Pulmonary Surfactant and its Relation to Disease*

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in respiratory physiology during the past decade is the discovery of the role of surface phenomena. This has been in large measure the result of pioneer work by Pattle, in England, and Clements, in the United States.

The following is a simplified and brief review of present knowledge of surface tension, as it relates to normal and abnormal pulmonary function. (For further reading on the subject pelase refer to these recent reviews: Clements, 1962a and 1962b, Pattle, 1958, 1961, and 1965, and Mead, 1960.)

First, *what is* surface tension? When a liquid is in contact with the air, the molecules at the surface of the liquid will be under tension (fig. 1). This is because, while the molecules away from the surface are attracted equally by other molecules from all directions, those at the surface are influenced only by molecules below and to the side, but none above. The net effect is that the surface molecules tend to be pulled down, and therefore, the surface tends to get smaller.

And because surface tension is a force acting in the same plane as the surface, e.g., like the pull on the cord of a window curtain, it has units of force per length, e.g., gm per cm or dynes per cm, whereas pressure has the units of force per area, e.g., gm per cm^2 or pounds per square inch.

Now, what could this have to do with what goes on in the lungs? We will begin to appreciate the link when we consider the case of a gas-liquid interface that has a spherical shape, like that of an alveolus. A soap bubble is a good example. Here, the tendency of surface tension to shrink the surface will ultimately result in collapse of the bubble. And it can be shown that the total forces tending to empty the bubble will amount to twice the tension in the wall divided by the radius of curvature. This relationship is known as the law of Laplace, and it appears to hold for alveoli just as well as it holds for soap bubbles. It means simply that for a sphere, the surface forces will increase if the tension in the wall increases or if the radius of curvature decreases. It

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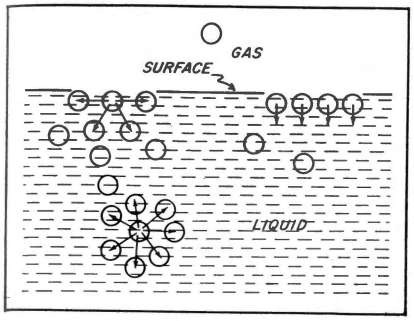

Fig. 1—Molecules at a gas-liquid interface are under tension (after Mead, 1960).

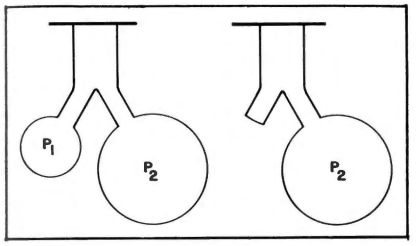

Fig. 2—A system of bubbles in parallel is unstable; smaller bubbles have greater surface forces (*P*) and therefore tend to collapse first (after Mead, 1960).

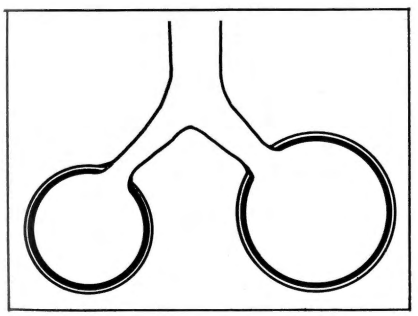

Fig. 3—Pulmonary alveoli are inherently unstable, but a surface-active lining (surfactant) lowers alveolar surface tension and thus protects them against atelectasis.

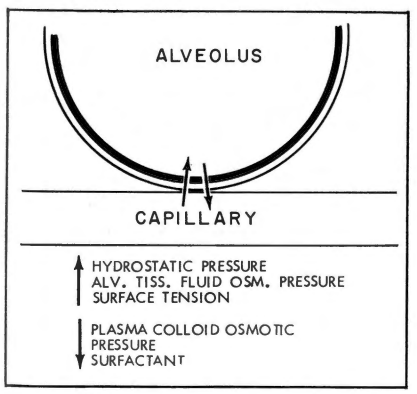

Fig. 4—Schema of fluid exchange in lung.

also means that, for the surface forces to remain balanced, a decrease in radius of curvature must be counteracted by a decrease in tension. A beautifully clear presentation of these relations was given by Mead (1960).

To get a step closer to the lung, we now examine what happens when two soap bubbles are blown at the end of a Y-tube and are arranged, so to speak, in parallel—like two alveoli with a common airway (fig. 2). If one bubble happens to be smaller than the other, we might expect that air would leave the larger bubble to enter the smaller bubble, until the two became equal in size. But this is not what happens. According to the law of Laplace, the smaller bubble must have a higher surface force (*P*), since its radius of curvature is smaller. In other words, the forces tending to collapse the smaller bubble are greater than those trying to empty the larger bubble. As a result, the smaller bubble empties itself into the larger one.

Turning now to the lung, we find that we have hundreds of millions of alveoli, offering a large area of contact between blood and gas (of the order of 70 M^2), sufficient to permit the exchange of oxygen and carbon dioxide. At the same time, we find that the alveoli also present, on their inner surface, a large area of contact between air and tissue fluid. This means that the forces of surface tension are bound to come into play. And since the alveoli are not all equal in size, and since all of them get smaller during expiration, then, just as the smaller soap bubble emptied into the larger one, the smaller alveoli would tend to collapse into the larger ones, until we were left with a single large air space. That, of course, would be disastrous, for the processes of gas exchange would no longer be possible.

Fortunately, however, this does *not* happen, because the lung is endowed with a special detergent, or surface-active material, which is capable of reducing surface tension and adjusting it when necessary. This is surfactant (fig. 3). Pulmonary surfactant, therefore, stabilizes the alveoli and protects them against an inherent tendency for collapse or atelectasis. It does so by decreasing surface tension in smaller alveoli, thereby balancing out the effect of their smallness and, consequently, maintaining uniform surface forces throughout the lung and throughout the respiratory cycle.

Another important function of pulmonary surfactant is explained in figure 4. Normally, a delicate balance of fluid exchange exists between alveoli on the one hand, and capillaries on the other; only a thin fluid film lines the alveoli. The forces of hydrostatic pressure, alveolar fluid osmotic pressure, and surface tension, all tend to drive fluid out of the capillaries and into the alveoli. In the absence of surfactant, these forces would be opposed only by the plasma colloid osmotic pressure, and fluid and blood tend to leak into the alveolar spaces. Pulmonary surfactant, therefore, protects the alveoli not only against atelectasis, but also against pulmonary edema and hemorrhage.

Consequently, we would expect lack of surfactant to result in three major pathologic changes in the lung; atelectasis, edema and hemorrhage—perhaps in varying degrees of predominance. This *is* indeed what happens when the surfactant is missing or ineffective (fig. 5).

At present, the available methods for evaluating lung surface tension properties are indirect and not quantitative. A sample of lung tissue (1 to 3 gm) is minced and extracted in saline. The extract is then filtered and poured onto the trough of a surface balance (Wilhelmy type) that permits automatic compression and re-expansion of the surface area and the simultaneous recording of surface tension (fig. 6). The latter measurement depends on the pull exerted on a thin platinum strip by the superficial layer of the fluid, which should contain any surface-active substances that may be present in the lung. The ability to reach low surface tensions (below 10 dynes per cm), and a wide variation of tension with changes in surface area, are characteristic of normal lung extracts. Lungs with abnormal surface properties give extracts that fail to reach a low surface tension even on maximal compression.

How is pulmonary surfactant normally formed? What is its chemical nature? And why is it deficient in some conditions of disease or experiment? The answers to these questions are only partially known. There is evidence that certain granular alveolar cells are responsible for manufacturing

this special surface-active material lining the alveoli. With the electron microscope, it has been suggested that mitochondrial activity in these cells, manifested as transformation into lamellar forms, is closely related to the formation of surfactant.

As for its chemical composition, pulmonary surfactant appears to be a complex of lipids and protein, the chief component responsible for surface activity being dipalmityl lecithin, a phospholipid. (Lecithin is commonly used commercially for its emulsifying properties, e.g., in candy and cookies.) The protein appears to be an α-globulin. Adult mammalian lung can actively incorporate circulating fatty acids into phospholipid and can also synthesize its own fatty acids.

Alveolar surfactant has been found missing or lacking in a number of clinical and experimental situations (table 1). The finding of abnormal surface activity of lung extracts from infants dying of hyaline membrane disease (respiratory distress syndrome) was the first time surface tension was linked to a disease entity. Thanks to Avery and Mead (1959), this discovery put the subject in a totally different light; from one largely of theoretical interest to a practical and tangible problem. Abnormal extract activity is also found in several conditions that are associated with impairment of pulmonary blood flow: occlusion of a pulmonary artery, following cardiopulmonary bypass through a pump oxygenator, and as a result of induced pulmonary edema. Pulmonary surface tension properties are also probably impaired following vagotomy in some small animals, in the rather unusual experimental preparation where an animal is made to breathe while immersed

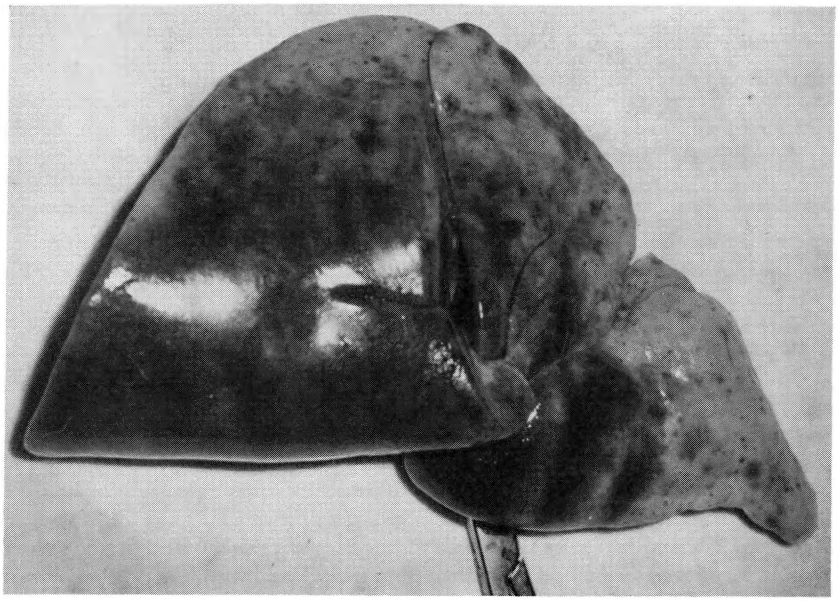

Fig. 5—Lung of dog showing edema, hemorrhage, and microscopically, areas of atelectasis. Surface tension of saline extract of this lung was abnormally high.

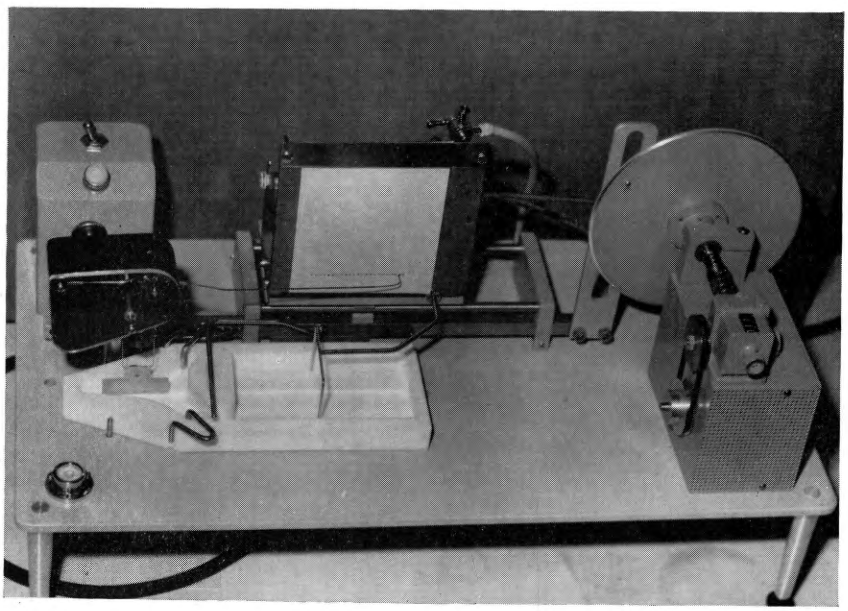

Fig. 6—Photograph of balance for measuring surface tension of lung extracts (manufactured by Kenneth Wilson, 508 W. Joppa Road, Towson, Md.

TABLE 1

Clinical and Experimental Conditions That May Be Associated with Insufficient or Ineffective Surfactant

1. Immaturity
2. Hyaline membrane disease
3. Pulmonary artery occlusion
4. Pulmonary edema
5. Cardiopulmonary bypass
6. Vagotomy (in some species)
7. O_2 poisoning
8. Severe respiratory acidosis

TABLE 2

Present Knowledge of Pulmonary Surfactant

1. A surface-active material (surfactant) lines the pulmonary alveoli of adult mammals.
2. It is probably a lipoprotein (phospholipid + globulin).
3. It is probably synthesized in the lung, by alveolar cells.
4. Impaired synthesis, excessive depletion, or inhibition of surfactant leads to alveolar instability: atelectasis, hemorrhage, and edema.

under fluid—thus using its lungs as gills, and in oxygen toxicity, due to prolonged breathing of pure oxygen, particularly under increased pressure. This latter condition has received considerable attention because of its importance to astronauts and other space travelers and in therapy with hyperbaric oxygenation. The list of conditions in which surfactant may be altered gets longer as more work is being done on the subject.

The manner in which pulmonary surface activity is altered in these conditions is not clear. In some cases there is probably impaired synthesis of surfactant, in others, a circulating inhibitor, and in others yet there may be too rapid dissipation. In any event, the importance of surface tension in pulmonary disease is now fully recognized, and future work will no doubt provide more answers.

To summarize (table 2), alveoli of mammalian lungs are normally lined by a surface-active material or surfactant, composed chiefly of phospholipids and protein. Surfactant is normally synthesized in the lung. Formation depends, among other things, on normal pulmonary blood flow, intact vagus, and the activity of certain alveolar cells that have reached an adequate level of maturity. Its absence leads to alveolar instability: atelectasis, pulmonary hemorrhage, and edema.

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"The diver is generally safe enough on the bottom, but when he comes up care is needed. His danger is from bubbles which may form in his blood or tissues when the pressure is taken off, just as they form in a bottle of lemonade or soda water. There is a story that when one of the first tubes was being driven under the Thames, the directors of the company celebrated its arrival under the middle of the river by having lunch in the tunnel. They went into an air lock, the steel door was shut behind them, and the pressure raised till it reached that in the end section of the tunnel. Then a door at the other end was opened, and they went on to lunch. As we know, company directors always have champagne for lunch, and these were no exception to the rule. But when the bottles were opened the champagne did not fizz. The pressure outside the bottles was as big as that inside them. However, the directors drank the wine. After lunch they went back to the lock, and the pressure was lowered. They soon began to feel very uncomfortable. As the pressure fell the wine began to fizz, and the financiers to suffer from inflation!"

J. B. S. Haldane, *Adventures of a Biologist.* New York: Harper and Brothers Publishers, 1940, pp. 80–81.