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Hyaline Membranes in Full-Size Infants*

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An apparent difficulty with pulmonary prematurity as the basis of the respiratory distress syndrome (RDS) is the frequency of this condition in full-size infants (weighing more than 2500 g). This group represents up to 20% of all fatal cases with hyaline membranes, but it includes many infants that are premature by gestational age although full-size. An example of this paradox is the overweight infant prematurely born to a diabetic mother.

This study attempts to evaluate the chronologic maturity of autopsied, full-size infants with hyaline membranes and to examine the clinical factors and associated pathologic findings in these cases.

Methods

The lung sections of liveborn infants weighing 2500 grams or more and surviving less than seven days during a 22 year period (1944—1965), Johns Hopkins Hospital (J.H.H.) and 1954—1965, Sinai Hospital (S.H.)] were reviewed. In cases with hyaline membranes organ weights, crown-heel length, and the degree of renal and pulmonary development were used to estimate the stage of maturation. The presence of pneumonia, aspiration, pulmonary and central nervous system hemorrhage was tabulated. The clinical records provided information on the estimated gestational age, obstetrical course, birth weight, mode of delivery, and perinatal complications. The significant factors in the death of the infants were determined from the combined data.

A *probable* gestational age was assigned to each case on the basis of organ weights, histologic maturity and the stated gestational age. The body and organ weights were compared to tables of normal growth and development (GRUENWALD, 1963a, 1966). The state of histologic development was determined by comparison with that of groups of infants of known gestational age (weeks from the first day of the last menstrual period) and normal birth weight. In determining the *probable* age, preference was given to the stated gestational age when it was known with certainty, if the differences from the other data were small.

The cases with hyaline membranes in full-size infants were compared to the total number of autopsied cases in this weight group *(autopsy frequency)*. The *incidence* of this finding in liveborn infants was calculated for the two hospital populations using the total number of livebirths and neonatal deaths over 2500 g.

Observations

The detailed data in the 46 cases in this study are listed in Table 1. A history of maternal dianetes was present in three infants and a prediabetic state in a fourth. The latter are grouped together and are not considered further.

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Table 1. *Gestational age, clinical and pathological findings in full-size infants with hyaline membranes*

Infants with a gestational age of 39 weeks or longer are indicated by Bold Face numerals. Autopsy weigths are listed in parentheses when birth weights were not available. The number listed under Probable Age is the correction (in weeks) assigned to the stated gestational age. Five digit reference numbers are J.H.H. cases, four digit numbers refer to S.H. cases. The abbreviations used to describe the pattern of aeration indicative of pulmonary maturity are: *M* mature, *P* atelectasis of prematurity, and *E* exaggereted atelectasis of prematurity.

Case number	Age, race, sex	Birth weight	Stated Gest. age (weeks)	Probable age (weeks)	Clinical Factors	Pulmonary maturity	Aspiration	Pneumonia	Pulmonary hemorrhage	CNS hemorrhage
1. (20,198)	2 da. C ♂	2500	31	+4	"Traumatic delivery"	P	0	+	+	+
2. (20,949)	4 hr. W ♂	(2500)	36	+4	Erythroblastosis fetalis, exchange transfusion	M	0	0	+	0
3. (6,180)	52 hr. W ♀	2525	34	0	Cesarean section, abruptio placentae	P	0	0	0	0
4. (6,334)	36 hr. C ♂	2550	36	0	Prolonged rupture membranes, precipitous labor	P	0	0	0	0
5. (20,943)	22 hr. C ♂	2550	36	0	Breech extraction	E	+	+	+	0
6. (29,332)	31 hr. W ♂	2550	35	0	Hydramnios, abruptio placentae	P—M	0	0	0	0
7. (3,552)	43 hr. W ♂	2552	40	−4		P	0	0	0	0
8. (4,372)	6 da. W ♂	2566	40	−4	Maternal sepsis	E	+	0	0	0
9. (20,723)	2 da. C ♀	2600	38	−1	Cesarean section, disproportion	P	0	+	0	0
10. (21,391)	24 hr. W ♂	2620	45	0	Cesarean section, fetal distress, severe meconium staining	P—M	+	0	0	+
11. (31,002)	12 hr. W ♂	2635	38	0	Abruptio placentae	P—M	+	0	+	0
12. (5,637)	24 hr. W ♂	2685	36	0	Cesarean section, toxemia	E	+	0	+	+
13. (20,712)	1 da. W ♂	2700	38	−1	Cesarean section, disproportion	P—M	+	0	0	+
14. (33,145)	10 hr. W ♂	2725	38	0		M	+	0	+	0
15. (25,463)	12 hr. C ♂	2725	35	0	Prolonged rupture membranes	P—M	+	+	+	+
16. (21,522)	16 hr. W ♂	2740	37	0	Cesarean section, toxemia	E	0	0	+	0
17. (26,694)	17 hr. C ♂	2750	39	−4	Cesarean section, disproportion	E	0	0	+	0

18.	(28,545)	1 da.	W	♂	2770	—	37	Prolonged rupture membranes	P	0	+	+	0
19.	**(21,872)**	4 hr.	W	♀	(2770)	40	0	"Fetal distress"	M	+	0	+	0
20.	(5,304)	3 da.	W	♂	(2778)	33	+4	Fetal bradycardia, cesarean section, abruptio placentae	E	+	0	—	0
21.	(29,221)	32 hr.	W	♂	2825	36	0	Prolonged rupture membranes, breech extraction	?	0	0	0	0
22.	(3,742)	2 da.	W	♀	2835	38	0	Cesarean section (elective repeat)	P	0	+	0	+
23.	(4,062)	3 da.	W	♂	2835	40	−4	Cesarean section, prolonged labor	P	0	+	0	0
24.	(5,464)	31 hr.	W	♂	2840	36	0	Cesarean section, placenta previa	M	0	+	0	—
25.	(32,847)	30 hr.	C	♂	2880	41	−4	Maternal bleeding, cesarean section, placenta previa	P	0	+	0	0
26.	(5,171)	2 da.	W	♂	2927	40	−4	(Neonatal hypoglycemia)	P	0	0	+	+
27.	(29,209)	2 da.	W	♂	3020	37	0	Unexplained abdominal pain, repeat cesarean section	P	0	+	0	0
28.	(32,506)	27 hr.	W	♀	3020	"term"	37	Cesarean section, prolonged labor	P—M	0	+	0	0
29.	**(22,051)**	20 hr.	W	♀	3025	43	0	Meconium staining	M	+	0	+	0
30.	(5,076)	8 hr.	W	♂	3062	39	−2		?	0	+	+	+
31.	(20,231)	3 da.	W	♂	3090	38	−2	Cesarean section, disproportion	P	0	+	0	0
32.	(4,151)	3 da.	W	♂	3175	37	0	Fetal bradycardia	E	0	+	0	+
33.	**(4,954)**	37 hr.	W	♀	3240	39	0	Cesarean section (elective repeat)	E	0	+	+	0
34.	(5,868)	24 hr.	W	♂	3250	37	0		E	0	0	0	—
35.	(5,692)	20 hr.	W	♂	3367	38	−1	Decidual necrosis, placenta	P—M	+	0	0	+
36.	**(28,113)**	45 hr.	W	♂	3410	45	0	Toxemia, fetal distress, meconium staining	M	+	+	0	+
37.	**(20,205)**	1 da.	W	♀	3459	—	40	Traumatic breech delivery	M	+	+	0	0
38.	**(30,234)**	16 hr.	W	♂	3500	40	0	Prolonged rupture membranes, severe meconium staining	M	+	+	+	+
39.	(33,090)	31 hr.	W	♂	3550	37	0	2nd trimester bleeding	P	0	+	0	+

Table 1 (Continued)

Case number	Age, race, sex	Birth weight	Stated Gest. age (weeks)	Probable age (weeks)	Clinical Factors	Pulmonary maturity	Aspiration	Pneumonia	Pulmonary hemorrhage	CNS hemorrhage
40. (20.729)	7 hr. C ♂	3700	40	0	Disproportion, forceps breech delivery	M	0	+	+	0
41. (20,792)	11 hr. C ♀	3700	42	−4	Prolonged rupture membranes, prolonged labor	M	+	+	0	+
42. (25,626)	25 hr. C ♂	3850	39	0	Prolonged rupture membranes, cesarean section for "maternal indications"	P—M	+	+	+	+
					Infants of diabetic mothers					
43. (32,049)	17 hr. C ♀	2505	34	0	Cesarean section, toxemia	P	+	0	+	0
44. (5,793)	17 hr. W ♂	(2560)	38	0	Cesarean section	P—M	0	0	+	—
45. (22,747)	7 hr. C ♀	3470	—	37		P—M	+	0	+	+
46. (20,305)	38 hr. W ♂	5160	—	40	Cesarean section	P—M	+	+	+	+

An estimated gestational age was available in 39 of the 42 infants of nondiabetics; it ranged from 31 to 45 weeks and in 16 cases was 39 weeks or longer. The youngest *probable* age was 34 weeks, but only 10 (24%) were judged to be 29 weeks or older. The cumulative probable ages in these cases were compared to those of a control group of live-born infants weighing more than 2500 g (Fig. 1). The mean age in the study was 36.5 weeks in contrast to 39.2 for the control group. In the majority of cases in which the estimated gestational age was incompatible with the *probable* age, the difference was consistent with a four week interval. A difference of less than four weeks was present only in cases in which the expected date of confinement was somewhat uncertain. The crown-heel length was in agreement with *probable* age, but the normal range of this measurement was too great to be useful. In eight infants the *probable* age was considered four weeks less than the stated gestationalage. The reverse was true in threcases.

The birth weight of the infants ranged from 2500 grams to 3850 grams, excluding the infants of diabetic mothers; more than one-third (16 of 42) weighed over 3 kilograms. The birth weight was below the range of one standard deviation for gestational age (Gruenwald, 1966) in two cases, and above this range in four cases.

The male to female ratio was 33:9 (79% males). More than one-third of the cases were first-born infants, but of the remaining cases, over one-half were born to mothers with a history of previous abortion or premature delivery.

Seventeen of the 42 infants (40%) were delivered by cesarean section. In 14 the *probable* age was 38 weeks or less, and in all but two moderate to severe fetal indications (detailed in Table 1) were present. Serious ante- or intra-partum complications occurred in fifteen vaginally delivered infants, so that fetal distress of varying degrees of severity was present in two-thirds of the cases (30 of 42).

Fourteen of the 42 infants (33%) lived longer than 36 hours; but only one survived longer than three days. The earliest deaths were at four hours. Duration of life was related neither to birth weight nor to gestational age in the present

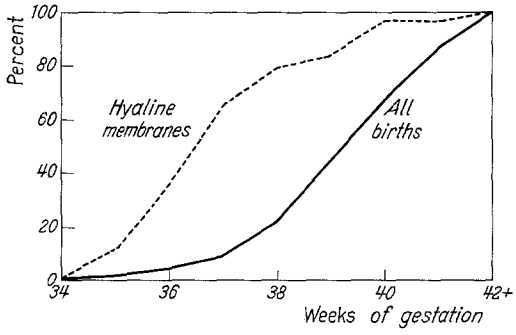

Fig. 1. Cumulative gestational age of the 42 full-size infants with hyaline membranes (broken line), and of a control group of live born infants with a birth weigth over 2500 g (solid line). The mean gestational age in the cases with hyaline membranes is nearly three weeks less than the control group

cases. Three-fourths of the total cases had pathologic findings in addition to hyaline membranes, sufficiently severe to contribute to the death of approximately one-half of the cases. Pneumonia was present in 23 infants, most of whom survived the first day of life. Pulmonary hemorrhage was noted in 18 cases and hemorrhage in the central nervous system in 15.

The ten cases with a *probable* age of 39 weeks or longer (bold face, Table 1) had histologically mature lungs and kidneys and were of heavier than average weight for this group but included the two infants of low birth weight for gestational age; no other factors (length of survival, sex, history of obstetrical complication, cesarean section, parity, pneumonia or hemorrhage) were sigificantly different from the infants of lower gestational age.

The *autopsy frequency* and *incidence* per 1,000 live births over 2500 g are listed in Table 2.

Table 2. *Frequency and incidence of hyaline membranes in full-size infants*

	Total live births over 2500 g	Neonatal deaths	Cases Examined	Cases with hyaline membranes	Frequency in autopsies	Incidence per 1,000 live births
J.H.H. (1944—1965)	54,320*	316	334**	30	9.0	0.55
S.H. (1954—1965)	35,700*	133	126	16	12.7	0.45
Total	90,020	449	460	46	10,0	0.51

* The numbers for 1964—1965 were extrapolated from the previous 5 years.

** The number of autopsies exceeds that of deaths because the former includes extramural births.

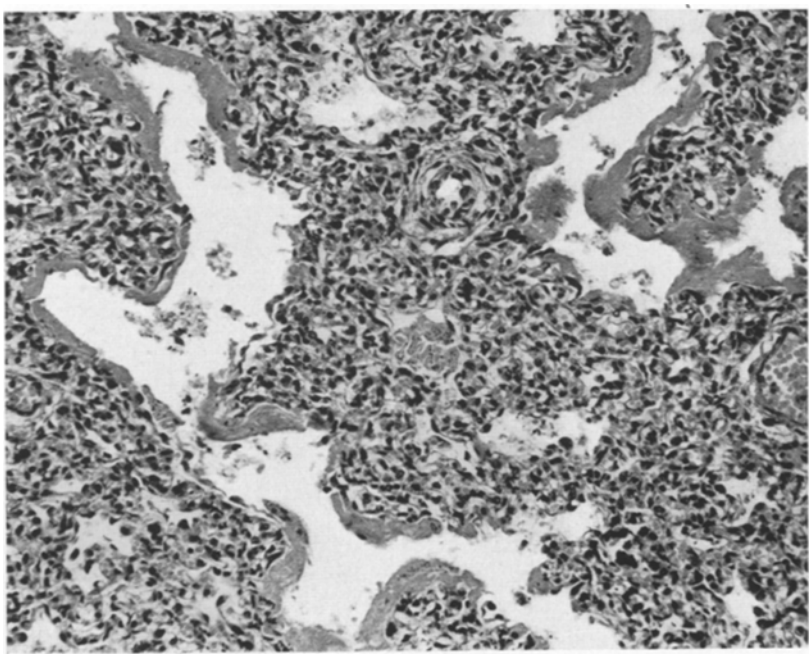

Fig. 2. Peripheral atelectasis and hyaline membranes lining respiratory bronchioles are characteristic of RDS in the premature lung. This 2525 g infant was delivered at 34 weeks by cesarean section because of abruptio placentae (Case No. 3). H and E ×166

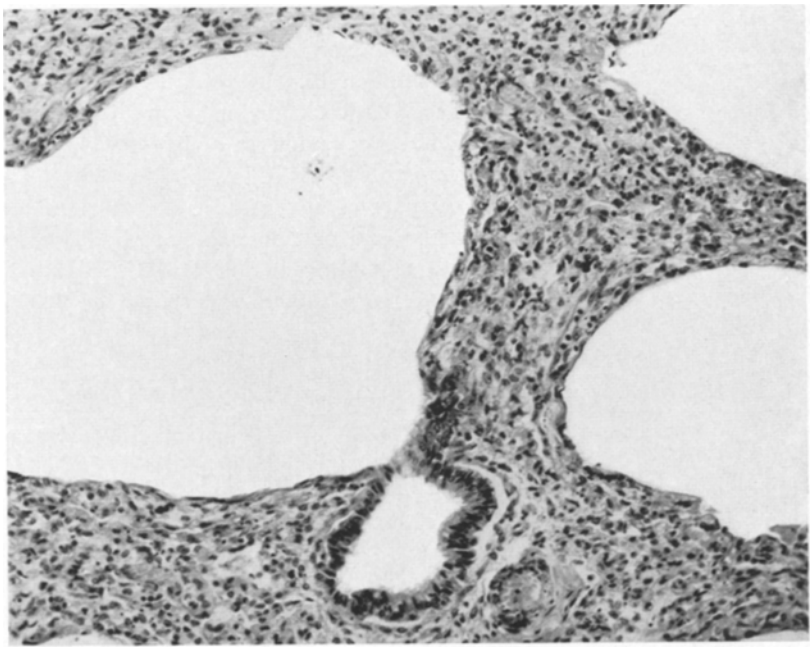

Fig. 3. In exaggerated atelectasis of prematurity the bronchioles are greatly distended; membranes are present in less distended bronchiales (not shown). This pattern of aeration is often present at a time when recovery from RDS is anticipated, as in this 3 day old infant (Case No. 20) H and E ×166

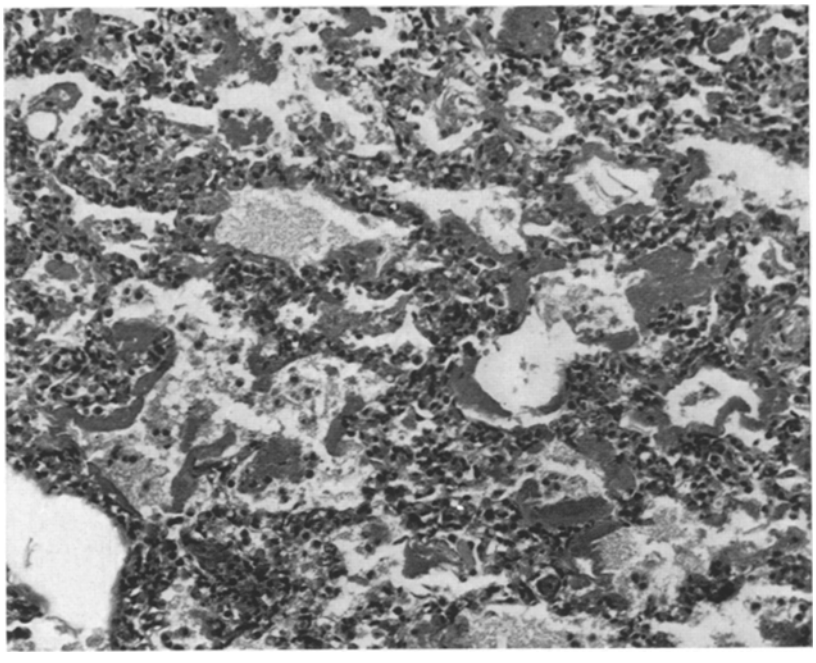

Fig. 4. Hyaline membranes are scattered among respiratory bronchioles and alveoli in the lung of this 3459 g full-term infant (Case No. 37). The expansion of alveoli as well as the distribution of membranes is different from that found in a premature infant (Fig. 2). H and E ×166

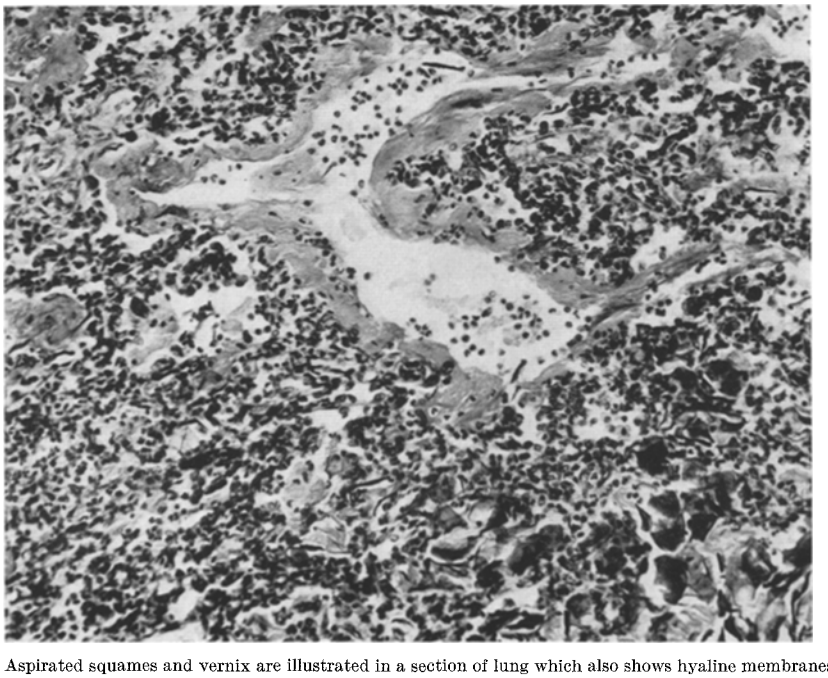

Fig. 5. Aspirated squames and vernix are illustrated in a section of lung which also shows hyaline membranes and pneumonia (Case No. 36). The aspirated material and hyaline membranes are present in adjacent airways and not superimposed. H and E ×166

In addition to hyaline membranes which were the basis for selection, congestion and atelectasis were present in all cases. Only trace amounts of pulmonary edema were seen. Because alvealor stability is independent of both the number of membranes and their thickness, cases with *any* membrane formation were included in the study. Atelectasis of prematurity, characterized by distended respiratory bronchioles and collapsed peripheral airways, reflects the ease with which bronchioles expand, and the high opening pressure of alveoli in the premature lung. The gestational age in these cases is typically less than 37 weeks, and the membranes are seen lining the distended bronchioles (Fig. 2).

A histologic variant, an exaggerated form of atelectasis of prematurity, was present in nine cases. The appearance is that of respiratory bronchioles excessively distended by air with greatly attenuated membranes and collapsed proximal bronchioles in addition to distal air spaces (Fig. 3). The degree of air trapping suggests compression of surrounding tissue with mechanical interference with ventilation at a time when recovery of pulmonary stability might be expected (age range in the present series: 16 hrs. to 6 days). Other causes of death were often lacking in these cases.

The mature lung no longer demonstrates atelectasis of prematurity (after 36—37 weeks), and in the 10 cases in which hyaline membranes occurred in mature lungs, they were distributed in alveoli as well as bronchioles (Fig. 4). Aspirated vernix in true membrane form was not identified in this material. When aspiration was present it was noted adjacent to, but not superimposed on areas with hyaline membranes (Fig. 5).

Comment

Numerous authors have included data on hyaline membranes in full-size infants in their observations on the respiratory distress syndrome. Studies including findings among 40 or more infants with hyaline membranes are listed in Table 3. Diverse geographic populations representing varying proportions of low birth weight infants are including among these and in other, smaller studies with similar findings (Sivanesan, Chuang; Rosahn and Sheanakul; Younazai). Several of these reports contain the data necessary for calculating the autopsy frequency of hyaline membranes in full-size infants (percentage of total autopsied infants weighing over 2500 g) and four list the incidence per 1,000 live births over 2500 g.

We have not examined cases with a birth weight of less than 2500 g. However, an approximate comparison with the total number of cases may be made using the data of Avery and Oppenheimer for premature infants in the same population for a 10-year period (J. H. H. 1944—1948, 1954—1958). Excluding outside births, 14 full-size cases died during the same 10 years, and represent 16% of the total autopsied cases with hyaline membranes in that interval. Because the criteria of hyaline membranes disease in the study of low birth weight infants (Avery and Oppenheimer) excluded cases with minimal membranes, the resulting proportion is somewhat high. Nevertheless this percentage, the autopsy frequency, and incidence per 1,000 livebirths are comparable to the findings in other studies (Table 3)

Three recent reports have considered the gestational age of full-size mature infants with RDS. In a large clinical study of cesarean section, Usher et al., found that none of 24 affected infants weighing more than 2500 g had reached a gesta-

Table 3. *Hyaline membranes in full-size infants compared to all cases with hyaline membranes and total number of autopsied and of liveborn full-size infants*

Author	Total cases with hyaline membranes	HM in cases over 2500 g			
		Number	Per cent of all cases with HM	Autopsy frequency	Incidence per 1,000 live births
Claireaux	108	22	20		
Harnaes and Torp	56	13	23		
Latham et al.	124	26	21	17	1.2
Gavaller	344	74	22		
Braun	63	7	11		
Ahvenainen	173	40	23		
Cohen et al.	73	15	21	18	0.7
Sivanesan	125	4	3	9.8	
Chuang	44	3	7	13	0.3
Driscoll and Smith	162	14	9	47	
Butler and Bonham	117	17	13	5.2	0.3
Shanklin	143	7	5		
Hirschmann	112	4	4		
Stowens	150	11	7		
Present study		46	16*	10	0.5

* For 10 years (J.H.H.), see text.

tional age of 270 days, and that only one of 24 vaginally delivered infants in the same weight group with RDS was born after 38 weeks (in a combined total of 13,303 live births). In a similar number of full-term deliveries, Lauweryns et al., reported five cases older than 38 weeks with hyaline membranes at autopsy. Dunn found no infants with RDS that were over both 2500 g in weight and 37 weeks gestation (in 2051 live births). Ten cases in our study had a gestational age over 38 weeks, and these occurred in about 70,000 live births of comparable weight and age.

From the data available in this study, it is possible to estimate the hazard of fatal RDS in the full-size, gestationally mature infant by adjusting for the proportion of deliveries after 39 weeks or longer in births over 2500 g. This "adjusted incidence" is in the range of 0.1/1000 full-term live births over 2500 g and is uncommon by any standard.

Accurate determination of gestational age is essential in this type of study. Our criteria have been based on the clinically estimated gestational age when it was compatible with body and organ weights and the degree of renal and pulmonary maturity. For weight standards we have used values within one standard deviation of the mean for infants of known gestational age. Similarly histologic development was compared to that of infants of normal birth weight and known gestational age. It may be argued that the pattern of aeration in the lung of a premature infant surviving for several days may appear mature (Gruenwald, 1963b). The diagnosis of maturity in this study, however, was usually confirmed by the presence of hyaline membranes in alveoli which is inconsistent with peripheral atelectasis in the immediate post-natal period when the membranes are forming. It is therefore unlikely that the lung of a premature infant recovering from RDS would be confused with that of a full-term infant with hyaline

membranes. Nevertheless, little is known about histologic changes in the late neonatal period; because of this and the possibility of hyaline membranes occurring in response to factors other than idiopathic respiratory distress, cases over seven days of age were excluded.

The ten full-term infants in this series could not be differentiated from the remainder on the basis of the clinical factors investigated, but several findings for full-size infants were in contrast to those noted for RDS in premature infants. The length of survival among full-size infants was related to neither birth weight nor gestational age, but the mean duration was longer than that reported for infants of low birth weight (Latham et al., Cohen et al.; Shanklin) and confirms Robertson's observation for full-size infants. Hyaline membranes are not present in the first hours of life and histologic examination alone does not identify all cases of RDS because death may occur before membrane formation (Gruenwald, 1964). Histologic diagnosis in full-size infants, however, is likely to be more complete because of longer survival.

The incidence of RDS is higher in infants delivered by cesarean section, but opinion is divided on the relationship between these factors. Strang et al. were among the first to emphasize that the indication for section was more important than the mode of delivery. Usher et al. have concluded, however, that the hazard lies in prematurity. Elective sections are usually performed near term, while "emergency" indications frequently arise earlier in pregnancy; according to Usher et al. the risk to the fetus after 38 weeks gestation irrespective of indication is nil. Delivery by cesarean section was 15 times more common for cases in this study than for live births of equivalent weight. Serious indications were present in most instances, but 14 of the 17 infants were of a gestational age of 38 weeks or less. Hence the present findings are consistent with either viewpoint, but the number of cases is too small to separate contributing factors.

The proportion of males in this series is striking, and larger than that found in RDS as a whole (Shanklin; Robertson; Schubel). Shanklin observed that the degree of male predominance rises with birth weight, and our finding suggests that this observation extends to infants over 2500 g. While there is no known explanation for this sex difference, it is an additional example of "the greater susceptibility to disease and to early mortality of the human male" (Childs et al.).

Summary

The respiratory distress syndrome, manifested by hyaline membranes at autopsy, was found in 42 full-size infants, and four additional full-size infants of diabetic mothers among 460 neonatal autopsies, and approximately 90,000 births. The mean gestational age was 36.5 weeks and the cases were predominantly males. Ante- or intrapartum complications were present in threefourths of the cases and death was attributable to factors in addition to hyaline membranes in over one-half of the total. Forty per cent were delivered by cesarean section, most for serious indications, but the gestational age in the majority was less than 38 weeks.

The findings in ten cases with a gestational age of 39 weeks or longer did not differ from the remainder. Hyaline membranes are uncommon in full-size infants when compared to the total number of live births, especially if corrected for full-term gestation (about 0.1/1000).

Hyaline Membranen bei Neugeborenen

Zusammenfassung

Hyaline Membranen, als patho-morphologisches Substrat des Membransyndroms der Neugeborenen ("respiratory distress syndrome") sind unter 460 obduzierten Neugeborenen bei 42 über 2500 g schweren Neugeborenen und bei vier Kindern diabetischer Mütter nachgewiesen worden. Dieses Untersuchungsgut bezieht sich auf eine Geburtenzahl von annähernd 90000.

Das männliche Geschlecht überwiegt mit 79%. Die durchschnittliche Schwangerschaftsdauer bei den Neugeborenen mit hyalinen Membranen beträgt 36,5 Wochen. Drei Viertel der Fälle verzeichnen Komplikationen, die vor oder während der Geburt aufgetreten sind; mehr als die Hälfte ist daher mit weiteren funktionell bedeutsamen pathologischen Befunden behaftet.

Kaiserschnittentbindung liegt in 40% vor mit einer durchschnittlichen Schwangerschaftsdauer von weniger als 38 Wochen. Die Befunde an 10 Neugeborenen mit einer Schwangerschaftsdauer von 39 Wochen oder länger unterscheiden sich kaum von den übrigen. Die Häufigkeit der hyalinen Membranen bei normalen Gewichten und termingerecht geborenen Kindern errechnet sich auf 0,1/1000.

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