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Pulmonary structural changes in neonatal hyaline membrane disease treated with high pressure artificial respiration

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Fourteen babies with hyaline membrane disease were treated with artificial respiration using intermittent positive pressure. At present six children are in good health; four still show alterations on the chest radiograph. Eight babies died; in these, high pressures (50 cm. H_2O on the average) were used with high concentrations of oxygen (up to 100%). Severe pulmonary changes were found. The lungs were heavy and non-aerated. There was emphysema only in the child treated for six weeks. Bronchi and bronchioli showed a marked epithelial hyperplasia as well as squamous-cell metaplasia, whereas at other sites epithelial necrosis was apparent. The muscular layer was hypertrophic and mucous glands appeared hyperplastic. Hyaline membranes containing bilirubin pigment were found in six of the eight cases. The alveolar epithelium was extremely atypical. The interstitium showed a proliferation of fibroblasts which resulted in a pronounced interstitial fibrosis in the child treated for six weeks. It is suggested that this treatment may aggravate the pathological changes caused by the hyaline membrane disease itself. Therefore, artificial positive pressure respiration should be used only when other measures fail to help the infant during the period when spontaneous recovery is possible.

In spite of many clinical investigations and of much experimental work the aetiology and pathogenesis of the hyaline membrane disease (H.M.D.) of the newborn infant is still unknown.

The mortality in premature infants remains high, especially in infants born after a gestation of less than 34 weeks, in spite of treatment with oxygen and intravenous infusions of glucose and alkaline fluids.

In recent years, in many centres artificial respiration with intermittent positive pressure has been employed successfully in some children. In other infants, however, there was no improvement of the functioning of the lungs after some days of artificial respiration; on the contrary, it was necessary to use very high concentrations of oxygen and to increase the pressures during the artificial respiration. Both created new problems because of the fact that high oxygen concentrations as well as high pressures of 40 cm. H_2O or more may be deleterious to the lung tissue. Therefore the treatment may lead to a vicious circle and these infants ultimately die or survive with incomplete recovery from the disease.

From July 1965 until September 1968, 14 prematurely born infants (Table) with clinical respiratory distress syndrome were treated with artificial respiration, using the so-called Keuskamp Amsterdam infant ventilator, which is based on a modified Ayre's T-piece (Keuskamp, 1963).

The clinical diagnosis of H.M.D. was made on the following criteria: dyspnoea with sternal and intercostal retractions, expiratory grunting, a reticulogranular appearance with an air-bronchogram on the radiograph of the chest, excluding all other cases of respiratory distress like meconium aspiration, congenital diaphragmatic hernia, etc. All babies were initially treated with glucose 10% and tris hydroxymethyl aminomethane (THAM) intravenously in order to correct the metabolic and respiratory acidosis, which was frequently estimated with the Astrup-method. The indications for artificial respiration were apnoeic spells, increase of the P_{CO_2} above 80 mm. Hg, or severe hypoxia when given 100% oxygen. (During the period of these observations catheterization of the umbilical artery was not yet done in this hospital; the criterion of capillary oxygen saturation was

TABLE

Case	Sex	Clinical Data: Gestat. Age (Weeks)	Clinical Data: Birth Weight (g.)	Duration of Artificial Respiration (Days)	Maximum Pressure Used (cm. H_2O)	Follow-up
1	M	35	2,220	3½	35	Died after 4 days
2	M	30	1,680	42	45	Died after 6 weeks
3	M	33	2,180	4	35	Good health 24 months
4	F	34	2,010	6	40	Good health 20 months
5	F	27	1,320	1	30	Good health 19 months
6	M	30	1,710	7	50	Died after 8 days
7	M	31	1,720	3	50	Died after 3½ days
8	M	31	1,980	6½	50	Died after 7 days
9	F	32	1,960	2	30	Good health 11 months
10	M	32	1,840	4	30	Good health 9 months
11	F	28	1,030	½	35	Died after 1½ days
12	M	30	1,800	1½	50	Died after 3½ days
13	M	32	2,200	3½	35	Good health 6 months
14	M	33	2,310	4	50	Died after 5 days

therefore used instead of arterial oxygen tension.)

Six of these 14 children recovered and are at present in good health, although in four of them the chest radiograph is not yet completely normal. Some clinical and necropsy data of the eight children who died will be reviewed, whereas the severe structural alterations in the lungs will be discussed separately in greater detail.

CASE REPORTS

CASE 1 A boy weighing 2,220 g. and aged 35 weeks, born by caesarean section, was severely asphyxiated. Since spontaneous respiration failed, he was immediately intubated and artificial respiration was performed. Although a few gasps followed, extubation was not possible because of inability to ventilate the lungs. Artificial respiration was continued, using pressures up to 35 cm. H_2O, but the child died on the fourth day of life. At necropsy, apart from the atelectatic lungs, small subependymal haemorrhages were found. This case is unusual in that the extreme form of respiratory distress syndrome immediately followed the period of asphyxia without an intervening period of recovery as a result of the resuscitation procedures.

CASE 2 A boy weighing 1,680 g. and aged 30 weeks was admitted 5 hours after birth with severe signs of H.M.D. When the clinical condition deteriorated despite conventional therapy, artificial respiration by endotracheal intubation was started at 28 hours. During the first week radiographs showed progressive opacification of both lung fields; weaning from the respirator proved to be impossible. Pressures necessary for ventilation had to be increased and at last pressures of 60 cm. H_2O were used. After the first week radiographs of the lungs showed rounded areas of radiotranslucency scattered throughout the lungs, and finally, there was an irregular pattern of translucent areas alternating with areas of density. After six weeks the child died with signs of interstitial and subcutaneous emphysema and pneumothorax. The vocal cords were completely atrophied due to the continuous intubation.

CASE 6 This boy, weighing 1,710 g., who was the first of twins born after 30 weeks' gestation, developed signs of H.M.D. during the first half-hour. Artificial respiration was started 31 hours after birth because of apnoeic spells. This was continued for seven days, using 80% oxygen and increasing pressures up to 50 cm. H_2O because the function of the lungs did not improve. The general condition remained very poor and during the 8th day of life, signs of kernicterus appeared. The bilirubin content of the blood at that time was 13·7 mg./100 ml., but had been maximally 16·9 mg./100 ml. on the 6th day of life. As the baby was clearly succumbing and died a few hours later, no exchange transfusion was performed. (Subsequently, we have performed an exchange transfusion in babies with disturbances in acid-base balance when the bilirubin content is reaching 15 mg./100 ml.) At necropsy a kernicterus and an intraventricular haemorrhage were found.

CASE 7 A boy weighing 1,720 g., born after 31 weeks' gestation, developed the respiratory distress syndrome soon after birth and artificial respiration had to be started within 6 hours of birth. Pressures of 40 cm. H_2O and 80% oxygen were given, but the oxygenation of the blood decreased, probably as a result of a progressive right-to-left shunt of the blood. The baby died after three and a half days. At necropsy, a thrombosis of the portal vein and a focal necrosis of the liver were found.

CASE 8 This baby, weighing 1,980 g., was born after 31 weeks. From about four weeks there had existed severe hydramnios of unknown cause. The infant was oedematous and developed the typical signs of H.M.D. during the first half-hour. Artificial respiration was started after 24 hours, but the radiograph of the chest showed no improvement during the following days: there remained a complete opacity. The child died after seven days. At necropsy, periventricular leucomalacia and a subependymal haemorrhage were found. The vocal cords were atrophied.

CASE 11 Immediately after birth this girl developed H.M.D. Twenty hours after birth repeated episodes of apnoea made it necessary to apply the respirator. Despite the administration of 100% oxygen, blood

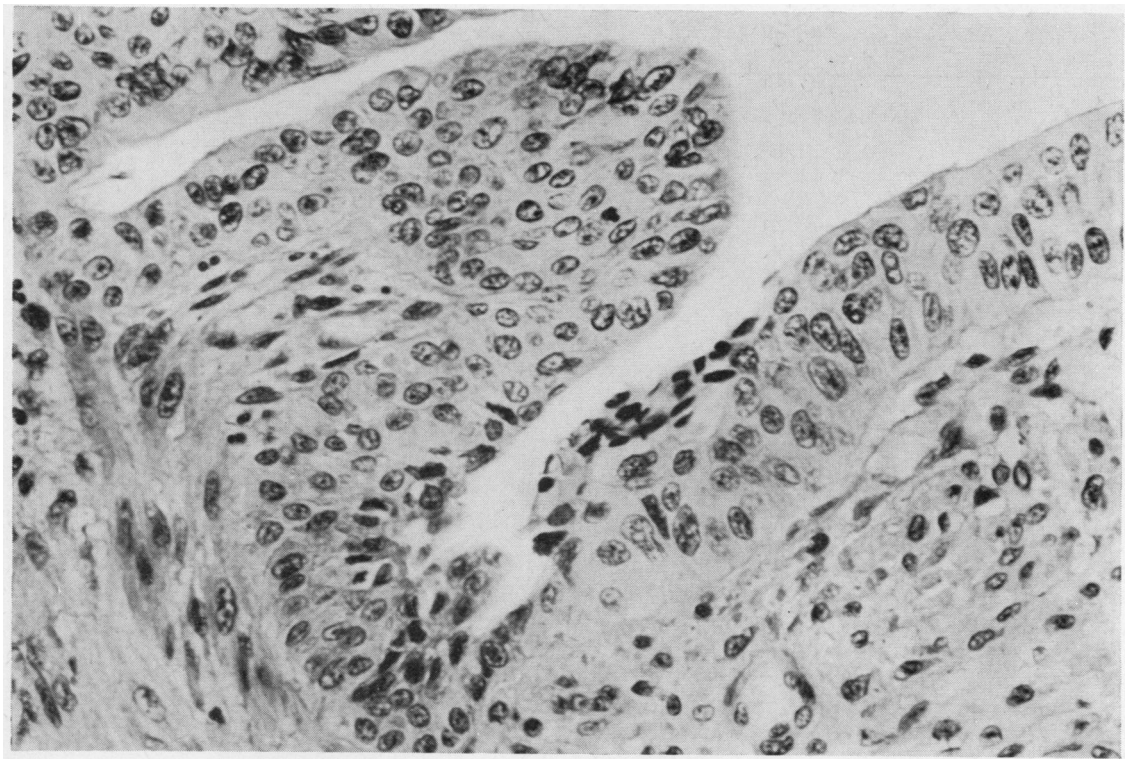

FIG. 1. *Squamous-cell metaplasia of bronchial epithelium* (*H. and E.* × 425).

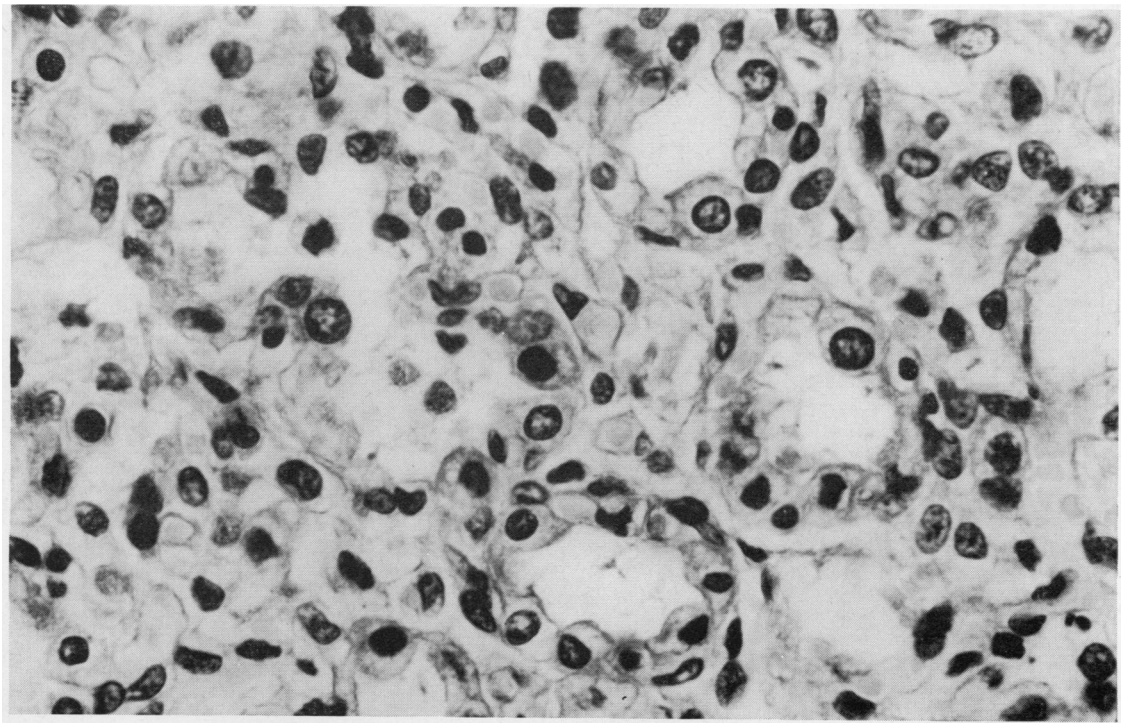

FIG. 2. *Atypia of alveolar epithelium* (*H. and E.* × 680).

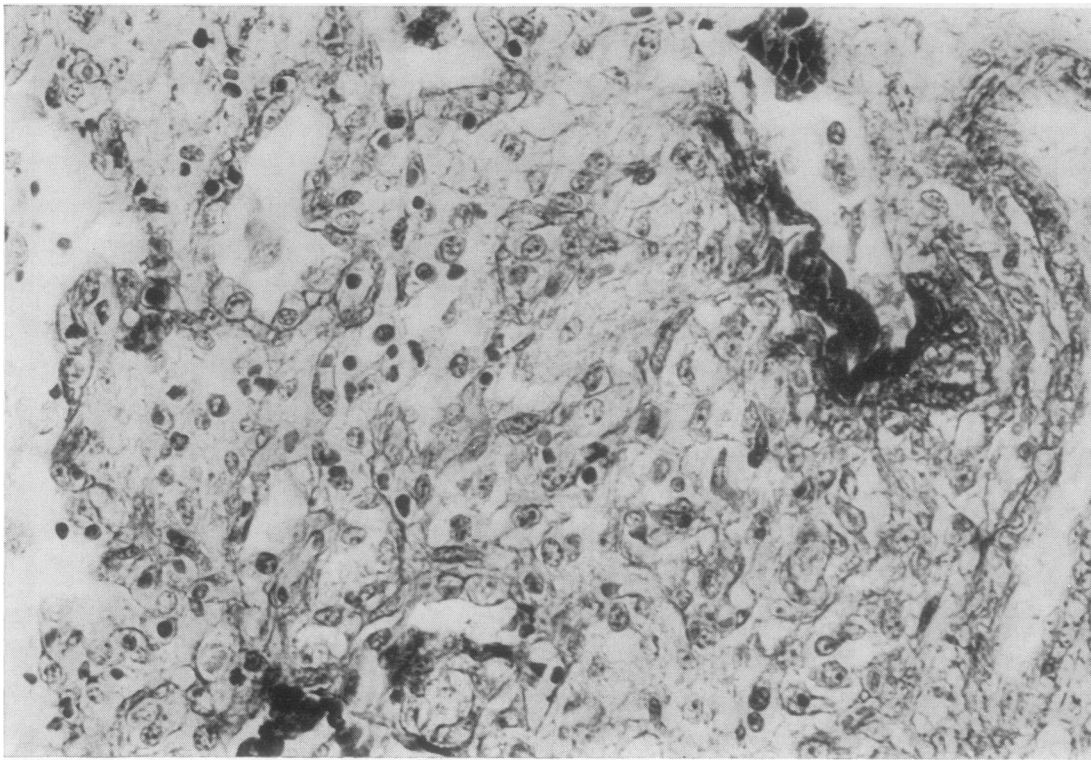

FIG. 3. *Proliferation of fibroblasts in the interstitium* (*Heidenhain's aniline-blue stain* × 425).

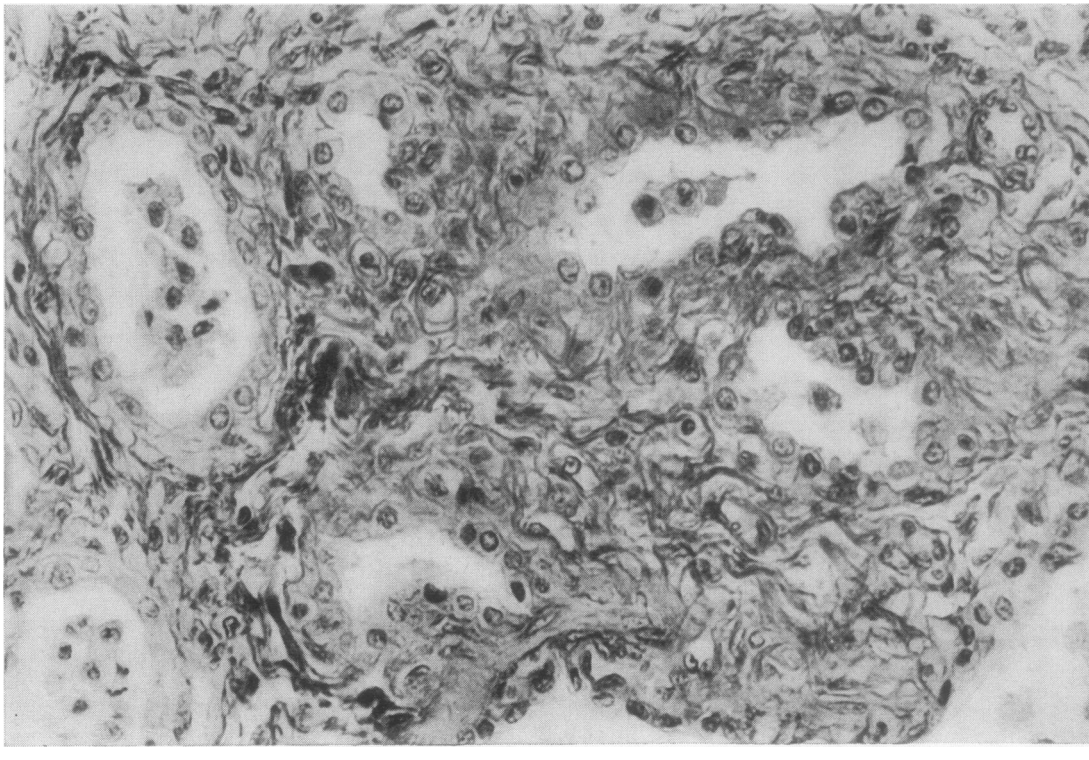

FIG. 4. *Pronounced interstitial fibrosis* (*van Gieson's stain* × 425).

oxygenation was inadequate with a maximum saturation of 66%. The baby died, hypoxaemic, 36 hours after birth. At necropsy, a subependymal haemorrhage was found.

CASE 12 This boy developed signs of H.M.D. during the first half-hour. The clinical condition deteriorated gradually despite conventional measures. Artificial respiration was started 58 hours after birth. Pressures of 50 cm. H_2O and a concentration of 80% oxygen were used. The baby died 32 hours later. At necropsy an intraventricular haemorrhage and a thrombosis of the sagittal sinus were found. The vocal cords showed haemorrhage and atrophy and there was degeneration of the left lobe of the liver.

CASE 14 After one hour this baby developed gradually progressive H.M.D. Generalized cyanosis persisted despite the administration of 100% oxygen. Arterial oxygen saturation of blood reached 80%, and the P_{CO_2} fluctuated between 60 and 80 mm. Hg. Spontaneous respiration stopped 24 hours after birth and artificial respiration was started. It proved to be necessary to use a pressure of 50 cm. H_2O and an oxygen concentration of 80%. Despite this treatment, the P_{CO_2} did not go below 60 mm. Hg, whereas the P_{O_2} reached a maximum level of 50 mm. Hg. After five days the child died, and at necropsy, thrombosis of the sinus transversus and tracheitis were found.

PATHOLOGICAL FINDINGS

In all cases impressive pathological changes were found in the lungs. The lungs were heavy, the weights varying between 60 and 120 g. Moreover, they appeared to be compact and non-aerated except in one child treated for six weeks (case 2). In this particular case emphysema and distinct pools of mucous material were detected.

The microscopical changes could be divided into three groups: those in the bronchial system, in the alveolar apparatus, and in the interstitium.

The bronchi and bronchioli showed marked epithelial alterations. In several sites the epithelial cells appeared to be necrotic, whereas elsewhere the epithelial layer was detached. Apart from this, hyperplasia and squamous-cell metaplasia were noted (Fig. 1). Mitoses were numerous. Moreover, the muscular layer of the bronchi showed hypertrophy combined with hyperplastic mucous glands.

The alveolar epithelium was extremely atypical with signs of degeneration, including pyknosis of nuclei and eosinophilia of the cytoplasm, as well as signs of regeneration, such as mitoses (Fig. 2). Hyaline membranes were found in many alveolar ducts. Sometimes a mixture of hyaline masses with degenerated alveolar cells completely filled the lumen. In nearly all cases the hyaline membranes contained bilirubin pigment.

The alveolar spaces and ducts were widely separated by a loose connective tissue in which a distinct proliferation of fibroblasts was apparent (Fig. 3). This loose texture was seen in all cases except in the child treated for six weeks (case 2). In this case a pronounced interstitial fibrosis was found (Fig. 4). The pulmonary arteries showed medial hypertrophy, whereas the lymphatics were dilated.

DISCUSSION

Fourteen newborn infants with H.M.D. were treated with artificial respiration using intermittent positive pressure (I.P.P.). Eight babies died with severe pulmonary changes. There appeared to be a marked difference in severity of the pathological changes between the seven babies treated for one to six and a half days and the one child treated for six weeks. In that particular case a distinct interstitial fibrosis existed, whereas in the other seven children only a proliferation of fibroblasts was apparent with little formation of fibres. This may be an indication that there is a progression towards an irreversible stage. However, in this small series an intermediate group was not present.

Northway, Rosan, and Porter (1967) studied 32 children with H.M.D. treated with I.P.P. artificial respiration and high oxygen concentrations. Nineteen babies died with severe pulmonary changes comparable to our findings, which they termed 'broncho-pulmonary dysplasia'. These authors distinguished four stages. First, there was a stage of the hyaline membrane disease *sui generis*, followed by the second stage between four and 10 days, where, at necropsy, necrosis and regeneration of alveolar epithelium were found with persistent hyaline membranes. In the third stage (between 10 and 20 days) a gradual transition into a chronic phase occurred which could lead to stage four, after one month, in which a distinct fibrosis was apparent. They were able to study two cases from the third stage, which is lacking in our series, and found a distinct proliferation of fibroblasts in the interstitium with spare formation of fibres. This strongly suggests that this process shows progression that ultimately may result in irreversible lung damage. In the series of Northway *et al.* (1967), none of the children treated for more than 10 days survived. Moreover, in their group of 13 survivors there were four babies, treated for five to 10 days, who showed pulmonary insufficiency.

The question arises as to whether these changes can be interpreted as the natural course of H.M.D. or whether these alterations are induced by the treatment. It has been pointed out by Boss and

Craig (1962) and by Robertson (1964), in studies of H.M.D. not treated with high pressure ventilation, that from the age of 3 to 4 days a reparative process in the alveolar walls may be found. However, in our seven babies treated for one to six and a half days the pulmonary structural alterations were distinctly more severe as compared to the changes described by these authors for the same period. This may indicate that I.P.P. artificial respiration may interfere with the natural course of H.M.D. in such a way that the reparative process is accentuated. The possible influence of this treatment may further be indicated by the work of Nash, Blennerhassett, and Pontoppiddan (1967), Regele (1967), and Barter, Finlay-Jones, and Walters (1968), who studied the lungs of adult patients treated with artificial respiration and high oxygen concentrations for various conditions. In their patients, hyaline membrane-like structures with interstitial fibrosis and metaplasia of alveolar epithelium appeared. It may be noted that five of the six babies in our series who survived were treated with relatively low pressures of 35 cm. H_2O, whereas the oxygen concentrations in three of these reached values of 50% and in only two cases 80%. One baby was treated for six days with pressures of 40 cm. H_2O and oxygen concentrations of 80%. However, four of these children still present pulmonary alterations on the chest radiographs. Although it is tempting to speculate on the fact that the low pressures used exerted a favourable effect, it seems more likely that the natural course of the disease in these children would have been better than in the others.

The question remains as to the factors involved when studying the work of Stern, Ramos, Outerbridge, and Beaudry (1968) and Shepard, Johnston, Klatte, Burko, and Stahlman (1968), who treated babies with H.M.D. with a negative-pressure artificial respirator. Both reports give inconclusive data with regard to the effects of the treatment on the natural course of the disease. Likewise, the influence of the positive pressure and the oxygen concentration is not yet clear. Our data also give no distinct indication whether the pressures, the oxygen concentrations or both are responsible for aggravating the lung pathology.

A remarkable finding in our cases, which to our knowledge has not been described before, is the accumulation of bilirubin pigment in the hyaline membranes. The maximum blood level for bilirubin in our series was 19·6 mg./100 ml. The accumulation of bilirubin in hyaline membranes was found in all cases, except in one baby treated for only one and a half days, with a low level of bilirubin, and the baby treated for six weeks in whom no hyaline membranes could be found at all. We therefore assume that the intermediate period resulted in such severe damage to the capillary-alveolar structures that excretion of the albumin fraction with bilirubin was facilitated. As mentioned above, since we treated the one infant with kernicterus, exchange transfusion is now performed at lower bilirubin levels.

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