Pathogenesis of Bronchopulmonary Dysplasia Following Hyaline Membrane Disease

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The pathologic changes in the lungs of 112 infants dying from hyaline membrane disease (HMD) and 64 infants dying from other causes in the years 1967 to 1972 have been reviewed in order to obtain information about the pathogenesis of bronchopulmonary dysplasia (BPD). The results from the infants with HMD showed that: a) From the fourth or fifth day, the surface tension of lung extracts fell, inclusion bodies became more plentiful, and air sacculles with patent airways could be inflated with air, even when severe changes due to BPD were present. b) There was a highly statistically significant correlation between the most serious lesions of BPD—damage to airways followed by excessive repair and fibrosis—and the use of high (>35 cm H₂O) peak airway pressures during mechanical ventilation in life. c) Damage due to oxygen breathing could not be reliably identified although some of the lesions, particularly edema and fibroplasia in intersaccular septa, may have been caused by oxygen. d) Evidence of pulmonary hypertension was present in infants surviving for more than a month with severe lung damage, and the ductus arteriosus was always open. We conclude that the most important factor in the pathogenesis of BPD following HMD is mechanical trauma to the lung from the use of excessively high peak airway pressures during mechanical ventilation. (Am J Pathol 82:241-264, 1976)

MECHANICAL VENTILATION was introduced in the Neonatal Unit of University College Hospital as a routine method for the treatment of infants very severely affected by hyaline membrane disease (HMD) at the beginning of 1966. Although some of the ventilated infants survived, many died with fibrotic changes in the lungs similar to those reported by others, and usually described as bronchopulmonary dysplasia or pulmonary fibroplasia. In this paper, we have preferred the term bronchopulmonary dysplasia (BPD), taking it to imply the presence both of fibroplasia and disturbed lung growth.

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Preliminary observations suggested to us that at least two potentially preventable factors might be involved in the pathogenesis of BPD: mechanical trauma due to the use of very high peak airway pressures and fast respiratory frequencies, and damage to the lung resulting from oxygen toxicity. We therefore devised means for ventilating the infants at lower peak airway pressures, respiratory frequencies, and oxygen concentrations. During the development of these methods of ventilation, infants who subsequently died were subjected to various combinations of ventilator settings and inspired oxygen concentrations which had been carefully documented in life. The purpose of this report is to describe the pulmonary pathology with particular reference to factors which may have an influence on the pathogenesis of BPD.

Materials and Methods

Material for examination was available from 176 infants dying in the years 1967 to 1972 and comprising 56% of infants coming to autopsy in this period. These included 112 who had the clinical, radiologic, and pathologic features of HMD. Their median birthweight was 1310 g (range, 730 to 2910 g) and their median gestation 30 weeks (range 26 weeks to 39 weeks). Seventy-three were boys and 39 were girls. They died at a median age of 41 hours (range, 1.5 hours to 13 months). Their management while in the Neonatal Unit has been described elsewhere.

For comparison, the pulmonary pathology of 64 infants who died from a variety of illnesses such as congenital malformation, meconium aspiration, infection, and cerebral damage has also been reviewed. The median birthweight of these control infants was 2390 g (range 760 to 4270 g) and their median gestation was 36 weeks (range 26 weeks to 42 weeks). Thirty were boys and 34 were girls. Their median age at death was 3 days (range, 25 minutes to 9 months). Infants who died during the same period with the clinical and pathologic features of the Wilson-Mikity syndrome and infants who developed pulmonary fibroplasia following mechanical ventilation for apnea of prematurity have been excluded from the present analysis because the evolution of their clinical and pathologic features was quite different from that found in the infants with hyaline membrane disease. They will be reported separately.

Lung Biopsy

A needle biopsy of the lung was obtained from 59 infants immediately after death, fixed in glutaraldehyde, and embedded in Epon 812 after graded dehydration in ethanol. One-thick sections were stained by toluidine blue and used for estimating the numbers of inclusion bodies present in Type 2 pneumocytes. The number of these bodies was graded from − to +++ according to the following criteria: no inclusion bodies (IBs), −; a few IBs in rare cells in a few air sacs, ±; some IBs in a few cells in some air sacs, +; many IBs in several cells in numerous air sacs, ++; Numerous IBs in many cells in all air sacs, +++.

 Necropsy and Pulmonary Pathology

Necropsy was performed between 4 hours and 2 days after death. After noting the appearance of the lungs, one was sectioned, and pieces from the upper and lower lobes were fixed in formol saline; the remainder was fixed in formol calcium. The other lung was inflated with air from an air pump in a static system where the pressure was
stabilized and measured by a manometer. In infants who had been mechanically ventilated, the pressure used was the same as the peak airway pressure applied terminally in life. This pressure ranged between 20 and 60 cm H₂O. Lungs from infants who had not been mechanically ventilated (including many of the controls) were inflated to 20 to 25 cm of water. The inflated lung was fixed by flowing formol calcium into the pulmonary artery until the solution running from the pulmonary veins was free of blood and then suspended for 48 hours in a similar solution.

Paraffin sections were prepared from inflated and noninflated lungs and stained by standard methods—hematoxylin and eosin, van Gieson, elastic (orcein or Weigert), periodic acid–Schiff (PAS), PAS–alcian blue, reticulin, phosphotungstic acid–hematoxylin (PTAH), trichrome (Heidenhain azan), and Gmelin. Frozen sections from formol calcium–fixed tissues were stained with Sudan black. Linear counts of alveoli were made in the sections from infants surviving for more than 4 weeks.¹⁷

**Surface Tension**

For the measurement of pulmonary surface activity, 3-g pieces of lung tissue were minced and extracted with 0.9% sodium chloride solution.¹⁸ The extract was filtered into the trough of a modified Wilhelmy balance, and the surface tension was recorded during 15-minute cycles of compression and expansion of the surface.¹⁹ If the minimum surface tension during compression had reached previously defined normal values (<15 dynes cm⁻¹) after 5 hours, cycling was stopped; if not, cycling was continued for 24 hours, and the minimum value obtained during this time was recorded.

**Results**

**Terminology**

We have, in general, followed the recommendation of the Commission on Embryological Terminology.²¹ We use the term saccule rather than alveolus in the prenatal and newborn period (up to 2 months), acinus for the lung distal to a terminal bronchiule and lobule for those three to five terminal bronchioles and their acini which cluster at the end of any pathway. Inclusion bodies are defined as organelles approximately 1 μ in diameter found in Type 2 pneumocytes.

**Hyaline Membrane Disease**

**Macroscopic and Histologic**

All the infants dying with the pathologic features of HMD had been treated by mechanical ventilation. For descriptive purposes they have been divided into three age ranges: a) 80 infants dying at less than 5 days b) 26 infants dying between 5 and 15 days, and c) 6 infants dying between 4 weeks and 13 months. No infants died between 16 days and 4 weeks.

*Less then five days of age.* Fifty-six of the 80 infants in this group were males and 24 females. The period of gestation ranged from 26 to 38 weeks (median, 30 weeks), and the birth weight from 730 to 2910 g (median, 1310 g). They had been mechanically ventilated for between 1 and 120
hours (median, 28 hours) and they died at 1½ hours to 120 hours (median, 32 hours).

Macroscopically the lungs of these infants were usually heavier than expected,22 dark purplish red in those dying during the first 2 days of life, but thereafter becoming paler toward the hilum. A lobular pattern was visible on the dry cut surface.

Histologic examination showed marked distension of terminal airways (bronchioles and terminal bronchioles), together with complete collapse of air saccules. Eosinophilic material present in the expanded terminal airways did not always show a membranous structure in the first 12 hours and sometimes appeared as amorphous material containing pyknotic nuclei derived from bronchiolar epithelium which was no longer distinguishable under it. Hyaline membranes lining expanded airways and containing some fibrin (PTAH positive) were regularly present after 12 hours, at which time there was capillary congestion. However, the earliest age at which a well-formed membrane was seen was at 1½ hours in a baby born at 26 weeks of gestation. Histiocytes were occasionally seen deep to the membranes after the second day and were conspicuous by the fourth day, some showing mitoses. By this time the initial congestion had subsided and dilated capillaries were seen only in bronchiolar walls. Edema present in intersaccular septa from the first day had increased and lymphatic spaces remained distended.

Five to Fifteen Days. Twenty-six infants, 13 males and 13 females, died aged 5 to 15 days. Their gestational ages ranged from 27 to 38 weeks (median, 30 weeks) and their birth weight from 710 to 2760 g (median, 1120 g). They had been mechanically ventilated for 2 to 14 days (median, 7 days), and they died at 3 to 13 days (median, 8 days).

Repair and regeneration were the most important pathologic features at this time. The lungs were 25 to 40% heavier than weights recorded for normal infants.22 They often retained rib impressions and displayed a varied color. Prominent lobulation was visible on the cut surface which had a pale but mottled appearance. Golden dots could be seen in the center of the acini between 5 and 11 days. This color was due to a change in the hyaline membranes which were golden yellow in stained and unstained sections (Figure 1), and now extended proximally as far as medium-sized bronchi. Staining of the membranes by special techniques was negative except for Gmelin’s method which showed the presence of hematoidin.

The medium-sized and small bronchi, as well as the terminal airways, were lined by granulation tissue which grew from the deep surface of the hyaline membranes after 4 days and involved almost all of the membranes
by 8 days. Proliferating fibroblasts extended into the masses of cellular debris and exudate which filled the lumens of many bronchi and terminal airways producing an "obliterating bronchitis" (Figure 2) in about half the cases. Epithelial regeneration itself was often sufficiently excessive to reduce the lumens of small bronchi. This regeneration continued into the larger bronchi where much of the normal stratified columnar epithelium showed squamous metaplasia (Figure 2). It is uncertain whether the regeneration arose from residual epithelial cells beneath the hyaline membranes or whether it spread from uninvolved bronchi. Moderate numbers of mitoses were seen in the regenerating cells, and muscular hypertrophy was present in the walls of many bronchi.

The fibroblastic proliferation which affected many acini in the majority of infants extended from the peribronchiolar central zone to the periphery of the acinus, or else from septa separating air saccules. Reticulin was laid down by the fibroblasts, and the young fibrous tissue was often so excessive that it caused great distortion of saccules in some areas, leading to lobular fibrosis (Figure 3). (The term lobular fibrosis is used to indicate involvement of the whole of a lobule with distortion of its architecture). Cuboidal cells (Figure 2) lined many saccules, some of which contained numerous "alveolar macrophages." Patches of pneumonia were occasionally present. Any saccules and alveolar ducts which were open formed irregular air spaces with intercommunications and occasionally formed bullae separated by widened septa. The lymphatics were still distended and focal areas of hemorrhage in sacules or in septa were present. The lobular arteries had thick walls because of medial hypertrophy.

The gross and microscopic appearance of the lungs of infants dying at 10 to 15 days suggested that the lungs were divided into random areas, some of which were emphysematous with distended terminal airways and open saccules separated by thin fibrous septa, while the others had small contracted airways, wide fibrous septa, and some residual collapse. This random scatter appeared to have a lobular or multilobular distribution which was seen more clearly in inflated lungs (Figure 4).

Four Weeks to Thirteen Months. Six infants, 4 boys and 2 girls, died aged 4 weeks to 13 months. Their gestational ages were between 27 and 36 weeks (median, 32 weeks) and their birth weights between 1160 and 2000 g (median, 1700 g). They were mechanically ventilated for between 30 hours and 4 weeks (median, 7 1/2 days) and their median age at death was 68 days.

When the chest was opened, the lungs bulged out. They appeared bulky with haphazardly arranged emphysematous and collapsed areas.
and were deformed by deep fissures (Figure 5). The emphysematous areas
were formed of large bullae up to 2 cm in diameter protruding on the
pleural surface, or else were seen as flat areas with vesicles about 2 mm in
diameter. The collapsed areas were dark red and compact, both on
external examination and on sectioning.

On histologic examination the majority of these cases (5 of 6) differed
from the earlier groups in that repair and regeneration in bronchi and
terminal airways was not the main feature. Bronchi were lined by
stratified columnar epithelium which was less hyperplastic and showed
residual squamous metaplasia in only 2 infants (dying at 6 and 7 weeks).
An excess of mucus goblet cells in bronchial epithelium and hypertrophy
of mucous glands in their walls was present in 2 infants (dying at 7 weeks
and 6 months). Hypertrophy of muscle and subepithelial fibrosis were
present in the walls of medium-sized and small bronchi. The lumens of
terminal airways were not reduced in 5 of the 6 cases but residual stigmata
of damage in this site were an excess of muscle surrounding the
bronchioles, and reticulin and elastic fibrils extending to the origin of the
alveolar ducts.

The effects of fibrosis were still considerable in the parenchyma where
the air spaces in the multilobular emphysematous areas had remained
poorly branched as well as irregular in size and shape. The alteration of
the fibrotic, emphysematous, and other areas was again seen best in
inflated lungs (Figure 6). In many of these emphysematous areas the inter- and intralobular septa were widened by fibrous and elastic tissue. In
4 of the infants dying within 3 months, areas of lobular fibrosis were
present. The deep fissures led to areas of fibrotic, atrophic, and collapsed
lung in which air spaces were narrow, often slit-like, sometimes lined by

Text-figure 1—Relation between inclusion-bodies counts and
postnatal age. [HMD = 43 infants]; solid circles; controls = 27 infants;
open circles]
cuboidal eosinophilic cells and sometimes containing numerous alveolar macrophages.

The walls of the pulmonary arteries were thicker than in the few controls dying at a similar age (Figure 7). A preliminary statistical analysis has shown that these vessels had significant medial muscular hypertrophy and that the normal decrease in pulmonary artery wall area in neonatal life and infancy had not occurred. In addition, elastic plates were still present in the large pulmonary arteries. These indications of pulmonary hypertension were confirmed by distinct right ventricular hypertrophy. The hearts were enlarged, with a range of the weight of left ventricle and septum to right ventricle of 1.2 to 1.4 (method of Fulton et al.). The ductus arteriosus was always patent.

Inclusion Bodies and Surface Tension of Lung Extracts

These investigations were carried out to determine whether pulmonary surfactant was present in the lungs of infants dying from bronchopulmonary dysplasia and to correlate inclusion body counts with surface tension measurements. Counts in relation to age at death are shown in Text-figure 1, and the results of measurement of surface activity of lung extracts in both infants with HMD and controls are shown in Text-figure 2. The characteristic absence of inclusion bodies in an infant dying at 2 days of age with HMD is shown in Figure 8, and the abundant bodies in an infant dying at 7 days with HMD are in Figure 9.

In 21 infants with HMD, both inclusion-body counts and measurements of surface tension were carried out. In 5 of 8 infants with minimum surface tension values of 15 dynes cm⁻¹ or more, inclusion bodies were
absent, whereas inclusion bodies were present in all 14 infants with surface tension values of less than 15 dynes cm\(^{-1}\) (Text-figure 3).

**Inflated Lungs**

The purpose of lung inflation was to reproduce at postmortem the peak airway pressures used in life. We hoped to find out which areas of lung had been inflating during ventilation, and to see if there was any correlation between the expansion of air saccules and the presence or absence of inclusion bodies and pulmonary surfactant.

**Less Than Five Days of Age.** In these specimens, the saccules remained collapsed even when pressures as high as 60 cm H\(_2\)O were applied. Remarkable overexpansion of terminal airways was, however, visible, with the formation of large spherical spaces. The terminal airways always appeared much larger than those in the noninflated lung from the same infant. The overexpanded areas were lined by hyaline membranes. Inclusion body counts were low (Text-figure 1), and the surface tension of lung extracts high—greater than 15 dynes cm\(^{-1}\) (Text-figure 2), evidence that pulmonary surfactant was deficient.\(^{18,20,26}\)

**Five to Fifteen Days.** The saccules were open to air penetration to a variable degree (Figure 4). Overexpansion of terminal airways remained extensive but was irregular, so that some lobules were considerably more expanded than others. Thus the size of the air spaces varied greatly in different parts of the lungs. Recovery of the ability to inflate the air saccules coincided with an increase in the number of inclusion bodies in saccule cells and with a fall in the surface tension of lung extracts (Text-figures 1 and 2), indicating the presence of pulmonary surfactant.

**Four Weeks to Thirteen Months.** The irregularity of lobular expansion remained prominent. The random arrangement of irregularly
overexpanded, underexpanded, and even collapsed, areas on a lobular or often multilobular basis was more easily seen than in the noninflated lungs (Figure 6). In some areas formed by a lobule or a number of closely related lobules, expansion appeared quite uniform, giving the appearance of islands of normal lung tissue scattered among pathologic areas. Even in these islands, the number of alveoli was reduced in the places where it was possible to carry out linear counts 17 (Figure 10).

Relation of Bronchopulmonary Dysplasia to Ventilator Settings and Inspired Oxygen Concentration

In the early years of this study we often used very high peak airway pressures ($\geq 35$ cm H$_2$O) to ventilate the lungs of infants with hyaline membrane disease, together with fast respiratory frequencies ($\geq 60$/min) and very high inspired oxygen concentrations ($\geq 80\%$). Preliminary observations 8 and clinicopathologic correlation in the following years led us to believe that a particular pattern of severe, rapidly developing fibroplastic changes found in the lungs at autopsy might be due to mechanical trauma, whereas another pattern of less immediately damaging lesions might be the result of pulmonary oxygen toxicity. As improved methods were developed for ventilating the infants, we passed first through a phase when much lower peak airway pressures and respiratory frequencies were used but the inspired oxygen concentration remained high, and then to a more recent phase when the inspired oxygen concentration was reduced to lower levels as well. The changes in survival rate and the incidence of bronchopulmonary dysplasia which occurred during the development of these methods have been described in detail elsewhere 15.

Because of the alterations of ventilator management which occurred in our Unit, we were afforded the opportunity of testing our hypothesis 8 that some of the lesions seen in the lungs were largely the result of mechanical trauma, whereas others were largely the result of oxygen toxicity.

The pathologic sections from the 32 infants who had lived for 5 days or more were sorted by one of us (AT) into two groups according to whether the lesions present were thought to be predominantly due to mechanical trauma to the lung (the "mechanical trauma group"), or to oxygen toxicity (the "oxygen toxicity group"). This was done without any knowledge of the ventilator settings or inspired oxygen concentrations used in life, which had been noted by the other author. We suspected that peak airway pressures of 35 cm H$_2$O or more, and oxygen concentrations of 80% or above, were likely to damage the lung, and that in order for identifiable damage to occur, these pressures or oxygen concentrations
would have to be present for at least 2 days. We therefore tested our ability successfully to identify lesions due to mechanical trauma against the finding that the infant had been ventilated at a peak airway pressure $\geq 35$ cm $H_2O$ for more than 2 days, and our ability to identify lesions due to oxygen toxicity against the finding that the infant had breathed an oxygen concentration $\geq 80\%$ for more than 2 days. The results are illustrated in Text-figure 4.

**Mechanical Trauma.** Among 16 infants assigned to the mechanical trauma group (Text-figure 4), 13 had been ventilated with peak airway pressures of $35$ cm $H_2O$ or above for more than 2 days, whereas none of the infants in the oxygen toxicity group had been ventilated in this way ($X^2$ with Yates correction = 18.08, $P < 0.001$). We conclude that lesions associated with the use of very high peak airway pressures can be reliably identified. High respiratory frequencies were almost always used at the same time as high peak airway pressures, and the mean respiratory frequency of the mechanical trauma group (58 cycles/min) was higher than that of the remaining infants (32 cycles/min, $t = 5.08$, $P < 0.001$). The most striking features of the mechanical trauma group were the damage in bronchi and terminal airways with narrowing and obstruction of the lumens by epithelial hyperplasia and fibroblastic proliferation. In addition, severe parenchymal damage was present, with extensive peribronchiolar fibrosis, usually confined to the center of the lobules, but sometimes spreading to involve a whole lobule (lobular fibrosis, Figures 3 and 11).

In only 3 of those infants who had not been subjected to peak airway pressures of more than $35$ cm $H_2O$ for more than 2 days were...
these features present. They were not present in any of the control group, none of whom had been ventilated with such high airway pressures for this length of time.

**Oxygen Toxicity.** Among 14 infants assigned to the oxygen toxicity group, 12 had breathed an oxygen concentration of 80% or above for more than 2 days, but so had all the infants assigned to the mechanical trauma group. Our attempt positively to identify lesions due to oxygen toxicity therefore failed. This does not, however, mean that none were present, since all the infants breathed increased concentrations of oxygen. We conclude that while lesions due to the use of very high peak airway pressures can be identified, those which may be caused by oxygen breathing cannot be reliably separated from the lesions of the underlying disease.

In the lungs of infants where lesions associated with mechanical trauma could not be identified, the principal changes (some of which may have been related to oxygen breathing) affected the parenchyma rather than bronchi and terminal airways. They were, in the earlier stages, congestion and edema of septa between air sacules and in the later stages the effects of an irregular fibrosis in these septa (Figure 12), together with reduced alveolisation.

**Controls**

Mechanical ventilation had been used in the treatment of 47 of the 64 infants dying without hyaline membrane disease. However, their lungs were well aerated and showed no evidence of bronchopulmonary dysplasia. Inclusion body counts were high, and the surface tension of lung extracts was within normal limits (Text-figures 1 and 2). Postmortem inflation of these lungs was easy and produced normal expansion.

Thirty-two of the ventilated infants had received inspired oxygen concentrations above 50% for periods between 1 hour and 6 days (median, 17 hours). In 26 the concentration was above 80% for one-half hour to 4 days (median, 12½ hours). Six of these 26 infants were mechanically ventilated with peak airway pressures above 35 cm of water for 80 minutes to 20 hours (median, 4½ hours). The lungs of those infants who had been exposed to oxygen at high concentration showed focal areas of collapse and moderate to considerable subepithelial capillary congestion together, in a few cases, with lymphangiectasis. There was no evidence of damage to the epithelium or walls of the airways.

**Summary of Results**

The lungs of infants dying during the first 3 days from HMD showed collapse of air sacules with few inclusion bodies in their epithelium, a
high surface tension in lung extracts, and hyaline membranes lining damaged terminal airways. After 4 or 5 days it became possible to inflate air sacculles distal to unobstructed airways with gas. The number of inclusion bodies increased and the surface tension of lung extracts fell, indicating that pulmonary surfactant was present. Lung damage persisted, however, because of the effects of repair and regeneration in airways, and of collapse, fibrosis and emphysema in lung parenchyma. The damage and excessive repair in airways often progressed to lobular fibrosis, and was significantly correlated with the use of high peak airway pressures during mechanical ventilator therapy in life.

Other forms of persisting damage to lung parenchyma, particularly intersaccular edema and fibrosis, may have been caused by oxygen breathing, although we were unable definitely to separate any effects due to oxygen from those due to the underlying illness.

Evidence of pulmonary hypertension was present in infants surviving for more than a month with severe lung damage, and the ductus arteriosus was always open. The terminal airways were largely restored, but there was evidence of slowing of alveolar growth.

Discussion

Atelectasis and Hyaline Membranes

It is generally accepted that the most important factor in the pathogenesis of hyaline membrane disease is deficiency of pulmonary surfactant, due mainly to immaturity of lung development. Inadequate production of pulmonary surfactant leads to severe atelectasis and is associated with the development of hyaline membranes in terminal airways. Our observations on infants dying during the first few days of the illness confirm the presence of necrotic epithelium as a constituent of the membranes. In toluidine blue-stained preparations of tissue embedded in epoxy resin, damage to the epithelium of air sacculles has also previously been described and confirmed by electron microscopy. Fibrin and other plasma proteins, together with the products of red blood cell breakdown, have been shown in this and previous studies to be present in the membranes. It seems clear, therefore, that they form mainly from the condensation of substances passing from blood into the expanded interstitial spaces and then through the damaged epithelial lining of the lung, which is normally exceedingly impermeable to protein but breaks down in association with deficiency of pulmonary surfactant.

Our studies on inflated lungs showed that the air sacculles were impossible to inflate during the first 4 or 5 days of life (Figure 11), even if
pressures as high as 60 cm H$_2$O were used. During this stage of the illness, pulmonary surfactant was not detectable, and inclusion bodies were absent or very scanty. Because the air saccules of infants dying early in the course of hyaline membrane disease can easily be expanded with liquid the most important reason for failure to inflate them with air when very high pressures were applied is probably that the resistance offered by a surfactant-deficient air–liquid interface with a small radius of curvature at its entrance was very large. For example, if the radius of curvature was as small as 10 μ and the surface tension was that of tissue fluid or plasma (about 55 dynes cm$^{-1}$), then it can be calculated, from La Place’s relationship ($P = 2T/r$, where $P = $ pressure, $T = $ surface tension, and $r = $ radius), that a pressure of as much as 100 cm H$_2$O might be required to open the air saccules.

By contrast, the terminal airways in inflated lungs from infants dying during the first 5 days appeared enormously dilated, a finding previously reported by Gruenwald. The characteristic localization of hyaline membranes to terminal airways may therefore be because this part of the respiratory tree is particularly susceptible to distortion and mechanical damage during breathing.

Evolution and Pathogenesis of Bronchopulmonary Dysplasia

The main object of the present study was to obtain information about the pathogenesis of bronchopulmonary dysplasia. This condition developed in 32 infants, all of whom had been mechanically ventilated for hyaline membrane disease. The principal pathologic changes in the lungs of these infants were obliterative airway disease, interstitial fibrosis, persistent collapse, and atrophy of parts of the lung, diminished alveolization and evidence of pulmonary hypertension.

Recovery of Air Saccule Epithelium and Surface Activity

From the fourth or fifth day, the epithelium of the air saccules was progressively repaired and restored. Increasing numbers of inclusion bodies were seen (Text-figure 1 and Figure 9), and the surface tension of lung extracts became normal (Text-figure 2). At the same time, progressive reopening of those air saccules which had patent airways was demonstrated in the inflation experiments and is attributable to a falling surface tension in the air–liquid interface. Since widespread changes of bronchopulmonary dysplasia were usually by then present in the lungs, we conclude that persisting deficiency of pulmonary surfactant is not involved in the evolution of this condition.
Mechanical Damage to Airways and Effects of Oxygen Breathing

The most striking lesions in infants dying after 5 to 15 days were regeneration and hyperplasia in the bronchi and terminal airways, often leading to obliteration of their lumens. This was associated with obstructive or compensatory emphysema and, distal to totally obstructed airways, collapse and atrophy of lung parenchyma. A very characteristic lobular fibrosis developed in some infants (Figure 3) which appeared to be due to the outward extension of the repair process from the terminal airways. The correlation between the presence of florid lesions of this type and the use of peak airway pressures above 35 cm H₂O during ventilator therapy in life was highly significant (Text-figure 4). This finding provides strong evidence that mechanical trauma to the lung plays a very important part in the pathogenesis of bronchopulmonary dysplasia. We suggest that the main factor initiating the process is distortion and disruption of terminal airways caused by the use of very high peak airway pressures at a time when the air sacculi are difficult or impossible to inflate because of surfactant deficiency. Further evidence that mechanical trauma to the lung is importantly involved in the pathogenesis of bronchopulmonary dysplasia comes from the finding that when, at the end of 1969, steps were taken in our Neonatal Unit to limit peak airway pressure to about 25 cm H₂O and to use a slower respiratory frequency (about 30 per minute), we experienced a sudden increase in the survival rate of our ventilated infants which was largely accounted for by an equally sudden reduction in the incidence of bronchopulmonary dysplasia.¹⁵ This change was apparent at a time when we were still using inspired oxygen concentrations above 80% during ventilation. Quite possibly, the varying incidence of bronchopulmonary dysplasia in different units can be accounted for by differences in ventilator variables, particularly peak airway pressure. For example, Becker and Koppe,⁴ who used pressures of up to 50 cm H₂O, found a high incidence of this condition, whereas other authors, particularly those using negative pressure ventilators, with which it is often difficult to obtain a high peak airway pressure, report a low incidence.⁵ ³⁵ ³⁶

Previous investigators³ ⁶ have considered that oxygen toxicity was the most important factor in the pathogenesis of bronchopulmonary dysplasia, although the difficulty of separating the effects of mechanical ventilation from those of oxygen breathing have repeatedly been pointed out. In the present study, we were unable to distinguish, from the pathologic appearance of the lungs, those infants who had been treated with very high inspired oxygen concentrations from those who had been treated with lesser concentrations (Text-figure 4). We were,
therefore, unable to separate any changes due to oxygen breathing from those caused by the underlying illness or by the repair processes of the lung. All the infants had, however, been treated with increased oxygen concentrations and it is possible that some of the changes in their lungs were due to oxygen. Subepithelial congestion was often seen, together with edema in septa between sacculles which proceeded to fibrosis, atrophy, and reduced alveolization. Early lesions of this type were found in oxygen-treated control infants and have also been produced by oxygen breathing in monkeys, lambs, mice, and guinea pigs. In all these animals, the site of damage was the alveolar capillaries and their endothelial lining, and not the airways. Tissue culture experiments on neonatal lung exposed to high concentrations of oxygen have shown some damage to bronchial epithelium with an increase, and later a loss, of mucin secretion. The lesions produced in this way bear little resemblance, however, to the airway lesions seen in the present investigation and attributed by us to mechanical trauma.

Infants with hyaline membrane disease who are not subjected to mechanical ventilation but who breathe very high concentrations of oxygen for 5 days or more are capable of making such a rapid recovery that their gas exchange is normal within 1 to 3 weeks, and bronchopulmonary dysplasia has never been described in nonventilated infants however much oxygen they have breathed. While we accept, therefore, that some of the pathologic lesions of bronchopulmonary dysplasia could be caused by oxygen breathing, we believe that mechanical trauma to the lung from the use of unnecessarily high peak airway pressures during ventilation is much more important in the pathogenesis of the condition.

Other Factors

Obstructive airway lesions were not seen in 5 of the 6 infants who survived for more than a month, although severe damage to the lung was present, particularly subepithelial fibrosis, hypertrophy of muscle, and in 2 infants residual squamous metaplasia in bronchi and slight scarring around terminal airways. Linear counts of air sacculles indicated some reduction in alveolization despite the successful restoration of airways. The capacity of bronchial and bronchiolar epithelium to regenerate and reconstitute itself in an orderly fashion is well known in the absence of a continuing insult and it is noteworthy that regeneration took place even though most of the infants continued to breathe high concentrations of oxygen. Progressive parenchymal damage eventually leading to the death of these infants may have been caused partly by mechanical forces acting on collapsed or fibrotic areas of lung, since disruptive pressures much
greater than transpulmonary pressure probably act round the periphery of such areas.\(^4\) Airway obstruction due to retained secretions and infection may occasionally have added to the damage. Our observations indicating the presence of pulmonary hypertension are to be expected in a situation where the lungs are severely compromised, and the presence of pulmonary hypertension is likely to be one reason why the ductus arteriosus is commonly found to be patent in infants dying from bronchopulmonary dysplasia.\(^7\)

Reports of the later prognosis of surviving infants show, rather surprisingly, normal lung function.\(^4\) Whether there are residual pathologic changes in the lungs of these infants awaits further study.

References

40. Hudson LH, Erdmann RR: Pulmonary vascular changes in newborn mice following exposure to increased oxygen tensions under moderate hyperbaric conditions. Angiology 17:819–824, 1966
Figure 1—Hyaline membranes (golden yellow) with granulation tissue on their undersurfaces. Most of the air saccules are collapsed and squamous metaplasia can be seen in bronchial epithelium. Gestation, 27 weeks; age at death, 5 days. (H&E, X 100)  
Figure 2—The terminal airway on the right is obliterated by proliferating fibroblasts; some irregular air saccules are lined by cuboidal epithelium and a bronchus on the left is lined by hyperplastic squamous epithelium. Gestation, 31 weeks; age at death, 14 days. (H&E, X 100)
Figure 3—Lobular fibrosis. Gestation 38 weeks; age at death, 15 days. (H&E, X 100)

Figure 4—Random distribution of emphysematous, collapsed, and fibrotic areas. Gestation, 28 weeks; age at death, 12 days. (H&E, X 7.5)
Figure 5—Emphysema, collapse, and a deep fissure deforming the outlines of the lung. Gestation, 36 weeks; age at death, 13 months.  
Figure 6—Collapse, fibrosis, emphysema and reduced alveolization. Gestation, 33 weeks; age at death, 42 days. The lung was inflated to 32 cm H2O. (H&E. X 10)
**Figure 7A**—Medial hypertrophy of a pulmonary artery. Gestation, 36 weeks; age at death, 13 months. (Elastic-van Gieson, X 400)  
**Figure 7B**—Control infant. Gestation, 40 weeks; age at death, 4 months. (Elastic-van Gieson, X 500)  
**Figure 8**—Hyaline membranes lining terminal airways. Few inclusion bodies are present. Gestation, 27 weeks; age at death, 40 hours. (Toluidine blue, X 500)
Figure 9—Inclusion bodies in Type 2 pneumocytes. An occluded airway can also be seen. Gestation, 32 weeks; age at death, 7 days. (Toluidine blue, X 500)

Figure 10—Lung inflated at 28 cm H₂O showing reduction in alveoli between the respiratory bronchiole on the left and the septum on the right. Gestation, 32 weeks; age at death, 91 days. (H&E, X 125)
Figure 11—Lesions associated with the use of a peak airway pressure of greater than or equal to 35 cm H$_2$O for 13 days. The epithelial hyperplasia and squamous metaplasia in the bronchus (at right) together with fibroblastic obliteration of bronchioles and deformation of acini (at left) are characteristic of mechanical trauma. Gestation, 31 weeks; age at death, 14 days. (H&E, X 80)

Figure 12—Lesions in an infant never ventilated with a peak airway pressure greater than or equal to 35 cm H$_2$O, who breathed an inspired oxygen concentration of 80% or greater for 10 days. Wide septa and poor alveolization but no residual bronchial damage are suggestive of previous oxygen toxicity. Gestation, 32 weeks; age at death, 91 days. (H&E, X 12)