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Pulmonary surfactant

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PULMONARY SURFACTANT

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INTRODUCTION

The lung has long been the focus of philosophical and experimental endeavor and, because of its uniqueness (along with the heart) in being "close to the line of life", has stimulated a vast amount of research and questions on its physiologic mechanisms. Not the least among these has been: (1) What keeps most alveoli air-containing at the end of expiration? (2) What is the mechanism of ateleotasis? (3) Why do some alveoli inflate fully before others begin to inflate? and (4) Is there anything unique about air-liquid interfaces that has an effect on lung mechanisms? These questions, and many others, have produced a continually increasing body of literature on various aspects of what is now referred to as "pulmonary surfactant." Pulmonary surfactant is that material, primarily lipoprotein in nature, which lies at the air-tissue interface of the lung and, because it exerts surface tension (an attraction between uncharged particles), has a direct effect on lung mechanics and alveolar stability.

This paper is an attempt to summarize the literature on pulmonary surfactant and formulate conclusions justifiable therefrom that are likely to be efficacious to those dealing with the lung clinically. Articles included in the bibliography were selected for one of the following reasons: (1) The article stated a "new" conclusion from the data; (2) The article provided the needed confirmation of an hypothesis previously presented; or (3) The article was a summary of conclusions to date and contained an appropriate bibliography. An honest attempt was made to insure that experimental design and results were consistent with the conclusions drawn therefrom.

DEFINITIONS

Surfactant - that material lining the air-tissue interface of the lung.

Surface tension - an attraction between uncharged particles.

"Extract activity index" - a measure of the effectiveness of changing surface tension relative to surface area.

"Active extract" - an extract of lung tissue which exhibits a surface tension of less than 15 dynes/cm. on compression to 20% of original surface area and also exhibits marked hysteresis on reexpansion.

Hysteresis - the behavior of a mechanical system in which the result of an applied force lags behind the force itself- volume change of lungs lags behind the transpulmonary pressure changes which produce it.

"Lung stability index" - a measure of the tendency of an alveolus to collapse on return to low pressure.

SURFACE FORCES IN THE LUNG

Surface forces operate in such a manner as to decrease the area of the surface upon which they act. Witness the fact that a drop of liquid completely surrounded by a gas phase will attempt to assume the shape of a sphere in order to minimize surface area. According to the law of La Place, the mechanical advantage of surface forces is enhanced by a more sharply curved surface:

$$\text{tension } (T) = \text{force } (F) \,/\, \text{distance } (2\pi r)$$

$$\text{pressure } (P) = F \,/\, \text{unit area } (\pi r^2)$$

$$P = \frac{T \cdot 2\pi r}{r^2} = \frac{2T}{r}$$

It may be seen from the above that the more sharply curved the surface, the shorter the radius, and the greater the pressure, as long as tension remains constant. If this were true in the lung, which may be thought of as a system of communicating spheres (alveoli), a small alveolus would have a greater pressure than a large alveolus and, consequently, the small alveolus would collapse by expelling its contents into the large alveolus. This is not observed in the lung and requires explanation.

One can readily deduce from the above that, in order for small alveoli not to collapse, a change in tension must occur to keep the pressure minimized. It must therefore be concluded, even without any evidence, that in order for alveoli to expand and contract physiologically, a substance must be present which can alter the surface tension of the alveolus. In view of this, then, the existence of pulmonary surfactant must be admitted and presumed to act in such a manner that surface tension is decreased as an alveolus deflates. Because of this

property, Clements[21] suggested that surfactant is and "anti-atelectasis factor".

Studies demonstrating very little change in the pressure-volume characteristics of the lung following death[59] or in the excised lung,[92] have made comparison of results from the various preparations more valid. Mead et al[60] noted that the volume-pressure hysteresis of the lungs of both humans and animals after slow deep-breathing could not be accounted for solely on the basis of ordinary pulmonary flow resistance (instantaneous transpulmonary pressure is a function of the corresponding volume and flow rate).

This concept implies that as flow resistance approaches zero during progressively slower cycles, a plot of pressure against volume would yield a straight line. This is not observed. They noted that the degree of hysteresis in lungs filled with saline was small but in those filled with air it was large and, therefore, they concluded that much of the hysteresis observed in the lung was due to surface forces. It has also been observed that the compliance of the lung at low transpulmonary pressure, decreases during shallow ventilation. This decrease in compliance has been attributed to an increase in surface tension.[86]

Clements[20] gave a mathematical expression for the degree of activity of a sample so that transfer of results would be more meaningful. His expression states that the "extract activity index" is equal to twice the difference between maximum and minimum sufface tensions divided by their sum (possible range of values is 0-2). A high value indicates a significant change of tension for a change in area and a decrease in average tension. Gruenwald[38] calculated lung stability (a measure of the tendency of an alveolus to collapse at

low pressure) from the deflation part of the pressure-volume curve, and found that lung stability correlated well ($r = +0.68$, $P < .001$) with extract activity.

An easily prepared, reproducable chemical model for the study of surfactant has been prepared.[51] An ethanol solution of lecithin is precipitated with albumin and 1 drop of the suspension, containing 0.04 mg. lecithin is spread on the surface of 0.9% sodium chloride solution. This has proven to be an active sample (surface tension decreases to less than 15 dynes/cm. on compression to 20% of original area and shows marked hysteresis on reexpansion). This model facilitates study of effects of various agents on surfactant.

The theory that pressure-volume characteristics of the lung are dependent upon surface forces is based on the premises that the lung is lined with a surface-denaturable material and that alveolar sizes deviate significantly from the mean.[19] One appreciates the magnitude of this surface activity when it is remembered that the total lung surface area of man approximates 70 square meters (equivalent to 500,000,000 alveoli with mean diameter of 150μ)[15,75] That lung surfactant has very little to do with elasticity has been adequately demonstrated.[61] For purposes of convenience, lung extracts may be dryed into powder and stored without losing their properties.[11]

MORPHOLOGIC STUDIES

The controversy about the existence of a pulmonary epithelium covering the capillary endothelium in the lung was conclusively resolved by Low[52] when he demonstrated a cytoplasmic layer covering the capillary endothelium by electron microscopy in the rat lung. He also later demonstrated evidence that the alveolar epithelium was an entodermal derivative.[53] He showed by electron microscopic study, that the alveolar epithelium was in direct continuity with the cuboidal epithelium of the bronchioles and hypothesized its entodermal origin because of this fact and: (1) There is an uninterrupted epithelial lining of the alveoli; (2) These epithelial cells are non-phagocytic; (3) Cells of entodermal origin are usually non-phagocytic; (4) Cytoplasm of some epithelial cells closely resembles that of macrophages; and (5) The phagocytic macrophages found in the lung are free in the alveoli and rest on the epithelium.

Macklin[56] demonstrated the existence of three types of cells in the lung epithelium- membranous pneumocytes (Type I), phagocytic cells, and granular pneumocytes (Type II). It was presumed that the granular pneumocytes possessed an exocrine function whereas the membranous pneumocytes did not. Electron microscopic evidence of the exocrine function of granular pneumocytes was obtained in 1964 when Bensch, et al[9] published a photomicrograph showing the lamellar body in a granular pneumocyte discharging into the alveolar space. It was also noted that in CO_2-induced hyaline membrane disease, the time course of changes in lamellar bodies and pulmonary surface tension paralleled each other closely. This was taken as suggestive evidence that the lamellar bodies are the site of origin of pulmonary surfactant.

The lamellar (inclusion) body was concluded not to be mitochondrial in nature by electron microscopic, histochemical, and surface tension activity studies, by virtue of the following findings:[16] (1) The inclusions were positive in the periodic acid-Schiff test after digestion with diastase; (2) They formed myelin figures; (3) They possessed alkaline phosphatase activity; (4) They were not stained with toluidine blue; and (5) Both the typical surface tension activity and inclusions developed two days before birth in the rat. Further electron microscopic studies[8] demonstrated that the granular pneumocyte inclusion bodies (osmiophilic granules) were formed and "secreted" in greater numbers in late fetal life and early infancy and appeared to result from "focal degradation of any cytoplasmic membrane in rapidly changing cuboidal epithelium." It was concluded that the inclusion bodies were lysosomal structures on the basis of morphologic characteristics and on the distribution of the acid phosphatase reaction.

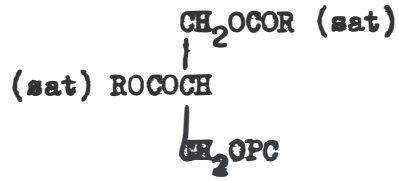
TIME OF APPEARANCE OF SURFACTANT

It has been noted[71] that lungs too immature to produce a complete lining film have never been found to spontaneously aerate. This can occur only after the lung acquires the capacity to produce a lining film, which takes place when the larger lumina of the lung ceasesto be lined with cuboidal epithelium. Since this capacity is acquired in the human lung at 24 wks. gestation, it is not felt that inability to produce a lining layer is responsible for the respiratory distress syndrome of infants.

It has been demonstrated in fetal mice[16,93] that the osmiophilic inclusion bodies of the granular pneumocyte first appear in the 18 day old fetus (term gestation in the mouse is 19 days) and that the large majority of fetuses of gestational age less than 18 days failed to achieve the low surface tension of lung extracts recorded by all term fetuses and newborns. Gruenwald[39] concluded that infants may be predisposed to the respiratory distress syndrome in utero because of the differences that exist in surface activity and stability between infants with respiratory distress syndrome and infants who have never breathed (stillborn). Electron microscopic studies[17] of the human lung support the appearance of lamellar inclusions at the time in fetal development in which there is a decrease in glycogen content of the alveolar epithelium (5-6 months gestation) and the appearance of surface activity. It was also noted that in species lacking inclusion bodies (e.g. the pigeon) there is no surfactant.

CHEMICAL STUDIES

Isolation and identification of dipalmitoyl lecithin for the first time from the lung occurred in 1946.[84] It was later shown[72] that the light spectrum of a water extract of lung was qualitatively identical to that of purified egg lecithin. Abrams[1] analyzed the lipoprotein from lung extracts and found it to be an α-globulin with a molecular weight of 2.4 $\pm 0.5 \times 10^5$ and contain 40.2 $\pm 0.6\%$ lipid. The only phospholipid which he found in the extract was dipalmitoyl lecithin. The structure of lung lecithin is:[42]



The composition of extracts from the lung has been determined,[32,48] and is approximately 60% phospholipid, 19% triglyceride, 6% FFA, 5% free cholesterol, and 0.9% cholesterol esters. Of the phospholipid fraction, 48% was lecithin, 12% was phosphatidyl ethanolamine, and 9% was sphingomyelin. The lecithin had 60% saturated fatty acids (14% palmitic, 46% stearic). Webb[91] categorized the components of surfactant on a functional basis- unsaturated phospholipid to give low tensions, nonphosphated lipids to protect the phospholipids from oxidation, and protein as a skeleton which holds the lipid together.

Surfactant can be attacked by pancreatin and trypsin, indicating a protein constituent.[69] An increase in the minimum surface tension of lung extracts has been observed after exposure to mercuric chloride, dilute acids, and acetone;[70] petroleum ether extracts of dried tissue, edema foam, and oleic acid;[87] KOH, K_2CO_3, and $NaHCO_3$;[81] amniotic fluid;[33] polysorbate 20 (Tween 20);[74] 0.5% octyl alcohol;[95] lecithin,

lysolecithin, and Tween 80.[68] Surface tension and hysteresis are not affected by irritants that are not surface active.[68] It has also been noted[70] that protein precipitants make the foam of pulmonary edema vulnerable to surface active anti-foams.

It has been demonstrated that with an increase in temperature, alveolar surface tension rises more rapidly[86] and decreases the stability of normal lungs.[40] Clements[22] found that heating produced a decrease in hysteresis, decreased minimal volume on deflation, decreased inflation pressure and increased deflation pressure, All these changes were reversible on cooling.

SYNTHESIS OF SURFACTANT

Biochemical studies relating to the synthesis of pulmonary surfactant have dealt primarily with the synthesis of lecithins. This is understandably so, inasmuch as the body of evidence presented elsewhere in this paper leaves little doubt that lecithins are the primary constituent of pulmonary surfactant. Brown[14] completely precipitated the surface active material from saline extracts of lung with trichloroacetic acid and subsequently extracted all of the activity from the precipitate with ethyl or methyl alcohol. The surface active material was identified chemically as dipalmityl phosphatidyl choline. He noted that the only known pure phospholipids that show surface activity at body temperature are sphingomyelin and saturated lecithins. There was an absence of sphingomyelin from his prepared precipitate.

In support of the hypothesis that alveolar epithelial cell mitochondria are the source of surfactant, the following have been noted:[49]

(1) Surfactant has been found in significant quantities only in the washed mitochondrial fraction of mammalian lung;

(2) Associated with the loss of lung surface activity following vagotomy, there is almost a complete loss of mitochondrial lamellar forms;

(3) In animals that show no lamellar forms in their alveolar lining cells, there has been a notable absence of surface activity in lung extracts.

The initial biochemical finding which implicated that the lung itself might be involved in actual synthesis of surfactant was the observation that there was an "astonishingly high degree of utilization" of acetate in the production of fatty acids by the lung.[73] It has been shown by Day and Fidge[25,26], using C^{14} labeling, that macrophages

(which bear close resemblance to alveolar epithelial cells) take up both sodium palmitate and acetate. The sodium palmitate was converted primarily to triglyceride and phospholipid, with small amounts of cholesterol ester and mono- and diglycerides. The acetate was converted to cholesterol, cholesterol ester, triglyceride, mono- and diglyceride, and phospholipid. It was subsequently demonstrated that the mitochondrial-rich fraction of lung tissue is by far the most active of the subcellular fractions in the utilization of acetate for long chain fatty acid synthesis.[88]

The following reactions have been observed in the rat fetus by C^{14} labeling:[35]

(1) CDP-*choline + D-α,β diglyceride $\longrightarrow$ *lecithin

(2) CDP-*ethanolamine + D-α,β diglyceride $\longrightarrow$ *phosphatidyl-ethanolamine(PE) $\xrightarrow{+3CH_3}$ *lecithin

(3) (*CH_3)-S-adenosyl-C-methionine + PE $\longrightarrow$ *lecithin

(4) *Serine + PE $\longrightarrow$ *phosphatidylserine(PS) $\xrightarrow{-CO_2}$ *PE $\xrightarrow{+3CH_3}$ *lecithin

Term gestation in the rat is 30 days. Reaction (1) was found to be maximum at 21 days gestation and then gradually decrease to term. Reaction (2) was found to be highly active throughout gestation with a sharp increase on days 24-2 and sharp drop after day 26. Reaction (3) showed a steady increase to maximum at day 28 and subsequent decrease. Reaction (4) showed maximum activity at day 26. These findings, if species transfer is allowed, may be part of the explanation for variation and relatively poor correlation of gestational age with hyaline membrane disease. It may also be assumed that there are several biochemical pathways of synthesis of surfactant with variable controlling factors.

CONDITIONS IN WHICH SURFACE TENSION IS ALTERED

Hyaline Membrane Disease (HMD)

Hyaline Membrane Disease (Respiratory Distress Syndrome) of infants is characterized by increased respiratory rate and minute volume, normal or decreased tidal volume, decreased alveolar ventilation, increased respiratory dead space, a variable ventilation-perfusion ratio, decreased diffusing capacity, decreased lung compliance, and respiratory and metabollic acidosis.[45,50,64] The pattern of metabolism in HMD (excessive tissue destruction, shift of water from cells to extracellular fluid, hyperkalemia, and excessive excretion of sodium) may also occur to a lesser degree in prematures or infants of diabetic mothers without distress, and even to greater degree in prematurity alone.[66] Delay in onset of respiration, immaturity of enzyme systems, cesarean section, and immaturity of capillaries have been thought to be important in the etiology of HMD. The radiologic pattern is nonspecific.[27]

The membrane of HMD has been produced by intratracheal injection of human liquor amnii in the rat.[18] It has been described by electron microscopy as overlying the alveolar epithelium and having a fibrillar matrix (apparently fibrin), presumably derived from plasma.[13] Gitlin[79] felt that the membrane was formed by syneresis of fibrin which had come from fibrinogen which effused from the pulmonary vasculature. He noted that the production of fibrin is enhanced by a thromboplastin material in amniotic fluid.

An increased incidence of HMD is found with low birth weight, infants delivered by cesarean section, premature infants of diabetic mothers, placenta previa, premature separation of the placenta, toxemia, and history of prior stillbirth.[23] Placental transfusion and gravity flow techniques have reportedly decreased the incidence of HMD.[12] Functional residual capacity and total lung volume have been shown

to be decreased in HMD,[37] and in younger animals.[6] The cause of HMD is admittedly as yet unknown and treatment has been as extravagant as hibernation.[80]

Lynch[55] analyzed hyaline membranes histochemically and felt that there was probably a deficiency of the cytochrome/oxidase / cytochrome C enzyme system. There is an increase in surface tension[7] and decreased phospholipids and decreased percentage of lecithin[2] in lung extracts of infants with HMD and an increase in surface tension in infants of less than 1200 grams birth weight.

That respiratory difficulties are more common in prematures is well documented.[63,65] That surface tension plays an important role in the resistance of infants lungs to aeration is also well known.[41] Atelectasis by itself does not produce an increase in surface tension[31] as witnessed by the facts that: (1) Extracts from lungs still collapsed after 10 weeks following ligation had normal surface tension; and (2) In cases of pulmonary artery occlusion, the increase in surface tension of extracts occurred before development of atelectasis.

Pulmonary Edema

Acute pulmonary edema[77] and instillation of fluid into the lungs[46,47] have both been shown to produce an increase in surface tension of lung extracts and a tendency towards atelectasis. Atelectasis by itself was not observed to produce an increase in surface tension. It was hypothesized that the amount of fluid remaining in the lungs at birth might be important in the etiology of the respiratory distress syndrome. Said, et al,[76] prompted by the observation that acute pulmonary edema produced a decrease in lung compliance out of proportion to lung volume, also noted an increased tendency to premature alveolar

closure as a result of an increase in minimum and maximum surface tension.

Harlan, et al[43] demonstrated the uptake of radioactive palmitic acid by the lung and noted a decrease in lung tissue radioactivity in the presence of pulmonary edema. It has also been shown[83] that an inhibition of clot retraction and lysis is produced when surface-active lipoprotein extracted from the lung is mixed with plasma exudate. The surface activity of this lung lipoprotein was inhibited by fibrinogen whereas the activity of dipalmityl lecithin was not inhibited. Herein lies evidence for the hypothesis that a lack of fibrinolytic activity is important in the pathogenesis of the membrane in hyaline membrane disease of the infant.

Cervical Vagotomy

In 1937, Farber[28] noted that bilateral cervical vagotomy produced a syndrome of increasing dyspnea with resultant asphyxia and death in the rabbit. Postmortem examination revealed acute pulmonary edema and congestion. It was later noted[62] that in the majority of rabbits after bilateral cervical vagotomy, membranes could be found in their lungs that closely resembled the membranes in infants with hyaline membrane disease. It was also noted that the time of appearance of the membranes after the operation in the rabbit, closely approximated the time of appearance of the membranes in newborns, suggesting a common mechanism.

A marked similarity in the gross appearance of lungs and an increase in the surface tension of lung extracts has been noted in:[89] (1) Infants dying with hyaline membrane disease; (2) Tracheotomized guinea pigs with pulmonary congestion following bilateral vagotomy; (3) Dogs with unilateral pulmonary artery ligation; (4) Dogs with

ligature of one mainstem bronohus; and (5) Dogs and humans following cardiopulmonary bypass. Accompanying the loss of lung surface activity after vagotomy is almost the complete loss of mitochondrial lamellar forms.[49]

Bolande and Klaus[10] have demonstrated the alveolar lining layer with phosphatide and polysaccharide stains and also by ultraviolet microscopy in which the lining layer is observed as a thin fluorescent line at the air-tissue interface. They observed that the lining layer was abolished by extraction with chloroform:methanol and decreased by digestion with Clostridium welchii α-toxin leoithinase, and concluded that the layer was composed of lipid which is a phosphatide and also has a mucopolysaccharide component. They too have noted with this method, a decrease in the fluoresoent lines and abnormal surface tension properties following bilateral cervical vagotomy.

Physical Stress

Faridy, et al[29] ventilated the excised lung of a dog 1-6 hours with room air, O_2, CO_2, and N_2 and found an increase in the minimum surface tension in all cases. This was also observed as a decrease in the percentage of gas volume remaining in the alveoli at all transpulmonary pressures. The effect was greatest with room air and N_2. After flushing the lung with room air and holding the lung at constant partial inflation for several hours, they found the effect to be reversed completely in room air and O_2 lungs but not for CO_2 and N_2 lungs. This finding suggested that CO_2 and N_2 might interfere with the production of surfactant. It was also noted that the changes in pressure-volume measurements and minimum surface tension were directly related to the tidal volume and duration of ventilation and inversely related to end-expiratory pressure. This suggested that the larger the change in surface area with each inflation, the greater the de-

pletion of surfactant. Greenfield, et al[36] also found that overly inflation ventilation produced a diminution in surfactant and gross atelectasis in 24 hours whereas ventilation at normal pressure and volume produced no alteration in surfactant.

It has been noted[34] that there is an increase in minimum surface tension to greater than 15 dynes/cm. in homografted lungs after 24 hours. Surfactant was found to be normal in autotransplanted, denervated, and homotransplanted lungs at less than 24 hours. The increase in surface tension in homotransplanted lungs is the earliest known sign of rejection.

Oxygen Toxicity

Studies measuring bubble stability[68] did not demonstrate alteration in surface tension of extracts after breathing 100% O_2. Fujiwara, et al[32] was likewise unable to demonstrate any change in surface tension or lipid concentration of lung extracts after breathing 100% O_2, but did observe the production of pulmonary edema. Collier,[24] however, demonstrated an increase in both minimum and maximum surface tension of saline extracts of minced lung after producing death by breathing 100% O_2 at one atmosphere, thus indicating an absence of surface activity. He hypothesized that O_2 poisoning may result in both the absence of surfactant and the presence of an inhibitor of surface activity.

It has recently been demonstrated[91] that hyperbaric oxygenation produces an increase in the surface tension of lung extracts and, microscopically, extensive congestion, edema, inflammatory infiltration of alveoli and interstitial tissues, and progressive focal atelectasis. An increase in surface tension indicates a loss of surfactant and

produces an increased expulsive force of the alveoli with an increased tendency of alveoli to collapse and result in progressive ateleotasis. It was hypothesized that the loss of surfactant was due to oxidation of the unsaturated phospholipid fraction of surfactant, This would be consistent with the fact that oxidative or proteolytic active chemicals and lipoidal also inhibit pulmonary surfactant.

CO_2 Poisoning

Humans respond to an increase in alveolar CO_2 concentration by increasing ventilation. In contrast to adults, the response curve of an infant is shifted to the left, which is consistent with their lower initial alveolar CO_2 and buffer base and higher metabolism per kilogram body weight.[5] Schaefer, et al[78] showed that after 1-6 hours of breathing 15% CO_2 there was a severe uncompensated acidosis with decreased blood pH and increased blood pCO_2 and associated marked alveolar edema, an increase in lung weight, no change in surface tension, and a decrease in the number of lamellar bodies in the granular pneumocytes. After 24 hours of breathing 15% CO_2, there was a demonstrable hyaline membrane in all animals with associated increase in minimal surface tension, decreased film compressability, and near absence of lamellar bodies. After 2-14 days of 15% CO_2 the acidosis became compensated, there was a gradual decline in pulmonary edema and hyaline membrane disease, and the surface tension and number of lamellar bodies returned to normal.

Asphyxia

It has been reported[3] that nearly 50% of asphyxiated monkeys (after delivery by cesarean section) demonstrated atelectasis and hyaline membranes like those seen in infants with hyaline membrane

disease. Avery[4], however, could not produce the typical histological picture of hyaline membrane disease (vascular congestion, diffuse ateleotasis, and hyaline membranes) by hypoxia alone in guinea pigs, rabbits, rats, or mice.

Aerosols

Alcohol vapor has been used in the treatment of acute pulmonary edema[54] because of its anti-foaming effect with improvement in 87% of cases and no serious side effects. Alcohol nebulisations produce an increase in compliance and a decrease in airway resistance. The response to alcohol is inhibited in the presence of pulmonary congestion compared to normal lung. Siliconized superinone and water produced a decrease in compliance and an increase in airway resistance.[67]

Others

An increased tendency to atelectasis and abnormalities of surface tension measurements on lung extracts have also been observed in acute mercury vapor poisoning,[58] radiation pneumonitis,[90] influenza virus pneumonia in both mice[44] and humans,[57] pulmonary artery occlusion,[30] following transection of mainstem bronchus,[94] and ateleotasis.[81]

SUMMARY

Pulmonary surfactant is a lecithin-like lining of the alveolar epithelial cells at the air-tissue interface of the lung. Film balance and bubble stability studies on extracts of lung indicate that there is a marked hysteresis of the pressure-volume measurements in the lung which requires the properties of a surface-active agent for full explanation. Surfactant serves to prevent ateleotasis by diminishing surface tension as volume is decreased.

"Surfactant" probably includes a variety of compounds as presently measured, but olosely resembles dipalmitoyl lecithin in its most active part. The mitochondrial fraction of granular pneumocytes is presently felt to be the locus of production of surfactant, apparently by several reaction sequences.

Evidence has been cited concerning significant alterations of surface forces in the lungs in a variety of clinical states. Although the mechanisms of interference are not yet known, the effects are real and add to ones understanding of lung function.

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