurrence of these membranes may be closely related to respirations 'in utero'. Questions which may arise, however,

are whether or not respirations of the fetus are physiologic, and whether or not amniotic fluid is aspirated into the pulmonary bronchioles and alveoli.

As early as the 16th. century, Vesalius observed that disturbance of placental circulation in the animal fetus brought about definite respiratory movements of the jaw and thorax with sucking in of amniotic fluid. There were many investigators of this phenomenon in the next several hundred years and many of these early experimenters believed the reason for respiratory movements was the interruption of blood supply between mother and fetus. Some also believed the fetus normally inspired and expired amniotic fluid which was evaporated and absorbed at birth. (76)

Ahlfeld, in 1888, noted movements of the abdominal wall in pregnant women which he believed were respiratory movements. He believed amniotic fluid is sucked in with these movements, but extend only to the bifurcation of the bronchi. Reiffersheidt, also a German, thought the power of suction is so slight that amniotic fluid reached, at most, only as far as the entrance to the larynx. (76, 26) Hess Thaysen, in 1944, Browne, in 1922 and Johnson & Meyer, in 1925, associated pneumonia in the newborn with the aspiration of infected amniotic fluid into the lungs. (26) Johnson deducted that the inhaled amniotic fluid adheres to the alveolar wall and may produce immediate asphyxia or subsequent pneumonia. He was unsertain wheter the amniotic fluid normally entered the trachea and bronchi, but in cases of intrauterine asphyxia, the

respiratory center was undoubtedly stimulated with resultant aspiration of the fluid. Like many investigators who were to follow in this work, he states, "The presence of a large amount of amniotic fluid in the lungs is indicative of...fetal asphyxia". (33) The significance of inhaled amniotic fluid was investigated by Perry (51) who became interested in the work of Johnson. She used an indicator to determine the presence of fluid in the lungs and found that amniotic fluid is not a constant finding in the lungs of human or guinea pig fetuses. When it is inhaled, it is the result of asphyxia, but it is seldom inhaled in quantities sufficient to cause obstruction in the bronchi. Farber & Wilson, however, showed that small amounts of the amniotic sac contents are present in the lungs of every newborn, and is aspirated with the first breath. They also conclude that large amounts may be aspirated and cause respiratory obstruction. Normally, however, Farber believes respiratory movements 'in utero' occur with a closed glottis, and amniotic fluid reached only to the larynx. (26, 83) Therefor, the presence of this material in the lungs indicates occurrence of premature attempts at respiration.

In 1936, Barcroft and Barron (6, 7, 59) experimented on the genesis of respiratory movements of the sheep fetus in an attempt to determine a respiratory pattern. The gestation period of the sheep is about 157 days, and it was noted that about the 35th. day, a gasp or spasm took place in the fetus. Rhythmic trunk movements associated with ordinary respirations are

developed between the 38th. and 49th. day. They cannot be initiated by asphyxial changes in the blood, but can be started by activity of the muscular system such as tapping on the uterus. Toward the 49th. day, their frequency becomes more regular and there is establishment of almost continuous respiration of a normal character. After this, the movements disappear - being dormant - but can be elicited again be subjecting the fetus to asphyxial conditions. These were important observations because what occurred in the sheep fetus might be expected to be found in the human.

Snyder & Rosenfeld (59, 60, 74, 75) re-introduced the question of the existence of a tidal flow of amniotic fluid. Using rabbit fetuses, they added india ink to the amniotic fluid, removed the fetus, and placed it in Ringers Solution. No anaesthesia was used. Direct observation of the fetuses revealed rhythmical respiratory movements. In these, the lungs were blackened from the ink. They concluded, therefor, that spontaneous respiratory movements of the fetus occur and cause a flow of amniotic fluid in the lungs. Furthermore, it is not a complication of prgnancy or labor, but is a normal function, and affords a means for the dilatation of future air passages. Several years later, Snyder (73) repeated the experiments and found that amniotic fluid entered alveoli in less than a minute, in breathing fetuses, but is not found in lungs of apneic ones.

Bonar, Blumenfeld & Fenning (14) reviewed the literature concerning this subject and suggested that, "From a purely

physiological standpoint, it would seem unreasonable to assume that the fetal respiratory tract remains inert in utero, awaiting some stimulus to initiate its hitherto unpracticed respiratory mechanism at birth, while the cardiovascular system with which it is so intimately related, the gastro-intestinal tract, and kidneys, function in utero". Concerning the aspiration of amniotic fluid, they conclude that it does occur.

Windle & associates (73, 81, 84, 85) , in a series of articles from 1939 to 1943 say that as early as the 12th. week of gestation, fetuses can perform respiratory movements, but they may be due to asphyxia. They seem to be inactive, but can be initiated by afferent nerve impulses or anoxia. They refute the statement of Bonar et al that respiratory movements are physiological. Experiments were done by them to determine the question of aspiration of amniotic fluid. They used guinea pigs and injected thorotrast. "In no instances could trachea, brônchi or lungs be seen in reentgenograms, although opaque material was found in the stomach". In 1942, they suggested that small quantities of the fluid in bronchi is a transudate and not of amniotic origin.

Ehrhardt (76) obtained similar results by injecting thorotrast into the amniotic cavity of the intact uterus. On one occasion, thorotrast was found in the gastro-intestinal tract and none in the lungs, but later, thorotrast was found in the lungs.

Two other Germans, Reifferscheid & Schmeimannn (76) injected a foreign material through the abdominal wall into the

amniotic cavity, and 48 hours later, following hysterectomy, the contrast media was seen in the lungs of five to six month old fetuses.

Nathan Shock (71), in 1941, experimented on rats to determine the effect of inspiration of amniotic fluid on viability. Their results show aspiration is not a normal process, and excessive respiratory stimulation as a result of anoxia or hypercapnia caused the animals to inspire the fluid.

MacGregor (39, 40) also believed that asphyxia may stimulate the fetal respiratory center and liquor amnii then flood the lungs. They have little doubt that any considerable quantity is abnormal and indicates severe fetal asphyxia.

Davis & Potter (21) presented new evidence that intra-uterine and extra-uterine respiration is similar. During intra-uterine life, respirations are intermittent, irregular, and shallow, and cause the flow of amniotic fluid throughout the lungs. Roentgenograms demonstrated the presence of the fluid in the lungs in fetuses as young as 12 weeks, or 39 grams. If intrauterine distress occurred, an excess amount of amniotic fluid is aspirated. They believed death occurs because the fetal circulation is embarrased and not because of the excess fluid.

Dr. Gruenwald (30, 59) studied the effect of surface tension on lung expansion. He contends that if fluid is inspired and expired continuously, it could not be concentrated in the lung. Therefor, the fluid must be absorbed and concentrated. His studies

on surface tension indicate the difference in the physiology of the lung when fluid and air enters. Aeration of lung tissue is resisted by surface tension in both atelectatic alveoli and those which contain little amniotic fluid. This resistence is not present when fluid enters the lung, thus explaining why fluid enters so easily. "The average pressure for air is twice that required for fluid to enter the lungs". If fluid is aspirated as a result of anoxia, all alveoli expand and it is destributed equally, whereas, air entering the lung will expand only a few alveoli and the remaining are collapsed. He, like Potter, believes defective circulation allows fluid to remain in the lungs.

Morison (47, 48), in 1949, stated that the presence of a hyaline membrane is the direct uncomplicated result of intra-uterine asphyxia. Small quantities of amniotic sac contents are not harmful, he says, but large amounts inhaled as a result of anoxia are harmful.

A few investigators tried to relate intra-uterine respirations to asphyxia as a result of changes in oxygen and carbon dioxide pressure in relation to uterine circulation. In Windle's (85) experiments, respiratory-like movements were induced by experimental anoxemia and amniotic fluid was aspirated. When, and if fetal requirements for oxygen exceed placental supply, the previously apneic fetus may respond with rhythmical respiratory movements. In the last days of gestation, oxygen values of fetal arterial blood decrease, and a physiological partial anoxemia exists.

Snyder & Rosenfeld (75) have demonstrated that a delicate balance between oxygen and carbon dioxide exists in the control of intra-uterine respiratory movements. Too much carbon dioxide will stimulate the fetal respiratory center with resultant aspiration of excess amniotic fluid. It must be stated that these men no longer believe that onset of respiration is precipitated by a chemical mechanism. Eastman (24) noted that mild degrees of anoxia increased the respiratory rate, but as anoxia progressed, the compensatory mechanism fails and respirations decrease and finally stop. The initial effect of slow anoxia, therefor, causes aspiration of large quantities of amniotic fluid. If anoxia doesn't cause death in utero, the inspired amniotic fluid will prolong the anoxia after birth.

As was pointed out in the introduction to this paper, the leading cause of death in newborn infants, particularly premature, is asphyxia and atelectasis. From the discussion just presented on the respirations of the newborn, it is seen that the majority of authors believe repeated, deep intra-uterine respiratory movements with resultant aspiration of large amounts of amniotic debris is not a normal consequence and the presence of large amounts of this material is evidence of fetal anoxia. The diagnosis of fetal anoxia, therefor, is based on the presence of large amounts of debris in the respiratory passages causing asphyxia and atelectasis, or, following birth, condensation of this material forming a membrane.

CONCLUSION

It is seen from a review of the literature, that the problem of pulmonary hyaline membrane in the newborn infant has remained virtually unsolved in the past 50 years, especially regarding its pathogenesis. However, much more emphasis has been placed on this entity during the last decade than at any other time previous, and much experimental work has been undertaken in an effort to determine the cause of the phenomenon which today is responsible for the highest incidence of neonatal deaths in the premature infant. It has been estimated by Edith Potter at the Chicago Lying-In Hospital that this condition accounts for 10,000 to 20,000 deaths annually. (55) It is often unrecognised, and an erroneous diagnosis of atelectasis is ascribed when the basic pathology is overlooked. Of the pulmonary abnormalities found in association with atelectasis of the newborn, the most striking is the presence of a hyaline membrane. A variety of names have been given to the entity, most of which depict, in the authors opinion, the anatomic or physiologic etiology of the membrane. Regardless of the nomenclature, certain clinical features of the condition are characteristic. It occurs only in liveborn infants (although Miller (45) reported three cases in stillborns) and primarily in prematures rather than full term infants. In 3,133 live births compiled from the literature, there were 619 cases of hyaline membranosis, or approximately 20%.

The various percentages in viable premature infants ranges from about 6% (86) to 100% (32). Most authors agree that the relative incidence is higher in infants delivered by Cesarian section, especially those born of diabetic mothers. Considerable disagreement still exists, however, in an attempt to correlate hyaline membranes and various complications of pregnancy and labor. Several investigators have found that age, race, parity, serology and anaesthesia or analgesia play no role in the development of the membrane. The clinical course following birth is also characteristic of this condition, although it is frequently misdiagnosed as intra-cranial hemorrhage from birth trauma. Classically, the onset of respiration is spontaneous following an uncomlicated delivery. The infant respires normally for an hour or two, following which breathing becomes more difficult. Cyanosis is a primary symptom, as reported in 65% of one series (67), and dyspnea is increasingly severe. Death usually occurs in 24-48 hours as a result of atelectasis.

Pathologically, the picture is typical. Microscopically, a dense, homogenous, granular, eosinophilic material is found lining alveoli and bronchiolar ducts. Death therefor results from an obstruction to the free exchange of gases between alveoli and pulmonary capillaries, with resultant atelectasis and asphyxia.

Beyond these findings which are characteristic of infants dying from respiratory distress and found to have a pulmonary hyaline membrane, most of the data concerning this

phenomenon is controversial. There is little unanimity of opinion regarding the origin of such membranes. Numerous causes have been given among which are; the aspiration and dispersion of amniotic fluid, condensation of amniotic sac contents, condensation of protein derived from amniotic fluid or from the blood, irritative substances, inspired vernix caseosa, infection, congenital malformation of alveoli, desquamation of epithelia, anoxia and oxygen poisoning. In general, it would appear that at the present time, two basic concepts are most popular, both of which favor the idea that the membrane is composed of protein. One theory upholds that amniotic fluid is aspirated in utero as a result of fetal anoxia, is concentrated and condensed into a membrane lining alvéoli and bronchiolar ducts following extra-uterine breathing and causes atelectasis of the lung. The other concept derives the protein from blood rather than amniotic fluid as a result of capillary damage in an immature circulatory system or increased capillary fragility from intra-uterine hypoxia.

The proponents of the first theory base their supposition on the facts that amniotic debris is imbedded in the membranes; that the presence of clumps of amniotic debris lying free in bronchioles and ducts is evidence of a transition between these clumps and the membrane; that the presence of fat is evidence of aspiration of amniotic sac contents including vernix. Objections to this theory are that the presence of cornified epithelial cells and fat is frequently absent; the membrane is more common in pre-

matures even though there is less debris in the amniotic fluid of these fetuses than is present at term; membranes similar to those seen in newborns are seen in older children and adults (influenza, war gases, irradiation injury, infection, pneumonia, etc.) even though they aspirated no amniotic fluid; experimental attempts to reproduce the membrane by intra-tracheal injections of amniotic sac contents have been unsuccessful.

In spite of the many experimental methods used in an attempt to reproduce these membranes, the majority of experimenters have been unsuccessful. Those who have been successful in producing the membrane have been unable to produce the atelectasis associated with this phenomenon. Those methods used in an attempt to produce the membrane have been intra-tracheal injection of amniotic fluid and foreign debris, oxygen poisoning and vagotomy.

The subject of intra-uterine respirations, assumed to be intimately associated with the formation of the membrane as a result of the aspiration of amniotic sac contents, is still a controversial one. Experimentally, it has been proven that intra-uterine respirations do occur in animals of many species. Consideration must be given to species, placental circulation in various species and gestational age differences. The occurrences of these movements under entirely physiological conditions has not been definitely established. Many questions still remain concerning the relationship of intra-uterine respiration, aspiration of amniotic fluid and extra-uterine pulmonary respiratory

abnormalities. Two main points of view are evident concerning this subject: (1) Many recent investigators believe that intra-uterine asphyxial or anoxic conditions must exist as a stimulus to the respiratory center before respirations 'in utero' occur. This, of course, is not physiological. (2) Others believe the fetus normally respires 'in utero', and aspirates the surrounding fluid. They argue that fetal respiration is essential for the normal developement of the lung in preparation for post-natal life (ie) that extra-uterine breathing of air is merely a later manifestation of the intra-uterine aspiration of fluid. It can readily be seen why the subject of fetal respiration is so closely associated with the pathogenesis of the pulmonary hyaline membrane in the newborn.

SUMMARY

Various aspects of the subject of pulmonary hyaline membrane of the newborn infant have been presented in this paper with special emphasis on a review of the literature concerning its pathogenesis. An introduction to the subject was made by presenting statistical material from various hospitals throughout the country in an effort to impress upon the reader the vast problem which we have concerning the mortality of the newborn infant, particularly the premature infant. Statistical evidence was also given showing the high incidence of pulmonary lesions associated with abnormal pulmonary ventilation as a leading cause of premature death and the time relation of these deaths. A list

of the nomenclature was presented and various aspects of the disease found to be in common with these terms was given. The clinical picture presented by these infants in respiratory distress was shown to be characteristic, and a typical case was presented. The pathology and, to some extent, the histochemical findings of these membranes were described. A complete review of the literature was made concerning the etiology and pathogenesis of the lesion. This was presented in chronological order in an effort to determine what theories have been advanced thus far, what the current trend of thinking is, and if a definite pathogenesis could be ascribed to the condition. Experimental studies proving or disproving the various theories were extracted from the literature and presented. Because many investigators believe there is a close association between hyaline membranosis and the presence or abscence of intra-uterine respiration, a discussion of respiration 'in utero' was carried on.

This author believes a series of events occur which lead to the formation of the hyaline membrane found primarily in the premature infant. Because of inadequate oxygen supply to the fetus 'in utero' and the developement of hypoxic conditions, the respiratory center of the fetus is stimulated, probably from increased carbon dioxide levels. This results in the establishment of respiratory movements by the fetus with subsequent aspiration of amniotic fluid and debris. This material lies loosely in the bronchiolar tree until air enters the lung at birth with the first extra-

uterine breath and forces the fluid against the alveolar walls. Here, the material is condensed, the fluid re-absorbed, and a membrane laid down on the alveolar walls preventing the exchange of gases between alveoli and pulmonary capillaries. Atelectasis results followed by death from abnormal pulmonary ventilation. This series of events can also explain the high incidence of the pulmonary hyaline membrane following delivery by Cesarian section. A high concentration of oxygen with inadequate humidification administered to infants with respiratory distress tend to increase membrane formation by causing a drying effect.

BIBLIOGRAPHY

1. Anderson, W. A. D. Pathology. 1st. ed. St. Louis, C. V. Mosby Co., 1948. pg. 710.

2. Arey, J. B.: Postmortem Observation in Twenty Two Premature Infants. New Orleans M. & S. J. 100:258. 1947.

3. Arey, J. B.: Pathologic Findings in the Neonatal Period. J. Ped. 34:44. 1949.

4. Arey, J. B. & Dent, I.: Pathologic Findings in Premature Infants. Am. J. Clin. Path. 20:1016. 1950.

5. Arey, J. B. & Dent, I.: Causes of the Fetal and Neonatal Death with Special Reference to Pulmonary and Inflammatory Lesions. J. Ped. 42:1-25, 205, 223. 1953.

6. Barcroft, J.: The Onset of Respiration at Birth. Lancet. 2:117. (Aug.) 1942.

7. Barcroft, J. & Barron, D. H.: The Genesis of Respiratory Movements in the Fetus of the Sheep. J. Physiol. 88:56. 1936.

8. Baty, I. M., Kreidberg, M. B. & Swenson, O.: Panel Discussion on Cyanosis of the Newborn. New Eng. J. Med. 219:899. 1938.

9. Baty, I. M., Kreidberg, M. B. & Swenson, O.: Medical Progress - Pediatrics. New Eng. J. Med. 247:24,937. (Dec) 1952.

10. Behrle, F. C., Gibson, D. M. & Miller, H. C.: Role of Hyaline Membranes, Blood, Exudate, Edema Fluid and Amniotic Sac Contents in Preventing Expansion of the Lungs of the Newborn Infants. Ped. 7:782. 1951.

11. Benitz, Major Roberto: Degenerative Changes in the Liver Associated with Aspiration of Vernix and Hyaline Membrane Formation in Lungs of Intrauterine Anoxia. Arch. Path. 54:378. 1952.

12. Benner, M. C.: Congenital Infection of the Lungs, Middle Ear, and Nasal Accessory Sinuses. Arch. Path. 29: 455. 1940.

13. Blystad, Wm., Landing, B., & Smith, C.: Pulmonary Hyaline Membrane in Newborn Infants, Statistical, Morphologic, and Experimental Study of their Nature, Occurrence, and Significance. J. Ped. 8:5. 1951.

14. Bonar, B. E., Blumenfeld, C. M., & Fenning, O.: Studies of Fetal Respiratory Movements. Am. J. Dis. Child. 55:1. 1938.

15. Brennemann.: Practice of Pediatrics. 1st. ed. W. F. Prior Co. 1948. Vol. 1. Chap. 42. Pg. 10.

16. Bruns, J. D., & Shields, L. V.: The Pathogenesis and Relationship of the Hyaline-Like Pulmonary Membrane to the Premature Neonatal Mortality. Am. J. Ob. & Gyn. 61:953. (May) 1951.

17. Bundesen, H. N., Potter, E. L., Fishbein, W. I., Bauer, F. C., Plotzke, G. V.: Progress in the Prevention of Needless Neonatal Deaths. J. A. M. A. 148:907-917. (Mar.) 1952.

18. Claireaux, A. E.: Hyaline Membrane in Neonatal Lung. Lancet. 15:749-753. 1953.

19. Clifford, S. H.: Roundtable Discussion. Am. J. Ob. & Gyn. 39:388. 1940.

20. Cruickshank, A. H.: Effects of Introduction of Amniotic Fluid into Rabbit's Lungs. J. Path. & Bact. 61:527. 1949.

21. Davis, M. E., & Potter, E. L.: Intrauterine Respiration of the Human Fetus. J. A. M. A. 131:1194. 1946.

22. Dick, F., & Pund, E. R.: Asphyxia Neonatorum and the Vernix Membrane. Arch. Path. 47:307. 1949.

23. Dunham, E. C.: Premature Infants. Child. Bureau Pub. No.325. U. S. Gov't. Printing Off. 1948.

24. Eastman, N. J.: Asphyxia Neonatorum. Internat. Clin. 2:46. pg. 274. 1936.

25. Farber, S.: Unexpected Death in Early Life. New Eng. J. Med. 219:836. 1938.

26. Farber, S. & Sweet, L. K.: Amniotic Sac Contents in the Lungs of Infants. Am. J. Dis. Child. 42:1372. 1931.

27. Farber, S., & Wilson, J. L.: The Hyaline Membrane in the Lungs: Experimental Study. Arch. Path. 14:437,450. 1932.

28. Gellis, S. S., White, P., & Pfeffer, W.: Gastric Suction: A Proposed Additional Technic for the Prevention of Asphyxia in Infants Delivered by Caesarian Section. New Eng. J. Med. 240:533-537. 1949.

29. Greenhill, J. P., & Delee, J. B.: Principles and Practice of Obstetrics. 10th. ed. Phila. & London. W. B. Saunders Co. 1951. pg. 770, 794.

30. Gruenwald, P.: Surface Tension as a Factor in the Resistance of Neonatal Lungs to Aeration. Am. J. Ob. & Gyn. 53:996. 1947.

31. Helwig, F. C.: Congenital Aspiration Pneumonia in Stillborn and Newborn Infants. Am. J. Ob. & Gyn. 26:849. 1933.

32. Johnson, W. C.: Pneumonia in Newborn Infants with Lesions Resembling Influenza. Proc. N. Y. Path. Soc. 23:138. 1923.

33. Johnson, W. C., & Meyer, J. R.: A Study of Pneumonia in the Stillborn and Newborn. Am. J. Ob. & Gyn. 9:151. 1925.

34. Jones, O. Hunter: The Trend in Caesarian Section in Recent Years. Am. J. Ob. & Gyn. 66:576,762. (Oct.) 1953.

35. Kaufman, N., & Spiro, R. K.: Congenital Alveolar Dysplasia of the Lungs. Arch. Path. 51:431. 1951.

36. Labate, J. S.: A Study of the Causes of Fetal and Neonatal Mortality on the Obstetrical Service of Bellevue Hospital. Am. J. Ob. & Gyn. 54:188. 1947.

37. Landau, D. B., Goodrich, H. B., Francka, W. F., Bivins, F. R.: Death of Caesarian Infants: Theory as to Its Cause and Prevention. J. Ped. 36:421. 1950.

38. MacGregor, A. R.: Pneumonia in the Newborn. Arch. Dis. Child. 14:323. 1939.

39. MacGregor, A. R.: The Causes of Fetal and Neonatal Death. Edinburgh Med. J. 50:332. 1943.

40. MacGregor, A. R.: The Pathology of Stillbirth and Neonatal Death. Brit. Med. Bull. 4:174. 1946.

41. McMahon, H. E.: Congenital Alveolar Dysplasia of the Lungs. Bull. New Eng. Med. Center. 9:48. 1947.

42. McMahon, H. E.: Congenital Alveolar Dysplasia: A Developement-al Anomaly Involving Pulmonary Alveoli. Ped. 2:45. 1948.

43. Miller, H. C.: Analysis of Fetal and Neonatal Deaths in 4117 Consequtive Births. Ped. 5:184. 1950.

44. Miller, H. C. & Hamilton, T. R.: The Pathogenesis of the Vernix Membrane. Ped. 3:735. 1949.

45. Miller, H. C. & Jennison, M. H.: Study of Pulmonary Hyaline-Like Material in 4117 Consequtive Births. Ped. 5:7. 1950.

46. Mitchell, Nelson, Waldo E.: Textbook of Pediatrics. 5th. ed. Philadelphia & London, W. B. Saunders Co. 1950. pgs. 330, 343, 344, 989.

47. Morison, J. E.: The Establishment of Extrauterine Respiration. J. Ob. & Gyn. Brit. Emp. 56:393. 1949.

48. Morison, J. E.: Discussion of Resuscitation of the Newborn. Proc. R. Soc. Med. 43:443. 1950.

49. Neuhouser, E. B. D., & Wittenborg, M. H.: Medical Progress. New Eng. J. Med. 249:2. pg. 63. (July) 1953.

50. Patterson, J. C. & Farr, J. T.: Pulmonary Collapse as a Cause of Neonatal Deaths. Canad. M. A. J. 41:31. 1939.

51. Perry, I.: An Experimental Study of the Inhalation of Fluid During the First Respiration. Anat. Rec. 50:303. 1931.

52. Potter, E. L., & Adair, F. L.: Fetal and Neonatal Death. 2nd. ed. Chicago. The University of Chicago Press. 1949.

53. Potter, E. L.: Respiratory Disturbances in the Newly Born Infant. Ill. Med. J. 83:100. 1943.

54. Potter, E. L. : Pathology of Prematurity. J. A. M. W. A. 5:391. (Oct.) 1950.

55. Potter, E. L.: Pathology of the Fetus and Newborn. Chicago Yearbook Publication. pg.252, 76, 84. 1952.

56. Potter, E. L.: Congestive Pulmonary Failure (Resorption Atelectasis with Hyaline-Like Membrane). Chicago Yearbook Publication. pg. 249. 1952.

57. Potter, E. L.: Pulmonary Pathology in the Newborn. Adv. in Ped. Levine. Vol. 6. Chicago Yearbook Publishers. pg. 172. 1953.

58. Reardon, Helen, Wilson, J. L., & Graham, B.: Physiological Deviations of the Premature Infant. Am. J. Dis. Child. 81:1. pg. 100-111. 1951.

59. Report of the Fifth M. & R.: Pulmonary Hyaline Membranes. Pediatric Research Conference. M. & R. Laboratories. 1953.

60. Rosenfeld, M., & Snyder, F. F.: Breathing of Amniotic Fluid as a Normal Function of Fetal Respiration. Proc. Soc. Exp. Biol. & Med. 36:45. 1937.

61. Rosenthal, M.: The Pulmonary Lesions Associated with Intrauterine Asphyxia. J. Med. 6:71. 1935.

62. Russ, J. D., & Strong, R. A.: Asphyxia of the Newborn Infant. Am. J. Dis. Child. 61:1-12. 1941.

63. Russ, J. D., & Streng, R. A.: Asphyxia of the Newborn Infant. Am. J. Ob. & Gyn. 51:643. 1946.

64. Russ, J. D., & Strong, R. A.: Resuscitation of the Asphyxiated Baby Delivered by Caesarian Section. New Orleans M. & S. Journ. 98:9. pgs. 415-417. 1946.

65. Ryder, G. E.: Unpublished thesis. 1951.

66. Schenken, J. R.: Personal Communication to the Author.

67. Schenken, J. R.: Case Report - Files Nebraska Methodist Hospital.

68. Schenken, J. R.: The Aspiration of Amniotic Fluid Contents by the Newborn. Nebr. S. & M. J. 32:362. 1947.

69. Schneider, G. T., & Sellers, T. B.: Fetal and Neonatal Mortality. South. Med. Journ. 45:211-217. 1952.

70. Schoenvogel, O. F., & Higgenbotham, W. H.: Stillbirths and Neonatal Deaths. A Three Year Survey. Am. J. Ob. & Gyn. 63:41. 1952.

71. Shock, N. W.: Fetal Aspiration of Amniotic Fluid. Am. J. Physiol. 134:769. 1941.

72. Simpson, J. W., & Geppert, L. J.: The Responsibilities of the Obstetrician to the Fetus. An Analysis of Fetal and Neonatal Mortality in 10,000 Deliveries. Am. J. Ob. & Gyn. 62:1062. 1951.

73. Snyder, F. F.: The Rate of Entrance of Amniotic Fluid into the Pulmonary Alveeli During Fetal Respiration. Am. J. Ob. & Gyn. 47:224. 1941.

74. Snyder, F. F., & Rosenfeld, M.: Direct Observation of Intrauterine Respiratory Movements of the Fetus and the Role of Carbon Dioxide and Oxygen in their Regulation. Am. J. Physiol. 119:153. 1937.

75. Snyder, F. F. & Rosenfeld, M.: Intrauterine Respiratory Movements of Human Fetus. J. A. M. A. 108:1946. 1937.

76. Tran-Dinh-De, & Anderson, G. W.: Hyaline Membrane Associated with Diseases of the Newborn Lungs: Review of the Literature. Ob. & Gyn. Survey. 8:1. pg. 1-34. 1953.

77. Tregillus, I.: The Asphyxial Membrane in the Lungs of Liveborn Infants. J. Ob. & Gyn. Brit. Emp. 58:406-413. 1951.

78. Tucker, B. E., & Benoron, H. B.: The Immediate Effects of Prolonged Labor with Forceps Delivery, Precipitated Labor with Spontaneous Delivery and Natural Labor and Spontaneous Delivery of the Child. Am. J. Ob. & Gyn. 66:3. pg. 547. 1953.

79. Warwick, M.: Pneumonia in Newborn and Stillborn Infants. Am. J. Med. Sc. 187:253. 1934.

80. West, R. H., Grier, R. M., & Lussky, H. O.: Premature Infant Mortality. Am. J. Ob. & Gyn. 64:6. pg. 1222-1230. 1952.

81. Whitehead, W. H., Windle, W. F., & Becker, R. F.: Changes in Lung Structure During Aspiration of Amniotic Fluid and During Breathing at Birth. Anat. Rec. 83:255. 1942.

82. Wile, S. A.: Progress in Reduction of Neonatal Mortality. Am. J. Ob. & Gyn. 66:1. pg. 133-134. 1953.

83. Wilson, J. L., & Farber, S.: Atelectasis of the Newborn. Am. J. Dis. Child. 46:572, 590. 1933.

84. Windle, W. F., & Becker, R. F.: Asphyxia Neonatorum. Am. J. Ob. & Gyn. 45:183. 1943.

85. Windle, W. F., Becker, R. F., Barth, E. E., & Schulz, M. D.: Aspiration of Amniotic Fluid by the Fetus. Surg., Gyn. & Ob. 69:6. pg. 705. 1939.

86. Winternitz, M. C., Smith, G. H., & McNamara, F. P.: Production of Pulmonary Infarcts by the Insufflation of Acid. J. Exp. Med. 32:211. 1920.

87. Zuelzer, W. W.: Pathological Conditions Resulting in Fetal Anoxia and Cyanosis of the Newborn. Am. J. Dis. Child. 76:679. 1948.