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WATER REPELLENCY INDUCED BY PULMONARY SURFACTANTS

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SUMMARY

1. Pure cotton fabric was partially carboxylated to produce a tough, porous, hydrophilic sub-phase to simulate the epithelial membrane of the alveolar wall from a permeability standpoint.

2. Two of the predominant pulmonary surfactants, dipalmitoyl lecithin (DPL) and dipalmitoyl phosphatidylethanolamine (DPPE), were found to inhibit wetting of this synthetic membrane and of human cutaneous epithelium as manifest by a large contact angle.

3. When treated with DPL *at physiological concentrations*, the porous synthetic membrane was found to support a head of saline well in excess of systolic pulmonary artery pressure with no penetration and could do so for periods well in excess of 1 hr; untreated control samples allowed almost immediate fluid filtration.

4. Filtration could be initiated in the DPL-treated membranes by wetting the reverse side, confirming that the threshold pressure for fluid penetration was afforded by capillarity and, hence, by water repellency induced by the surfactant.

5. Water repellency induced by the amphoteric surfactants occurring naturally in the lung is discussed as a possible factor contributing to the pressure threshold to be exceeded for alveolar oedema to form.

6. Evidence is reviewed and several advantages discussed for the implied concept of an essentially dry lining to the alveolus with a discontinuous liquid layer largely confined to convex corners which could slowly resolve any oedema by surface forces.

INTRODUCTION

The mechanism by which lung airways remain essentially fluid-free under normal physiological conditions has attracted much attention and has long been a centre of controversy (Staub, 1974) often linked to a deficiency, alteration or breakdown of the surfactant system (Pattle, 1958). Most theories of pulmonary homeostasis in general are basically variations of the original Starling hypothesis (1896) according to which opposing vascular and colloid osmotic pressures produce a net filtration of fluid into the interstitium which the lymph drainage can accommodate to varying degrees.

Restricting our attention to the alveolar wall as the last barrier to fluid entering the airway system, the situation is again one of opposing forces in which there is no doubt that the vascular pressure (or, at least, its influence in determing the interstitial

pressure) is the primary term representing the driving force on one side of the equation. This is now an equation of balancing *forces* rather than fluxes since there is no obvious counterpart of lymph drainage at the alveolar surface.

However, the forces *opposing* fluid exuding into the alveoli are much less obvious. If they were predominantly oncotic in nature, then they would represent essentially a restorative force which does not take effect until the fluid to be recovered has already escaped. Such a mechanism does not seem to reflect the all-or-none characteristics of alveolar oedema formation nor to offer an explanation for recovery being so much slower than onset (Staub, 1974), the two being mathematically asymmetric. Moreover, some studies have indicated that the alveolar wall is particularly permeable to macromolecular protein (Taylor, Guyton & Bishop, 1965), while no significant difference in protein concentration has been found between interstitial and alveolar fluids in anaesthetized dogs (Vreim, Snashall & Staub, 1976; Vreim & Staub, 1976).

These and many similar observations have led to careful analyses and comparisons of the experimental techniques employed, since it is so difficult to relate any sample obtained to true interstitial or alveolar fluid. Over-all, there are enough unexplained results for some workers in this field to question the relevance of colloid osmotic pressures altogether. Thus Guyton, Taylor, Drake & Parker (1976), even after allowing 10 mmHg for oncotic pressure, still estimate that there is a 'safety factor' of the order of 20 mmHg which must be exceeded for fluid to break through into the alveoli with subsequent oedema formation. The question then arises as to what phenomenon could be responsible for such a pressure threshold for flow across the alveolar wall. Guyton *et al.* (1976) propose a negative tissue pressure which must be exceeded for break-through to occur, but their attempts to measure it (Meyer, Meyer & Guyton, 1968) have produced average values which are only about one quarter of the threshold value needed.

An alternative mechanism proposed for the pressure threshold at the alveolar wall, termed 'safety factor' by Guyton and co-workers, is based upon the concept of water repellency induced by pulmonary surfactant (Hills, 1981). This mechanism is largely theoretical speculation based upon the finding that the predominant surfactant identified in the lung (Brown, 1964) is dipalmitoyl lecithin (DPL) and this can induce a contact angle (Hills & Ng, 1974; Barrow & Hills, 1979*a*) which has also been observed at the surface of excised pulmonary epithelium (Hills & Barrow, 1979). In surface physics (Adamson, 1967), a contact angle is the hallmark of non-wetting, and agents which impart this property to otherwise hydrophilic surfaces have many industrial applications of which one of the most common is imparting water repellency to hydrophilic sub-phases such as cotton. One of the more popular groups of substances used for this purpose are *cationic* surfactants, especially those with a quaternary ammonium ion at one end of the molecule and one or two long hydrophobic chains at the other. Although separated by a negative phosphatidyl ion, this is the same combination of active terminal groups found in the three most common surfactants positively identified in the lung, viz. DPL, dipalmitoyl phosphatidylethanolamine (DPPE) and sphingomyelin (Frosonolo, Charms, Pawlowski & Slivka, 1970). The basic theory underlying most industrial uses of cationic surfactants is that the strong positive charge of the quaternary ammonium ion effects strong

adsorption of the surfactant molecule onto the negative charges of the sub-phase, thereby orientating the hydrocarbon chains outwards to present a hydrophobic surface to any encroaching water. The resulting contact angle then impedes transmission of the water unless this has sufficient pressure to 'burst through' on to the surface; see eqn (1). While this concept may be attractive as an all-or-none phenomenon to provide a pressure threshold for alveolar oedema formation, it needs experimental evaluation, especially since a zwitterion would not be as strongly adsorbed as a pure cation, although the dipole would be ideally orientated for adsorption (see Fig. 4*E*).

No simple means could be devised for specifically testing *in vivo* for water repellency at the alveolar surface beyond re-interpreting previous work as discussed later. However alveolar surfactants can undergo standard tests for water repellency *in vitro*, e.g. British Standard BS2823 (1974), using sub-phases modified to stimulate the pulmonary membrane more closely than the kind of fabrics to which these tests are normally applied. This study describes the application of two very simple tests to lung surfactants, one a basic wettability test and the other a direct determination of the resistance they impart to penetration by water. The latter has added relevance insofar as the threshold can be measured directly as a break-through pressure.

METHODS

Principle

Since the evidence is conclusive that oedema does not reach the alveolar surface by secretion (Staub, 1974), any fluid exuding onto the alveolar surface must reach it by passing through some form of channel or 'pore'. The smaller the diameters of these 'pores', the greater the resistance, whether by fluid friction or by water repellency; in the latter case the pressure differential (ΔP) for break-through is given (Adamson, 1967) as:

$$\text{Flow if} \quad \Delta P + 2\gamma \cdot \cos(180-\theta)/r > 0 \tag{1}$$

where γ is the surface tension, r is the 'pore' radius and θ is the contact angle subtended by the fluid from the direction of invasion. It is difficult to estimate 'pore' size in the alveolar membrane but it must be several orders of magnitude smaller than those in the finest woven fabric. Thus, any water penetration pressure induced by the surfactant which is measured on a woven fabric is likely to be appreciably less than it might be capable of inducing *in vivo* where the value of r in eqn (1) would be so much smaller. In other words, we are likely to obtain a conservative estimate in simulating the porous pulmonary membrane by a woven fabric. Cellulose is used as the hydrophilic sub-phase in the form of finely woven cotton to produce a tenacious yet porous barrier. The cotton is carboxylated by a standard procedure to simulate carboxyl groups present in all natural membranes, including epithelium (Idson, 1967). This is important since fixed carboxyl ions represent negatively charged sites most conducive to the strong adsorption of cationic surfactants or dipoles with terminal positive charges.

One experiment is a simple test of the wettability of the cotton fibres by physiological saline after treatment with DPL, while the other is more a test of penetration of the woven matrix and, hence, the 'pores' by saline.

Wettability test

The wettability test adopted was the standard test BS4554: 1970 approved and published by the Textile Institute and the British Standards Institute (1970). It essentially consists of allowing a drop of liquid (saline in these experiments) to fall onto the fabric surface from the tip of a burette 6 mm above. The drop is then observed and the time noted at which it is no longer visible from above the fabric. This state is easily recognised by the sudden disappearance of diffuse reflexion from a light source placed more than 25 cm from the burette.

This test was performed upon 115 samples of carboxylated cotton treated with DPL, 115 treated

with DPPE and fifty controls dipped in chloroform only and then dried. Five concentrations of surfactant were used, ranging from an estimated physiological value of $3{\cdot}2 \times 10^{-1}$ $\mu g/cm^2$ down to $3{\cdot}2 \times 10^{-4}$ $\mu g/cm^2$.

Hydrostatic head test

The fluid penetration test adopted was, once again, the standard test for water penetration (BS2823:1974) approved and published by the Textile Institute and the British Standards Institute (1974). It consists essentially of applying a fluid pressure to one side of a sample of the fabric and then immediately increasing that pressure at the rate of 10 cm water gauge (w.g.)per minute until penetration occurs. That pressure is then recorded as the water penetration pressure.

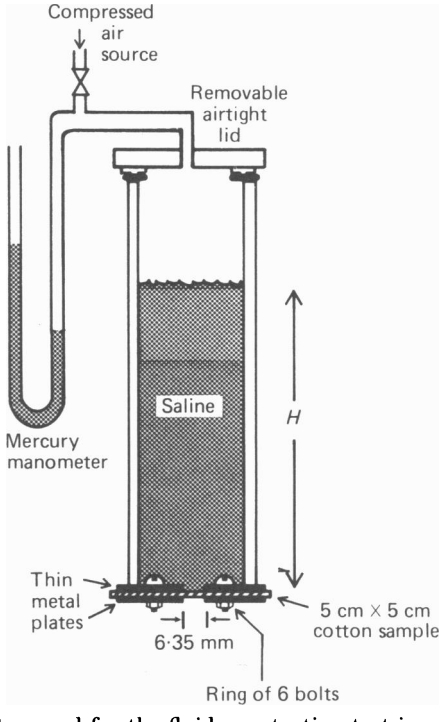

Fig. 1. An outline of the apparatus used for the fluid penetration test in which the head of saline (H) is increased at the rate of 10 cm/min until penetration is observed. Also indicated is the modification permitting an additional gas pressure of 300 mmHg to be applied to the top of the column if it reaches 58 cm without penetration.

The only variations from the standard test were to use physiological saline in place of water as the fluid and to take the penetration pressure as the head at the appearance of the *first* point of penetration rather than the third. Thus the results were more conservative than the standard test would allow.

Procedure

Samples of carboxylated cotton (5 × 5 cm) were securely clamped by placing them between metal disks held together with a ring of six bolts (see Fig. 1). Each disk had a hole $\frac{1}{4}$ in. in diameter as the 'window' through which the cotton was exposed to the fluid head. These precautions in clamping the fabric were found to be necessary in order to ensure that no fluid leaked around and initiated flow by wetting the underside.

If there was no penetration upon reaching a fluid head of 58 cm, the column was left for 4 hr. In another set of runs, a lid was placed upon the fluid column when no penetration occurred for

a head of 58 cm saline and the filtration pressure was further increased by applying a gas pressure to the top of the column using a sphygmomanometer apparatus. A further pressure of 300 mmHg could then be applied, also at the rate of 10 cm (w.g.) per min.

Materials

Fabric

The fabric selected was a fine-weave cotton supplied by the Shirley Institute, Manchester, as totally de-waxed and untreated. This was then carboxymethylated by a standard method (Daul, Reinhardt & Reid, 1952) which consists essentially of treating the fabric with sodium chloroacetate prepared *in situ* with 15% (w/w) chloroacetic acid and 5% (w/w) sodium hydroxide, picking it up wet and baking it for 6 min at 160 °C. It was then rinsed and treated with 2% (w/w) aqueous acetic acid to return grafted carboxyl groups to their free acid form. The fabric was then rinsed thoroughly, dried and ironed to remove wrinkles.

Following carboxylation, the exact carboxyl content was determined using the standard method of Cumberbirch & Holker (1966). By this method, an accurately weighed over-dried sample of the fabric was shaken for 2 hr in a solution of 0·1 N-KI, 0·1 N-KIO_3, 0·1 N-$Na_2S_2O_3$ and 50 gNaCl/l. Excess thiosulphate was then back-titrated against 0·1 N-iodine solution. This method gave a carboxyl content of 5·99% for the carboxylated fabric, i.e. six out of 100 hydroxyl groups on the cellulose had been converted to carboxyl groups.

Surfactants

The surfactants used were DL-α-phosphatidyl choline dipalmitoyl (dipalmitoyl lecithin; DPL) and dipalmitoyl phosphatidylethanolamine (DPPE) supplied by the Sigma Chemical Company and kept refrigerated. Each was dissolved in chloroform to give two solutions of 800 μg/ml. for the fluid penetration test and these and further solutions of 80, 8, 2 and 0·8 μg/ml. for the wettability test. 800 μg/ml. corresponds to a concentration of 32 μg/cm^2 based on gross fabric dimensions or 0·32 μg/cm^2 of actual filament surface available for adsorption of surfactant. This is comparable to a value of 0·38 μg/cm^2 for the surfactant concentration at the alveolar wall according to a review (Barrow & Hills, 1979*b*) of the best estimates.

Each sample of carboxymethylated cotton was soaked in 1 ml. of one of these solutions for 5 min, removed and dried for 4 hr. One set of controls was simply soaked in 1 ml. chloroform and dried following the same procedure; another set was soaked in a chloroform solution of non-lung lipids (800 μg/l.) extracted from dog adipose tissue following the procedure of Folch, Lees & Sloane-Stanley (1957).

RESULTS

The standard wettability test gave the results summarized in Table 1, showing that wetting time is a function of surface concentration and is generally longer for DPL-treated samples (e.g. 97·1 $\pm$ 14·0 sec) compared with DPPE-treated samples (e.g. 26·8 $\pm$ 5·6 sec) at the same concentration. In passing, it was noted that wetting times of the treated samples tended to be longer when water was used in place of saline.

Results of the fluid penetration test showed that all ten DPL-treated samples could withstand a pressure of 58 cm saline (43 mmHg) for at least 1 hr without any sign of fluid penetration, the last four samples being allowed to stand overnight. By comparison, both the chloroform controls and those with non-lung lipid showed almost immediate penetration, no head exceeding 2·5 cm saline (Table 2). DPPE-treated samples showed that they supported lesser heads than DPL (Table 2) but still appreciably larger than the controls.

When another ten DPL-treated samples were further pressurized after reaching a head of 58 cm w.g. some could withstand a further 300 mmHg to give a total fluid penetration pressure of 343 mmHg (Table 2). All results were obtained at 20–22 °C.

It was also noted, in passing, that penetration of the treated samples could be

initiated by applying fluid to the reverse side; water repellency was compromised if solutions were not freshly prepared or used shortly after removal from the refrigerator.

Qualitative experiments to study the contact angle induced by pulmonary surfactants showed that a larger contact angle could be observed when a drop of saline

TABLE 1. Wetting times of carboxylated cotton treated with surfactants

Surfactant	Surface concn. ($\mu g/cm^2$)	Number of tests	Wetting times ($\pm$S.D.)
DPL	0·32	50	> 1 hr
DPPE	0·32	50	> 1 hr
DPL	$3{\cdot}2 \times 10^{-2}$	5	3211 $\pm$ 34 sec
DPPE	$3{\cdot}2 \times 10^{-2}$	5	746 $\pm$ 41 sec
DPL	$3{\cdot}2 \times 10^{-3}$	5	162 $\pm$ 28 sec
DPPE	$3{\cdot}2 \times 10^{-3}$	5	143 $\pm$ 22 sec
DPL	$0{\cdot}8 \times 10^{-3}$	50	97·1 $\pm$ 14·0 sec
DPPE	$0{\cdot}8 \times 10^{-3}$	50	26·8 $\pm$ 5·6 sec
DPL	$3{\cdot}2 \times 10^{-4}$	5	34·9 $\pm$ 8·2 sec
DPPE	$3{\cdot}2 \times 10^{-4}$	5	21·9 $\pm$ 4·7 sec
Controls	0	50	18·6 $\pm$ 2·6 sec

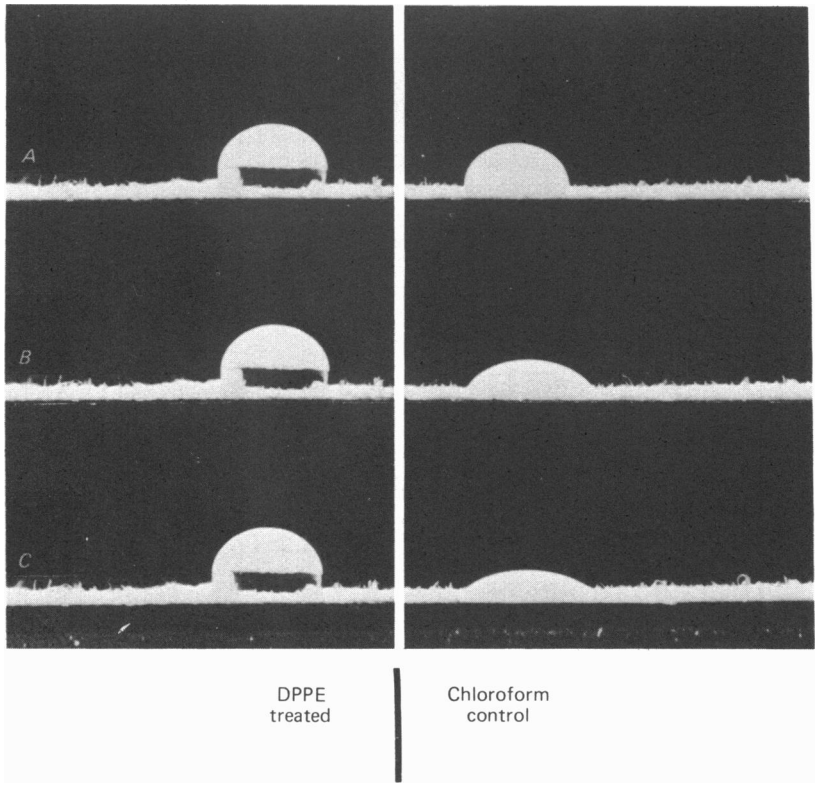

Fig. 2. A photograph of two drops of saline taken *A*, immediately, *B*, 5 sec and *C*, 10 sec after they were applied to the same carboxylated cotton fabric, treated with DPPE at an estimated surface concentration of 0·32 $\mu g/cm^2$ and the other a control. Note the large contact angle of over 120 deg. on the treated sample.

TABLE 2. Saline penetration pressure: head of saline (H) and time of any penetration for fifty separate samples

Surfactant Measurement units	DPL				DPPE		Controls: Chloroform only		Controls: Non-lung lipids	
	Head (cm w.g.)	Time	Head (mmHg)	Time (min)	Head (cm w.g.)	Time (min)	Head (cm w.g.)	Time (sec)	Head (cm w.g.)	Time (sec)
1	> 58*	> 1 hr	> 343*	> 46	15	1·5	< 0·5	1	1·0	6
2	> 58*	> 1 hr	> 343*	> 46	39	3·9	1·5	8	0·5	1
3	> 58*	> 1 hr	> 343*	> 46	20	2·0	< 1·5	8	2·0	11
4	> 58*	> 1 hr	> 343*	> 46	37	3·7	1·0	6	2·5	15
5	> 58*	> 1 hr	> 343*	> 46	15	1·5	< 1·5	8	0·5	2
6	> 58*	> 1 hr	25	$3\frac{1}{2}$	35	3·5	1·5	8	2·5	15
7	> 58*	> 16 hr	27	$3\frac{1}{2}$	21	2·1	1·0	6	1·5	8
8	> 58*	> 16 hr	> 343*	> 46	28	2·8	< 0·5	< 2	< 0·5	1
9	> 58*	> 16 hr	> 343*	> 46	37	3·7	< 1·0	6	1·0	6
10	> 58*	> 16 hr	> 343*	> 46	36	3·6	1·5	8	1·5	8
Average	> 58	> 1 hr	> 279·6	> 37·5	28·3	2·8	< 1·15	< 5·3	1·35	7·3
S.D.	—	—	—	—	±9·7	±1·0	±0·41	±3·1	±0·74	±5·2

* No penetration observed; > 58 cm w.g.: > 1 hr means that no penetration was observed after maintaining a head of 58 cm w.g. for 1 hr.

was placed on a cotton sample treated with DPPE at the higher concentration (0·32 μg/cm^2) than on one treated with DPL at the same concentration. The difference between DPPE and a control is clearly demonstrated in Fig. 2. A similarly large contact angle was observed when a saline drop was placed on my clean index finger after it had been coated with DPPE (Fig. 3).

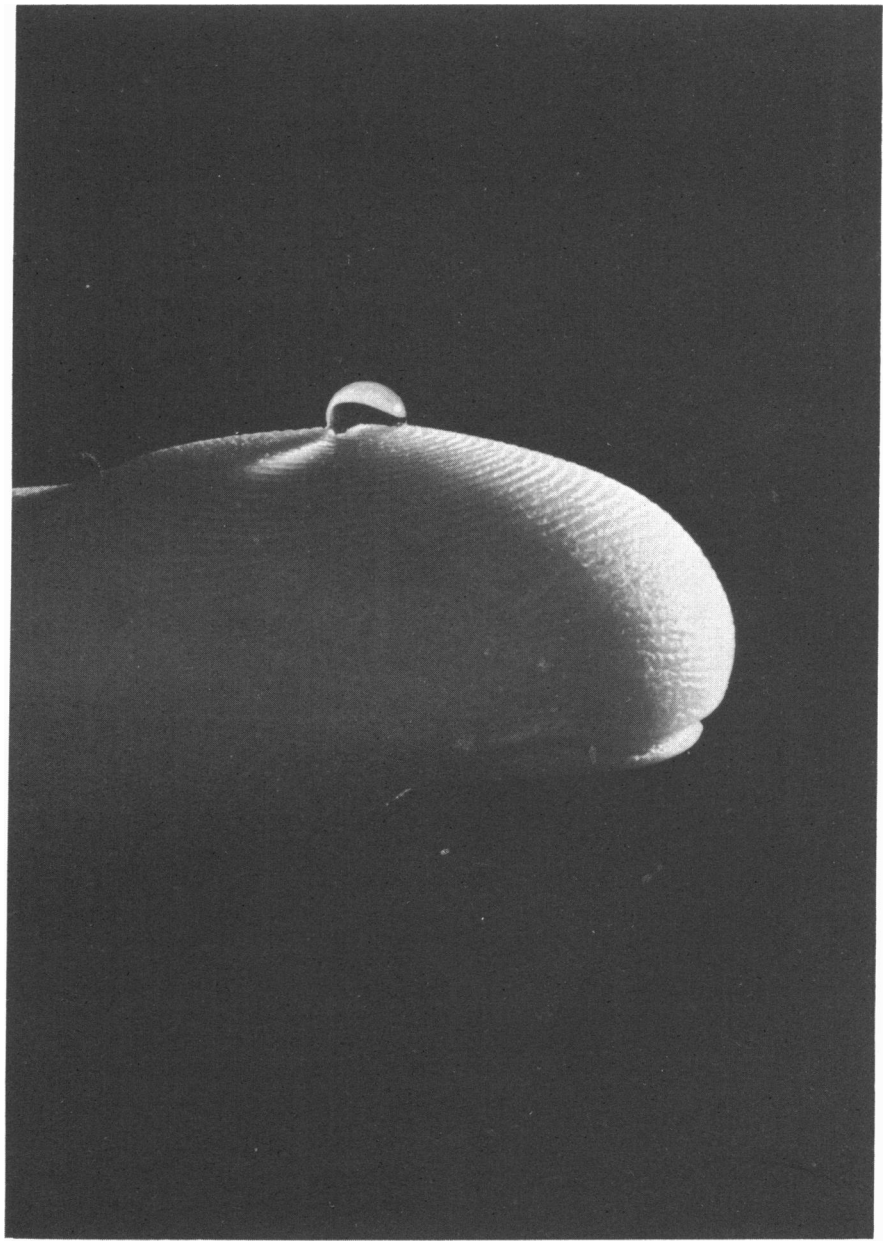

Fig. 3. A photograph of a droplet of 10 μl. saline taken 2 min after it was applied to the author's index finger which had been chloroform washed and coated with DPPE. Note the very large contact angle which remained for many minutes.

DISCUSSION

The results leave little doubt that the synthetic form of DPL, the surfactant present in the lung in the largest amount (Frosonolo *et al.* 1970) is particularly effective in imparting water repellency at physiological concentrations to a pure cotton fabric with grafted carboxyl ions. Both DPL and DPPE can inhibit wetting at much lower concentrations. The head of fluid which DPL-treated fabric can support (Table 2) is an order of magnitude in excess of normal systolic pulmonary arterial pressure of 25 mmHg (West, 1979) or the 'safety factor' of 20 mmHg estimated by Guyton *et al.* (1976) as the hydrostatic threshold for alveolar oedema formation. The ability to withstand these pressure gradients is not a transient phenomenon since they were maintained at 58 cm w.g. (42·6 mmHg) for at least 1 hr and sometimes overnight.

There is little doubt that the active agent inducing water repellency was the surfactant since both sets of controls were particularly permeable to saline and great care was taken to ensure that they were handled in the same way as the others. The fact that fluid break-through could always be induced by wetting the dry, low-pressure side of the membranes tends to confirm that the mechanism underlying the pressure threshold was hydrophobic capillarity, i.e. true *water repellency* rather than simply sealing pores by blocking them (waterproofing).

It was a little surprising to find that DPPE was not as effective as DPL in view of the particularly large contact angle which DPPE induces when a single drop is placed upon a treated cotton surface (Fig. 2) or cutaneous epithelium (Fig. 3). However, both substances would be predicted to impart hydrophobic properties and, hence, water repellency to the carboxylated cotton since industrial cationic surfactants, such as Zelan, are widely used to impart such properties to fabrics in general (Adamson, 1967). The theoretical basis is simply that the strongly positively charged quaternary ammonium ion is strongly adsorbed onto the negative charges in the sub-phase, orientating the hydrocarbon 'tails' outwards to present a strongly hydrophobic surface as envisaged in Fig. 4(*D*). This, in turn, inhibits wetting as reflected by a large contact angle (θ) for which larger values in eqn. (1) require higher pressure gradients (ΔP) before the fluid can penetrate the barrier. Water penetration pressures of the order of 35 lb/sq. in. (1760 mmHg) are often standard requirements by some industrial users (Hills, 1981). The fact that the ΔP values recorded with pulmonary surfactants are almost an order of magnitude lower can be attributed to the smaller force of attraction of the dipole of the zwitterion in DPL or DPPE for a negative charge in the sub-phase of the pulmonary membrane (Fig. 4*E*) than would apply for a true cationic surfactant (Fig. 4*D*). This is probably reflected in the values of contact angles of up to 67° recorded for DPL on tracheal epithelium (Barrow & Hills, 1979*b*) whereas they are invariably in excess of 90° in industrial applications. Another potential moderating factor is the possible deposition of multiple layers of surfactant where regions with odd multiples would be hydrophobic (Chapman, 1969) while those with even multiples would be hydrophilic (but probably not as hydrophilic as the original sub-phase). However, after allowing for these possible compromising factors, the degrees of hydrophobicity should still be adequate to provide the very modest fluid penetration pressures needed to provide physiological thresholds to fluid flow.

The results can only be claimed to demonstrate that DPPE, and especially DPL, have the capability to impart water repellency to certain hydrophilic sub-phases such as carboxylated cotton, but may not necessarily do so at the alveolar wall. The latter would be no less hydrophilic than cellulose (cotton) and, akin to biological membranes in general, must contain carboxyl ions and possibly a few sulphonate ions (Davson, 1964).

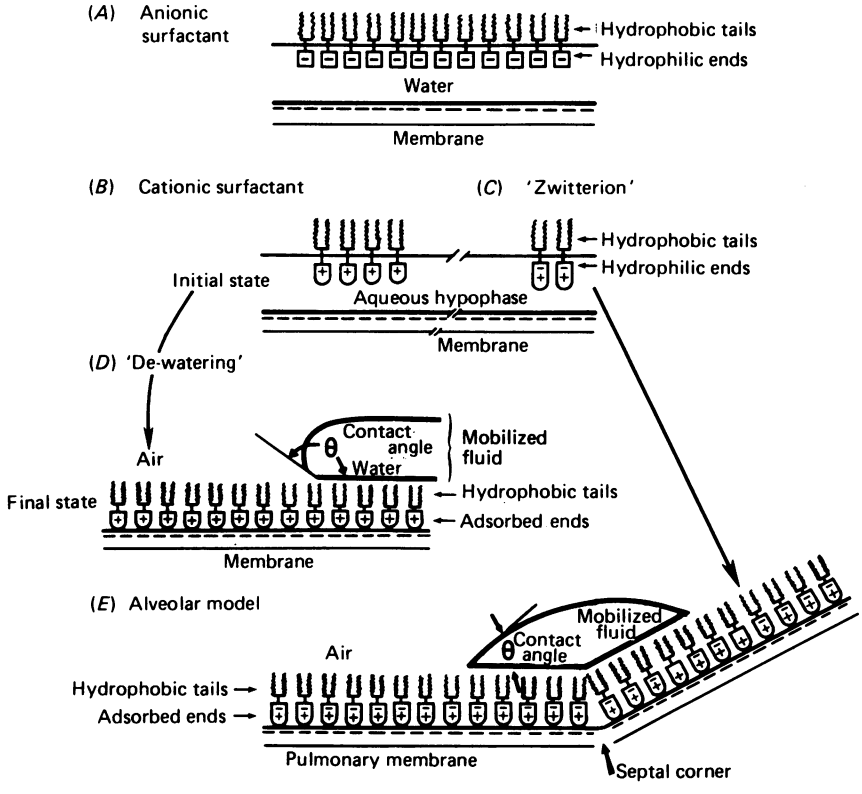

Fig. 4. A theoretical model for the action of surfactants upon a hydrophilic sub-phase containing fixed carboxyl ions and initially covered with an aqueous hypophase, indicating how *A*, an *anionic* detergent, *B*, a cationic surfactant and *C*, an amphoteric surfactant would locate at the air–aqueous interface with their hydrophobic 'tails' in the air according to the popular concept. In *D* it is shown how a truly cationic surfactant would be directly adsorbed onto the negative sites of the pulmonary membrane to give it a hydrophobic exterior and thus displace fluid according to the standard theory of 'de-watering' agents while, in *E*, it is shown how the orientation of the dipole in the amphoteric surfactants in the lung would produce a similar situation but with weaker adsorption. Also depicted are the 'corner pumps' for the resolution of oedema.

If the concept of water repellency were largely responsible for alveolar homeostasis, it would need to satisfy two questions. The first concerns what secondary mechanisms would be available for the eventual return of fluid across the alveolar wall following the episode of acute pulmonary hypertension or some other event which caused a break-through. The second question raises the very basic issue of whether there is really a continuous aqueous hypophase lining the lung, an assumption not seriously challenged from a functional standpoint since it was first assumed by von Neergaard

(1929). This is an issue because a barrier cannot retain fluid by capillarity if it is wet on the low-pressure side, as confirmed in this study. To address both questions together, it should be pointed out that any surfactant adsorbed onto the alveolar wall must act in the same sense as industrial 'de-watering' agents, such as quaternary ammonium compounds which are widely used to displace unwanted water layers (see Fig. 4*D*), usually for the purpose of preventing corrosion or permitting an oil to make true contact with the metal surface which it lubricates (Hills, 1981). In the lung, displacement of any fluid layer to the sides and as far as the septal corners (Fig. 4*E*) would have at least two distinct advantages.

The first is that 'de-watering' would reduce the blood–air barrier and so improve gas transfer. Morphological evidence can be cited to support this statement but it must be considered with caution since there are so many opportunities to introduce preparation artifacts. However, electron micrographs of lung sections seldom, if ever, show a *continuous* aqueous layer lining the *normal* mammalian alveolus, but the fluid collects in what Weibel & Bachofen (1979) term 'pools'. These are seen mainly at the corners and less regular areas – just as one observes when pouring water onto a rough hydrophobic surface *in vitro*. A dense osmiophilic layer indicative of surfactant can sometimes be seen at the pool–air interface, as Weibel & Bachofen (1979) point out, but in the same electron micrographs the same density can also be seen more often at regions of the epithelial surface where there is no perceptible liquid hypophase.

The second functional advantage of any 'de-watering' action of adsorbed surfactant concerns the mobilized fluid collecting at the septal corners where it can now exhibit a distinct edge to the pool permitted by a contact angle (Fig. 4*E*). Hence, if the fluid accumulation is sufficient, it can now display a convex profile with respect to the air and so exert a positive surface force tending to return exuded fluid to the interstitium. This force (ΔP) would be self-regulating since it would decrease as the oedema was resolved with the curvature of the corner pool decreasing ($r\uparrow$) according to the Laplace equation:

$$\Delta P = 2\gamma/r \qquad (2)$$

where γ is the surface tension.

Kisch (1958) has produced morphological evidence from oedematous lungs demonstrating distinct contact angles between the alveolar surface and adhering 'droplets' of diameters less than 2 μm. Substituting $r = 1$ μm in eqn. (2) and taking a value of $\gamma = 26$ dyne/cm determined under simultaneously simulated physiological conditions (Barrow & Hills, 1979*b*), the 'corner pumps' could exert a maximum pressure (ΔP) of up to 380 mmHg in resolving alveolar oedema. This might explain the remarkable finding of Matthay, Landolt & Staub (1981) that a 14% solution of macromolecular protein instilled into the alveoli can still be absorbed across the pulmonary membrane despite its theoretical oncotic pressure of 140 cmH_2O.

Compatibility of an essentially dry alveolar surface with the major features of pulmonary mechanics has been addressed elsewhere (Hills, 1981), but water repellency induced by adsorbed surfactants would seem to offer an interesting physical basis for the pressure-threshold resisting oedema formation which warrants further investigation *in vivo*.

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