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REVIEW ARTICLE

DRUG UPTAKE FROM THE AIRWAYS AND LUNGS

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Abstract : This paper reviews the mechanisms and physiological processes that act when drugs or chemicals are administered into the lower airways and lungs. Administration is usually by aerosol. Agents can be given, for example, either to treat pulmonary diseases such as asthma, or the test for airways' responsiveness or other functions, or as a means of access of a drug to the sytemic circulation. The first barrier to absorption is the airway surface liquid, including mucus. The thickness of this layer will determine the concentration of the drug in solution, and therefore its rate of entry into the tissue. The agent must then penetrate the airway epithelium, the strongest barrier for hydrophilic agents. Agents must then diffuse through the epithelial basement membrane and the interstitium. Finally, the agent may be taken up into the mucosal vasculature, and changes in blood flow will influence its uptake and distribution. If the drug is to reach a target organ, such as airway smooth muscle or glands, these barriers have first to be traversed.

Key words : respiratory system lungs aerosol drug uptake circulation airways pulmonary

INTRODUCTION

Drugs are administered into the airways and lungs for several reasons: to treat conditions such as asthma, to test for airways' responsiveness, and as a route for absorption into the systemic circulation. The drugs may be given as aerosols, liquid or solid, or as liposomes. In some instances, for example local anesthetics, they may be instilled or sprayed locally into the airways. Volatile anesthetics are administered as gases. Inert tracers are given to test functions such as airways' permeability in health and disease. Injurious chemicals, such as the pollutants sulphur dioxide, nitric oxides and oxone, all enter the body through the airways and lungs before they can exert their toxic effects.

This paper will deal with the general principles, mechanisms and physiological processes that determine the rate of uptake of such agents into the airways and lung

tissues, and thus into the body as a whole. These general considerations will apply to *all* soluble agents, including liposomes, that can penetrate into the tissues, but not to inert particles, dusts or chemicals of high molecular mass, which do not enter the tissues but are cleared by mucociliary transport.

The barrier for entry consists of: (1) a layer of liquid, the airway or alveolar surface liquid (ASL) in which the agent has first to dissolve, and which in turn is divided into an overlying layer of mucus (gel) and the periciliary liquid (sol) (Fig. 1); (2) the epithelium; (3) the epithelial basement membrane; (4) the interstitial liquid, almost absent in the alveolar wall; and (5) the vascular bed with its endothelium and basement membrane and which may distribute agents throughout the systemic circulation and body, and limit the amount of agent locally available to act on airway target organs.

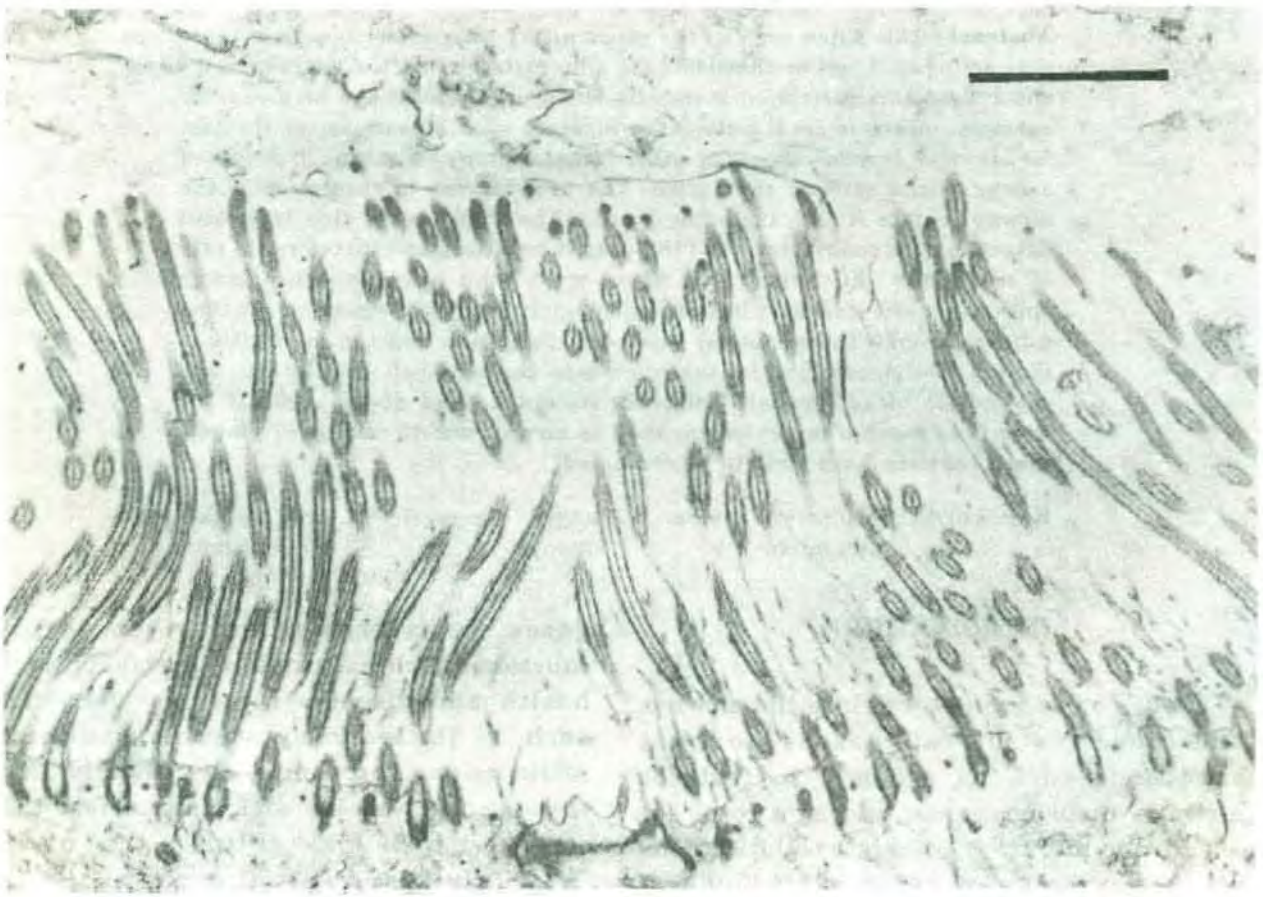

Fig. 1: Arrangement of the mucosal layers above the bronchial mucosa. There is a sol phase in which the cilia beat above the epithelial surface. Above the sol phase there is a gel phase consisting of fine flakey material. Dark lines of phospholipid partially separate the two phases. Transmission electron microscope. Bar, 2 μm. (From 38).

Airway surface liquid (ASL)

The thickness of the ASL is an important variable (1–3). When a soluble agent is inhaled and deposited in the airways or alveoli, the luminal concentration (C) of the chemical will depend on the volume, and therefore the thickness, of the ASL in which it dissolves; the volume of ASL equals surface area (S, relatively constant) times thickness (T, variable). The appropriate equation is:

$$C = Q/(S \times T) \quad (1)$$

where Q is the amount of chemical deposited in area S of ASL.

The concentration of the chemical determines its rate of passage or flux (dQ/dt) into the body. This follows the equation:

$$dQ/dt = -P \times \Delta C \times S \quad (2)$$

where P is the permeability coefficient (velocity of entry) for the agent, ΔC is the concentration difference across the mucosa, and the minus sign is directional (lumen to submucosa). Combining equations (1) and (2), and assuming that $\Delta C = C$ (see later), we get:

$$dQ/dt = -P \times Q/T \quad (3)$$

Thus rate of entry of the chemical varies inversely with the thickness of the ASL. It will be noted that rate of entry does not depend on surface area, since if the load of chemical is concentrated over a small area, the concentration gradient will be large and therefore so will the flux (equation 2), and vice versa if the area of distribution is large. It is often claimed that if a drug in aerosol form could be deposited in the alveoli rather than the airways, then the rate of entry into the body would be fast because the alveolar surface area is large compared with that of the airways. This conclusion is incorrect. The rate of entry from the alveoli would be high because the ASL thickness is small (equation 3); permeability coefficients have also to be taken into account, as will be discussed later.

We have assumed that the concentration difference across the epithelium is similar to the luminal concentration of an agent, i.e. that the submucosal concentration can be ignored. This is certainly true for hydrophilic molecules, even of small molecular weight, where the concentration difference is many thousand-fold, for preparations both *in vivo* and *in vitro* (4, 5). These molecules pass through the narrow paracellular pathways. For lipophilic molecules, that pass through the cell membranes, the difference is smaller, but the error introduced is only 0.3–5%.

Another index of rate of entry of a chemical into the body is to measure the percentage clearance of a tracer (as a percentage of total load per unit time), usually an inert agent such as DTPA , from the airways in which it has been deposited by aerosol. The influence of ASL thickness on this parameter follows the same general principles as for drug flux, and has been discussed elsewhere (1–3).

Values for ASL thickness :

Surprisingly, ASL thickness has never been measured in man. For animals, there are many measurements, usually for trachea and large bronchi, but with an enormous range of values (Table I) (6–18). There is general agreement that the cilia are surrounded with liquid (sol), probably held

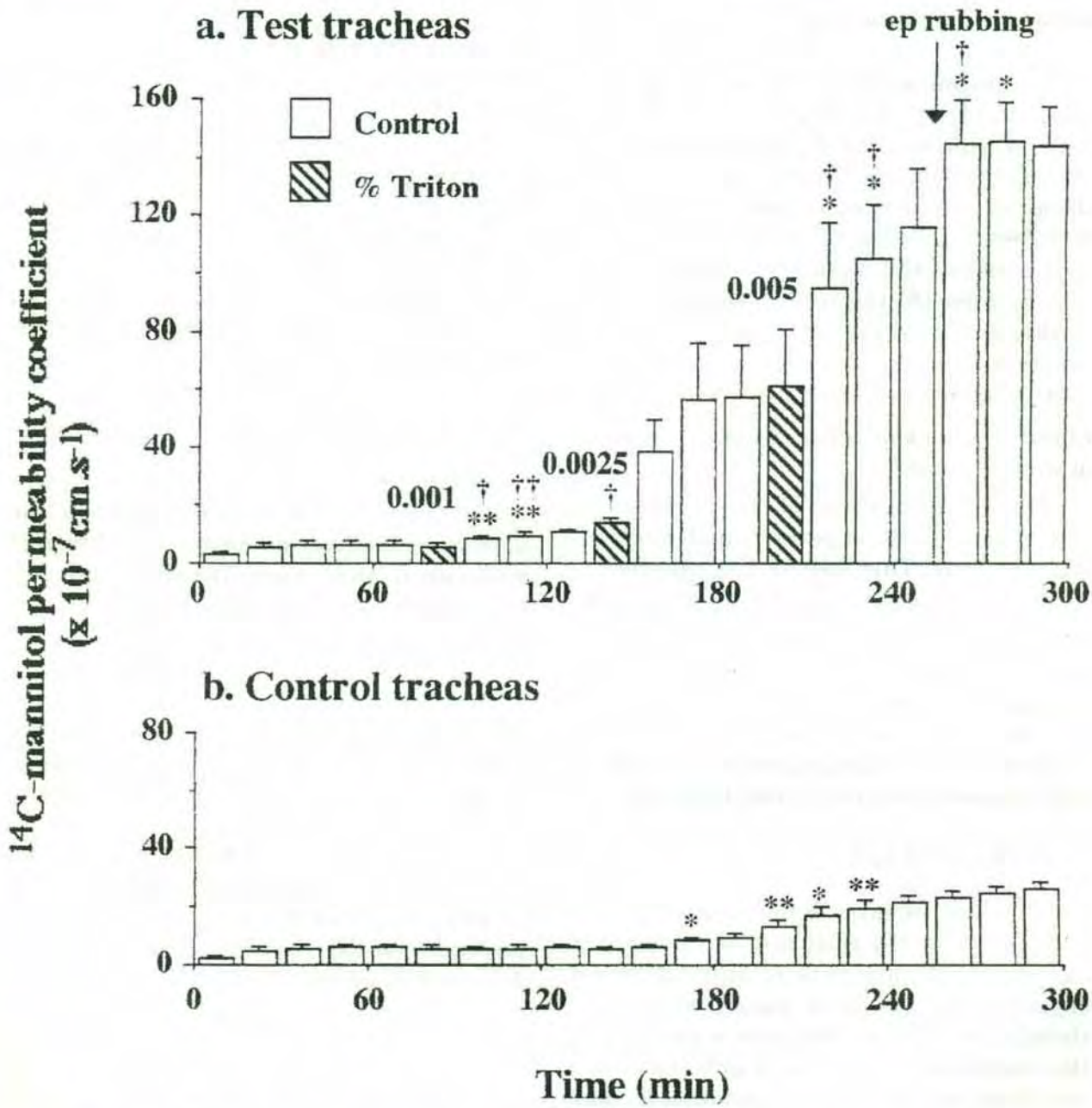

Fig. 2: Time course of change in permeability of the ferret trachea *in vitro* to ^{14}C-mannitol (a) in the presence of Triton X-100 (0.001, 0.0025 and 0.005%) and (b) in the absence of Triton X-100. Each column represents the mean permeability coefficient (± SEM) during a 15-min period. Ep rubbing represents the time of epithelial destruction by rubbing. N = 5. *P < 0.05, **P < 0.01 for comparison of response with pre-test level; paired t-test. †P < 0.05, ††P < 0.001 for comparison of change in test tracheas with corresponding change in parallel control. (From 26).

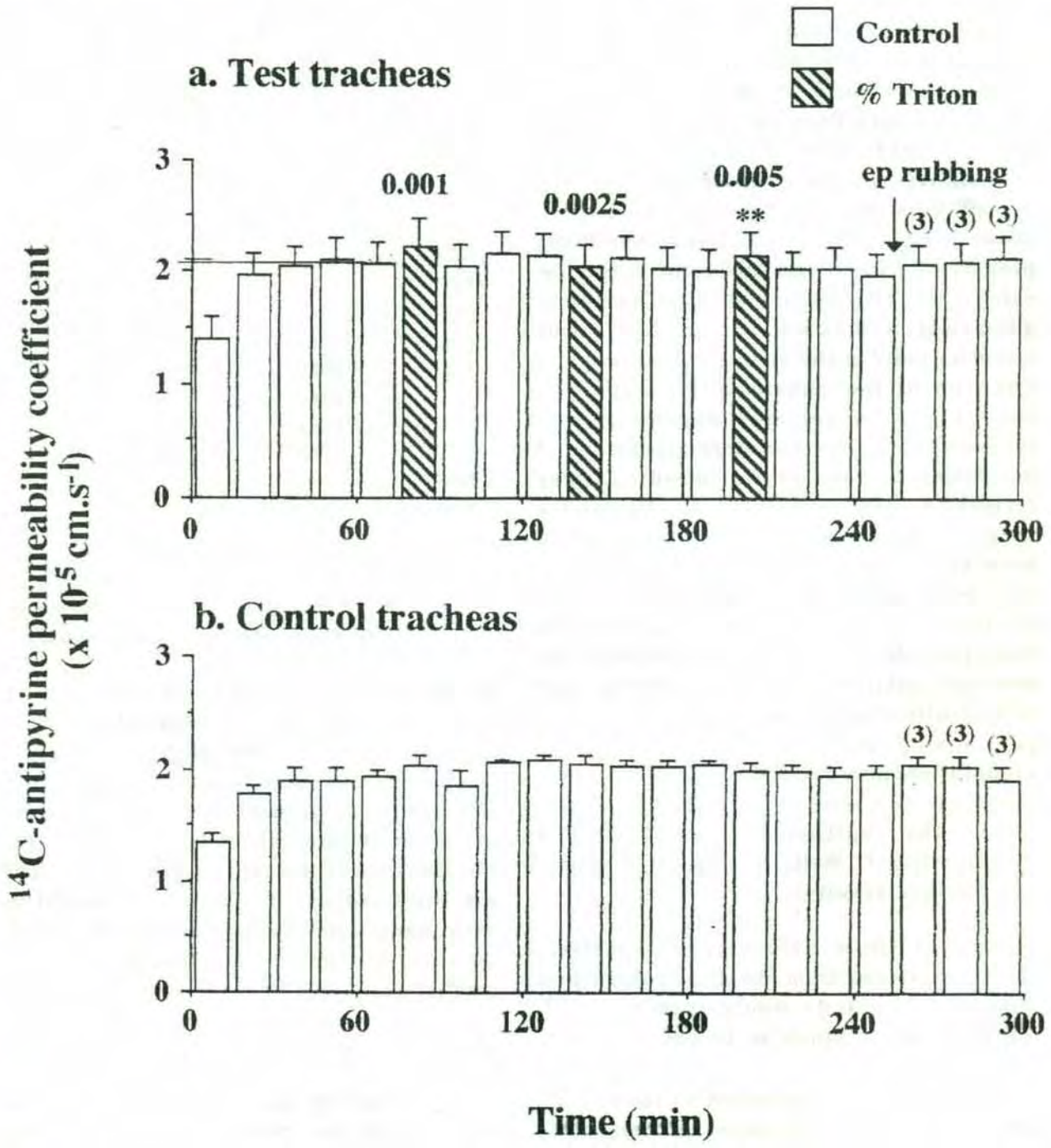

Fig. 3: As for Fig.2, but with the lipophilic tracer ^{14}C-antipyrine. (From 26).

in place by capillarity (19) and controlled by epithelial ion-pumps (20). The thickness of the sol is about 5–10 μm. However, values for the gel vary from zero to 250 μm. Some of the small values may be because mucociliary clearance would move all the gel off a small segment of the mucosa in about 1–2 min, while the tissue was being prepared for histology. Also some of the low values are with species such as hamsters, guinea pigs and rats which have few mucus secreting cells in the airway epithelium and often no or few submucosal glands. The existence of a gel may depend on the presence of mucus secretory tissues or of epithelial damage or irritation. Airway irritation increases gel thickness considerably, even in those species which have little gel in control conditions (6–8, 21). Some of the high values were with *in vivo* or *in vitro* preparations handled for long periods of time, during which the mucosal viability may have suffered. Our own results with ferrets, rabbits and guinea pigs, using an *in vitro* tracheal tube preparation, give control values in the range 40–60 μm (3), with a trebleing of values when the epithelium is destroyed (S. Duneclift, U. Wells & J. G. Widdicombe, unpublished results).

To put these values in perspective, strong secretion from the tracheobronchial submucosal glands would increase ASL thickness by as much as 10 $\mu m.min^{-1}$ (20).

It is obviously important to resolve the differences in ASL values for animals, since the total variation is fifty-fold (5 to 260 μm for sol plus gel), and this would correspond to a fifty-fold variation in rate of drug uptake. It is equally important to obtain values for man, although indirect analysis, based on various assumptions, gives a thickness for the large airways of 30–60 μm (1, 2). Nearly all the results given apply only to trachea and large bronchi, and we know that for small bronchi and bronchioles the gel is far thinner, about 0.3–3 μm (22, 23). For the alveoli the ASL is about 0.1 – 0.25 μm thick (24, 25), so absorption should be very many times faster than for the larger airways, assuming the same permeability coefficients (see later).

TABLE I : Thickness of ASL.

Species	*Method*	*Gel thickness (um)*	*Reference*
Hamster	EM	0	(6)
Monkey	EM	0.1–1	(10)
Cow	EM	0.5–2	(11)
Guinea pig	EM	c. 1	(7)
Guinea pig	EM	c. 1	(8)
Rat	EM	c.1	(8)
Cow	EM	1–2	(9)
Rat	EM	5	(12)
Rat	EM	5–10	(13)
Cow	EM	20	(14)
Sheep	Probe	30	(15)
Ferret	Tracer	50	(3)
Rabbit	Tracer	40	(3)
Guinea pig	Tracer	60	*
Guinea pig	Probe	100–200	(16, 17)
Guinea pig	Probe	250	(18)

Plus sol = 5 – 10 μm. *S. Duneclift, U. M. Wells and J. G. Widdicombe, unpublished results.

Epithelial permeability

Permeability coefficients for a number of chemicals have been measured for large airways and alveolar walls of various species, but not man. Measurements have been with both *in vitro* and *in vivo* models. Inert tracers, rather than active drugs, have been used; the latter might alter epithelial

TABLE II : Permeability coefficients and the effect of epithelial destruction.

Model	*Agent*	*Molecular mass (Da)*	*Solubility*	*Permeability coefficient ($X \cdot 10^{-7}$ cm.s^{-1})*		*Reference*
				Before	*After*	
Ferret *in vitro*	Mannitol	182	Hydrophilic	6.0±1.0	144±1.3	(26)
trachea	Antipyrine	188	Lipophilic	200±10	210±10	(26)
Sheep *in vivo*	DTPA	492	Hydrophilic	2.6±0.8	89.7±25.6	(5)
trachea	Antipyrine	188	Lipophilic	3312±878	2565±246	(5)

Values are means ± s.e.m.s. Before and after refer to values before and after destruction of the tracheal epithelium with Triton X-100 (ferret) or H_2O_2 (sheep).

function and therefore permeability. The molecular masses of the tracers are similar to those drugs used in treating and assessing airways' diseases. Table II summarizes some of the results for substances similar in molecular mass to those used in aerosol therapy of airways diseases. It will be seen that a lipophilic molecule (antipyrine) has a far higher permeability coefficient than do hydrophilic ones (mannitol and DTPA) for similar molecular masses, as would be expected.

Permeability coefficients for the airway epithelium and mucosa depend on several factors: the main ones are the molecular mass of the substance being studied, and its partition coefficient (the ratio of its solubilities in water and fat, or its relative hydro– and lipophilicities); molecular charge and shape may also affect the permeability coefficient. The permeability coefficient will be distorted (and therefore termed "apparent"), if there are unstable conditions, or if there is, for example, water flux through the epithelium.

Epithelial damage :

Epithelial damage increases the mucosal permeability to hydrophilic but not to

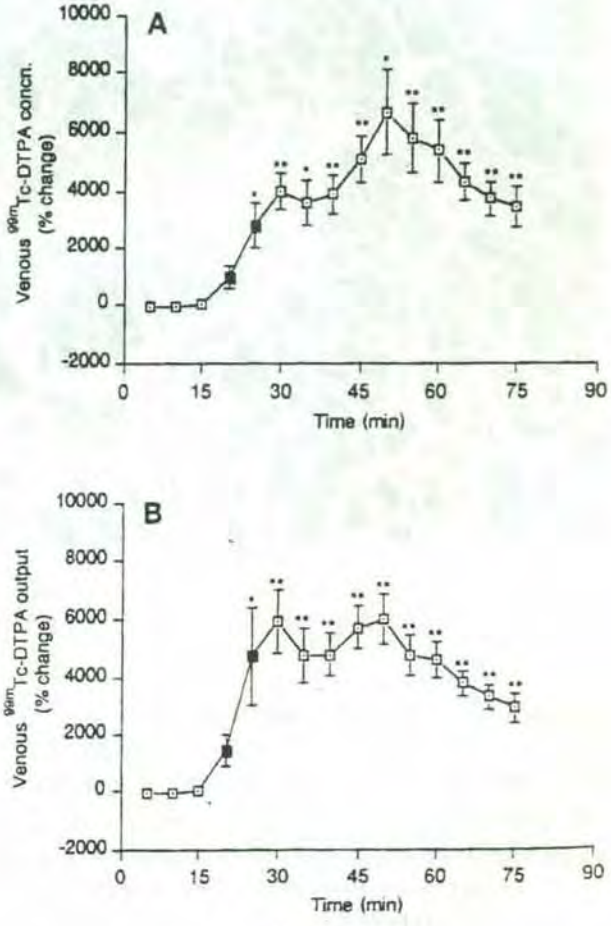

Fig. 4: Effect of 10 mM H_2O_2 in the lumen of the sheep trachea *in vivo* on the concentration and output of ^{99m}Tc-DTPA in venous drainage from the trachea. Values are means ± SEMs (n=5). Filled squares during exposure to H_2O_2 *P < 0.05,**P <0.01 compared with control (paired t-test). (From 5).

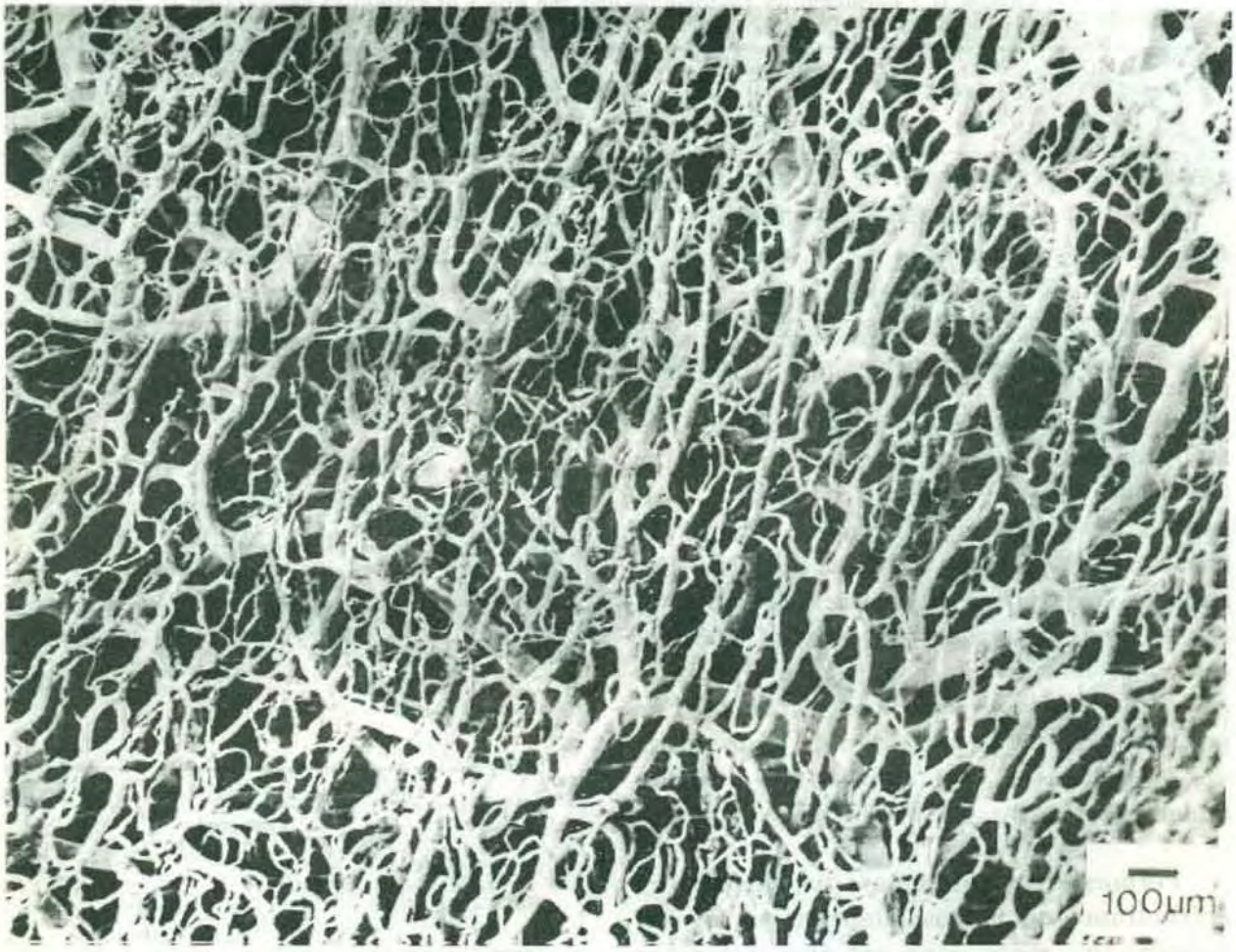

Fig. 5: Scanning electron microscopic picture taken from the lumenal side of a vascular cast from the lateral wall of the trachea over the fifth cartilagenous half-ring of a dog. A rich capillary network is shown. Bar, 100 µm. (From 38).

lipophilic substances for both *in vivo* and *in vitro* preparations (Table II) (Figs. 2–4) (4, 5, 26). This is seen with the application of platelet activating factor, which apparently opens paracellular pathways and reduces but does not abolish transepithelial potential difference (4), which implies damage to but not destruction of epithelium. With complete destruction of the epithelium by application of high concentrations of detergent (Triton X-100) and surface rubbing, there are even greater increases in permeability to hydrophilic tracers (27, 28) (Fig. 2), but no change in that to a lipophilic one (5, 26) (Fig. 3), for both *in vitro* and *in vivo* tracheas. Damage to the epithelium *in vivo* with, for example, sodium metabisulphite or hydrogen peroxide also greatly increases permeability to hydrophilic molecules (25, 29) (Fig. 5).

These results are relevant to the treatment of conditions such as asthma, where there is epithelial damage and even

its complete loss (30, 31). Hydrophilic drugs such as β-adrenoceptor agonists used to treat asthma, and agents such as methacholine and histamine used to test for responsiveness, would penetrate the epithelium far more readily. Lipophilic agents such at steroids would have their entry into the tissues hardly affected by epithelial damage or destruction.

We have almost no values for the permeability to drugs and tracers of small airways such as bronchi and bronchioles. However, it is generally assumed that these airways have a higher permeability than do the trachea and large bronchi, a view supported by one important study (32). For the alveolar wall, values for permeability coefficients for tracers such as DTPA indicate that they are probably thirty-times smaller than are those for the larger airways (1). The importance of the hydrophobic layer of alveolar surfactant needs to be assessed. Thus, since the ASL may be 300 times thinner in the alveoli than in the large airways, drugs deposited in the former should be taken up 10 times faster than are those in the latter.

Basement membrane and interstitium

We have no information about the extent to which the epithelial basement membrane and the interstitial liquid may act as a barrier for diffusion of agents into the airway mucosa or the alveolar wall. However, in asthma there may be considerable thickening of the basement membrane (30, 31), and in addition there may be interstitial oedema; both processes might be expected to handicap diffusion of chemicals from the airway lumen to target organs such as smooth muscle in the mucosa.

Mucosal blood flow

Under the airway epithelium of most species there is a copious network of vascular capillaries (33, 34) (Fig. 5), presumably related to the metabolic needs of the epithelium and glands. Changes in blood flow through this network influence the rate of uptake of agents from the airway lumen, and thus the apparent permeability of the mucosa. The original study (35) was with the vascularly perfused isolated cervical trachea of the sheep, with controlled or measured mucosal blood flow. Increases in blood flow, due either to increases in pump perfusion or to vasodilator drugs, decrease the uptake of labelled-DTPA into the tracheal venous blood, and decreases in blood flow have the opposite effect (35) (Fig. 6). This surprising result has now been confirmed in five other studies using the same preparation (5, 27–29, 36), and applies not only to the hydrophilic agent DTPA but also to the lipophilic tracer antipyrine (37).

There are several possible explanations for this result. One is that changes in blood flow might alter epithelial permeability, for example by the action of mediators from the vascular endothelium and released by changes in blood flow. However, this explanation is not consistent with the observation that antipyrine uptake is influenced by blood flow in the same way as is that of DTPA since, as already described, mucosal permeability to antipyrine is not affected by epithelial integrity or destruction. A second possibility is that induced changes in mucosal blood flow take place with a redistribution of flow through different components of the mucosal vasculature, for example the subepithelial

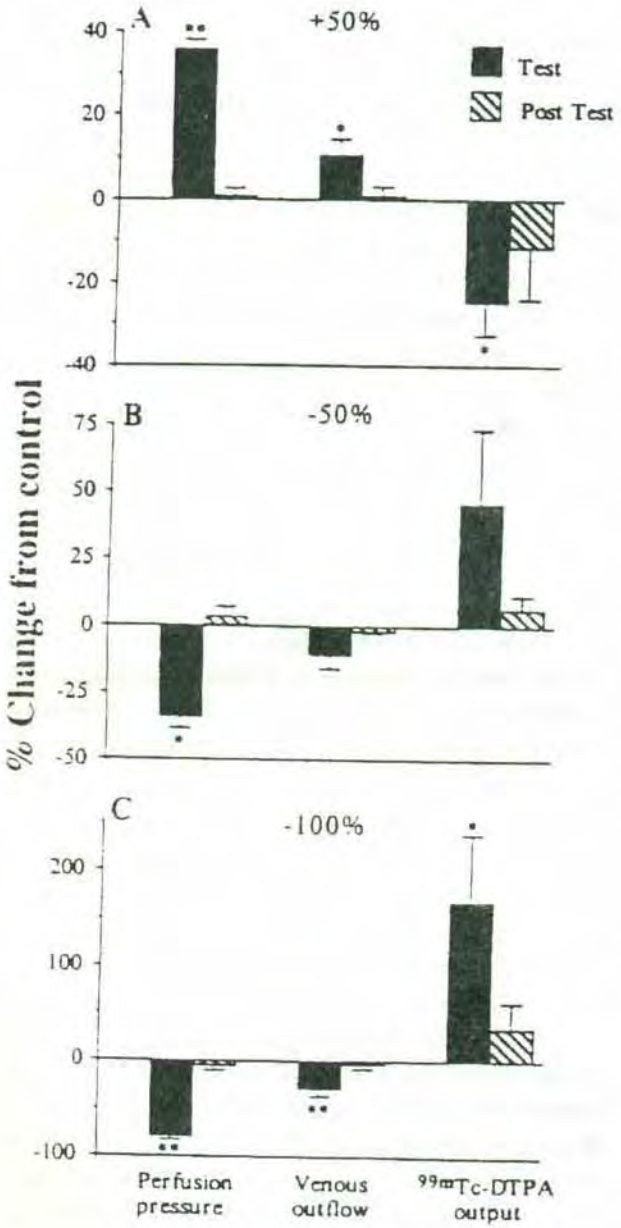

Fig. 6 : Blood perfused sheep trachea in vivo. Effects of 50% increase (A; n=5), 50% decrease (B; n=3) and 100% decrease (C; n=10) in perfusion flow rate on arterial perfusion pressure, venous outflow and ^{99m}Tc-DTPA output. Each variable is expressed as mean % change from 15-min pretest control, with SEM. Filled bars, 15-min changes in constant flow; hatched bars, 15-min posttest changes. $*P < 0.05$, $**P < 0.01$ for values compared with pretest controls. Sudent's paired two-tailed t-test (From 35).

and deeper capillary networks. This possibility cannot be ruled out, but there is no evidence to support it. The most likely explanation is that, when mucosal blood flow increases, the coincident increase in capillary pressure will result in liquid extravasation from the capillaries; this process will lead to "solvent drag" through the capillary endothelial wall, and possibly also the airway epithelium. This effect, when the liquid movement is directed towards the airway lumen, will limit the passage of drugs and tracers from the airway lumen towards that of the capillaries. In addition any increase in interstitial liquid volume would be a barrier to diffusion of agents through the mucosa. When blood flow, and therefore capillary pressure, decreases, the process would act in reverse. This hypothetical interpretation is consistent with the observation that osmotic gradients across the airway wall *in vivo* decrease the apparent permeability to DTPA from lumen to submucosa when the gradient is towards the lumen (27, 36); the associated water fluxes into the lumen, which have been measured, would limit agent flux in the opposite direction by "solvent drag". The opposite effect is seen with osmotic gradients directed towards the submucosa.

The experiments with osmotic gradients have implications for asthma. In exercise, hyperventilation- and cold air-induced asthmas, it is estimated that the osmolality of the ASL in the large airways may increase from a normal value of about 300 mOsm. kg^{-1} to as much as 1000 mOsm. kg^{-1} (20). The resultant flow of watery liquid into the lumen would restrict drug uptake into the mucosa, and decrease the apparent permeability of the airway wall.

Epithelial integrity

As already implied, damage to or destruction of the epithelium *in vivo*, with sodium metabisulphite (29), hydrogen peroxide (25) or the detergent Triton X-100 (27, 28), greatly increase the permeability of the mucosa to the hydrophilic agent DTPA, but has no effect on the permeability to the lipophilic molecule antipyrine (5). These results are consistent with those obtained with *in vitro* preparations. However, changes in blood flow affect the uptake of both molecules equally (37). This suggests that any action of "solvent drag" applies equally to hydrophilic and to lipophilic molecules.

CONCLUSIONS

Recent research has shown that the uptake of tracers, and therefore also of drugs similar in molecular mass, from the airway and lung lumens to deeper tissues, depends on several factors: (1) the volume and therefore the thickness of the airway surface liquid; (2) the mucosal permeability to the agent, usually assessed as a permeability coefficient; (3) the integrity of the epithelium, for small hydrophilic molecules but not for lipophilic ones; (4) subepithelial blood flow which may induce changes in liquid passage into the mucosa and, therefore, in "solvent drag", with associated changes in interstitial liquid volume; and (5) osmotic gradients across the epithelium which will also cause "solvent drag". In various forms of asthma all these variables may change and thus affect uptake of drugs and chemicals from the airways. These changes will in turn influence the effectiveness of drugs used to treat asthma and similar conditions, and the activity of agents used to test airways' responsiveness.

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