

## Plasma exudation in the airways: Mechanisms and function

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**ABSTRACT:** Inflammatory challenges of tracheobronchial and nasal mucosa produce prompt extravasation or exudation of plasma from the well developed microcirculation just beneath the epithelial base. Plasma exudation is not an exaggeration of the normal capillary exchange of fluid and solutes but a specific inflammatory response of post-capillary venules. The exuded plasma may not produce oedema. By a rapid, unidirectional, unfiltered and yet non-injurious process, plasma exudates cross the mucosal lining to appear on the airway surface at the site of challenge. *In vitro* data suggests the possibility that a slightly increased hydrostatic pressure moves the acellular exudate through valve-like openings between epithelial cells. By the venular-mucosal exudation mechanism all the potent protein systems of circulating plasma will operate in respiratory defence on the surface of an intact mucosa. A further inference is that exudative indices obtained from the airway surface quantitatively reflect the intensity and time course of mucosal/submucosal inflammatory processes. Irrespective of which particular cellular mechanism happens to fuel the inflammation. Mucosal exudation of plasma characteristically occurs in health and disease also when there is no airway oedema, no epithelial disruption, and no increased absorption ability. However, exuded plasma and its derived peptide mediators potentially contribute to several pathophysiological and pathophysiological characteristics of inflammatory airway diseases.

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The intriguing pathophysiology and pharmacology of airway plasma exudation, the potential physical effects of plasma exudates in and on the airway mucosa, and the exudate's content of inflammatory plasma-derived peptides are factors which may account for the attraction of the plasma exudation hypothesis of asthma as it was originally proposed [1]. In two reviews [2, 3] that followed, I added several pieces of circumstantial evidence in support of the 'hypothesis'. It was extremely exciting to discover that the literature of the past contained many widely scattered data, collected by astute observers, that could support my notion. I was surprised to learn that no one else had come forward with a similar hypothesis previously. The technique of using 'historic' material to support a novel hypothesis has its problems. One is that the work carried out by your own group, which is the true basis for the hypothesis, may not receive credit. Another problem is that the hypothesis may be accepted partly on false grounds. Such incorrect ideas may concern the luminal entry of plasma exudates.

First, I think an unfortunate confusion is caused by lack of distinction between airway exudations and airway secretions. The mechanisms involved, the

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pharmacology, and, above all, the potential roles in the pathogenesis of inflammatory airway diseases clearly distinguish mucosal exudation of plasma from actual airway secretions. Second, it is widely believed that luminal entry of plasma exudates only occurs when a marked airway oedema has been produced and that the mucosal passage of proteinaceous exudate disrupts and causes shedding of the epithelial lining. Third, luminal entry of plasma macromolecules, has been taken as firm evidence of a general "hyperpermeability" with increased mucosal penetration and absorption of airway surface material. Since these ideas have prevailed, the role of mucosal exudation in respiratory defence has not received any attention.

The 'established views' on the mucosal crossing of plasma may not be true. The data collected by my group several years ago suggested to me that the luminal entry of plasma exudates basically has a "primary role in airway defence" [1, 3]. Further work in guinea-pig tracheobronchial and human nasal airways (fig. 1) carried out in Lund [4-13] have now confirmed that the plasma exudation process may not produce or necessarily be associated with three reputed characteristics of asthmatic and rhinitic airways.

Oedema may not be induced because bulk plasma exudate readily enters the airway lumen. Epithelial disruption is not produced because the mucosal crossing of even unfiltered plasma exudates is a non-injurious process. Absorption is not increased because the mucosal exudation of plasma turns out to be a unidirectional flux of macromolecular solutes into the lumen.

#### *Luminal entry of Plasma exudates*

The luminal entry of plasma at mucosal provocations simply reflects the extravasation process of the subepithelial microvessels. Over the entire dose-response range mediators, allergen and other inflammatory factors applied on the airway surface thus do not selectively increase plasma exudation into the airway

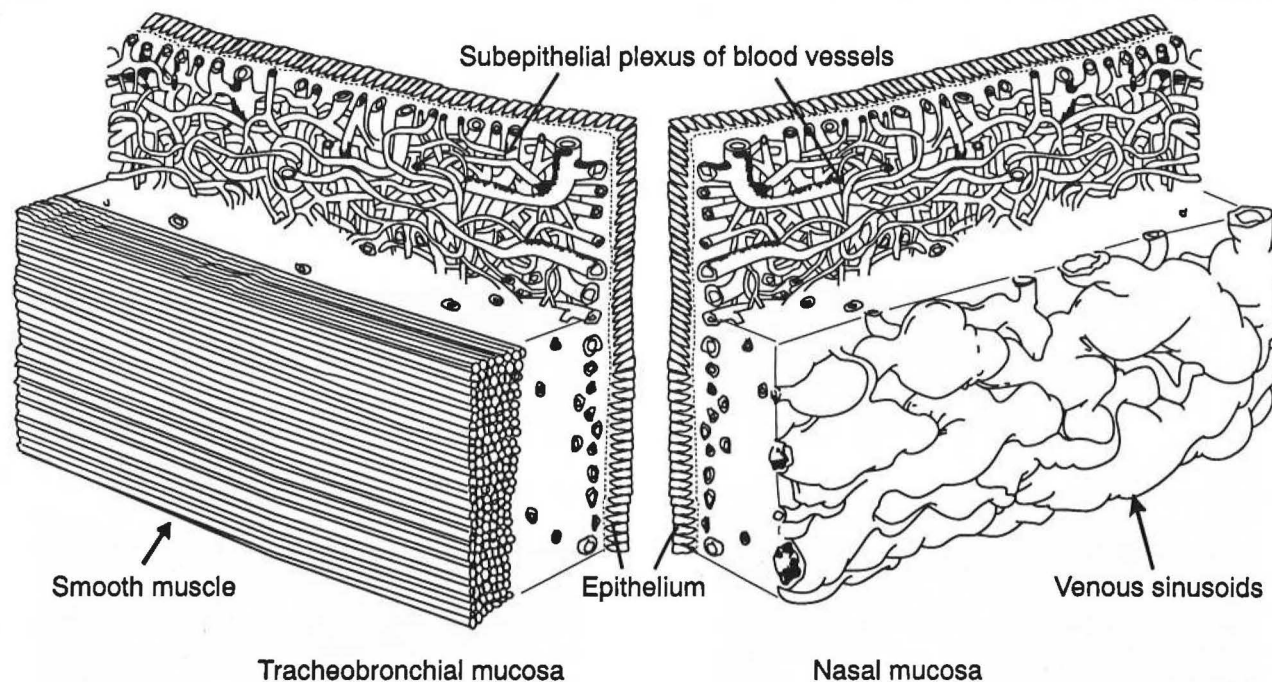


Fig. 1. — Differences and similarities between bronchial and nasal airway tissues are emphasized. A major obstructive mechanism of the nasal passages is filling of venous sinuses. Correspondingly there is tracheobronchial smooth muscle constriction in the lower airways. However, the epithelial lining and the profuse subepithelial network of microvessels are similar in nasal and tracheobronchial airways and so are exudative and absorptive mechanisms. Inflammatory mucosal processes of pathogenetic importance in airway diseases may, with great experimental advantage, be examined in human nasal airways.

The present brief update discusses mechanisms involved in airways plasma exudation and its roles in health and disease.

#### *Mucosal exudation. Definition and distinction*

- 1) "Mucosal or airway exudation" is the inflammatory stimulus-induced bulk flow of extravasated plasma, plasma-derived mediators, and attracted fluid across the mucosal (epithelial) barrier into the airway lumen.
- 2) The mucosal exudate may have attracted substantial amounts of fluid on its way to the mucosal surface. However, in contrast to the "transudation" of protein-poor fluid, the mucosal exudate is unfiltered and also contains the large plasma proteins.
- 3) Airway exudation of unfiltered plasma proteins reflects dramatic increases in the microvascular and mucosal permeabilities. However, the airway absorption ability remains unaltered during and after the plasma exudation process.
- 4) The mechanisms involved and the largely unfiltered nature of the plasma exudate distinguish mucosal exudation from airway secretory processes.

tissue [5, 14]. The persistent luminal entry of exudate has been observed with acute, biphasic as well as sustained inflammatory responses (fig. 2). Plasma exudation can thus occur without producing airway oedema. This may raise some doubt as to the presence of airway oedema in inflammatory airway diseases. As a matter of fact, quantitative data demonstrating airway oedema in asthma and rhinitis are scarce or lacking. Perhaps the inflamed airway mucosa may be thickened by the accumulation of cells, by fibrin formation, by collagen depositions and fibrosis rather than by the presence of plasma-derived oedema fluid.

#### *Separation between inward and outward airway 'permeabilities'*

By employment of techniques for controlled tracheobronchial distribution of solutes and tracers in guinea-pigs ERJEFÄLT and PERSSON [5, 10] and GREIFF *et al.* [11] have demonstrated that absorption of luminal solutes may not have been affected by allergen, neurogenic stimuli and mediator provocations. Even

during the acute exudation phase when plasma tracers such as albumin, fibrinogen, and large dextrans enter the lumen without being filtered, there was no increased absorption of small or large solutes from the lumen. Also, during prolonged histamine-induced plasma exudation into human nasal airways there was no change in the rate of absorption of a small-sized tracer (<sup>51</sup>Cr-EDTA) [12]. The separation between exudation-and absorption-processes agrees with the fact that there is now compelling supporting evidence that plasma exudation does occur in asthma, rhinitis, and bronchitis whereas no increase in airway mucosal absorption, however attractive the hypothesis, has been demonstrated in these diseases [15-18] (fig. 3). The latter possibility seems to me to be a subject where the attraction of a hypothesis has received greater weight than actual data.

separating endothelial cells and producing holes in the wall of postcapillary venules (fig 4). This is an active cellular response because receptors for mediators and autacoids are present on the endothelial cells [19]. Unfiltered plasma is moved through the mediator-induced holes in the venular wall by the hydrostatic pressure gradient between the venular compartment and the interstitial space. The venular endothelial cells have a strong ability to spontaneously close the venular holes. Hence, a plasma exudation response normally lasts for only a few minutes.

*Neurogenic extravasation/inflammation*

In 1981 ERJEFÄLT et al. [20] originally reported that local application of substance P increases the total amount of albumin (bound to Evan's Blue dye) in

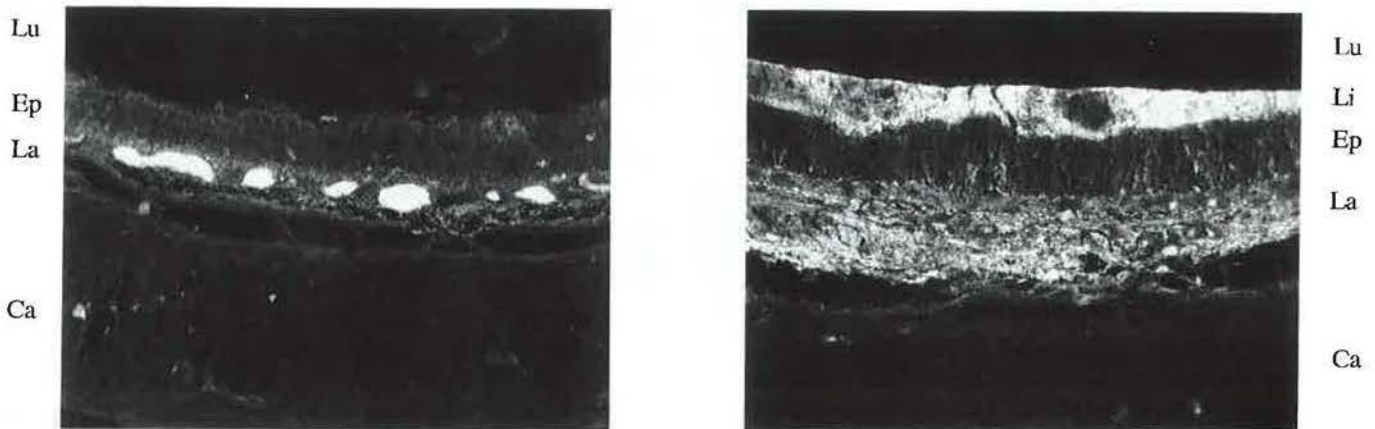


Fig. 2. - Fluorescence light microscopy of tracheal tissue slides obtained from guinea-pigs previously given fluorescein isothiocyanate-labelled dextran (FITC-dextran MW 156,000 D) intravenously. Left: In control specimens the fluorescent macromolecules stay within the vascular compartment showing the abundance of subepithelial microvessels. Right: Ten minutes after inflammatory challenge of the mucosa significant plasma exudation has occurred. The fluorescent plasma tracer is distributed in the lamina propria and submucosa, but it is particularly abundant in mucosal surface liquids. Note the lack of fluorescence in the epithelial layer. Electron microscopy has verified the normal appearance of the epithelial lining after this crossing of exudate [6, 9]. Lu: airway lumen; Li: mucosal surface liquids; Ep: epithelium; La: lamina propria; Ca: cartilage.

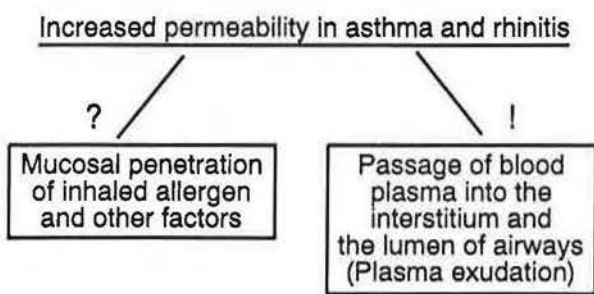


Fig. 3. - Airway exudation but, perhaps, not absorption is increased in asthma and rhinitis.

*Extravasation of plasma is regulated by venular endothelial cell separation and hydrostatic pressure*

The balance of the vascular versus interstitial fluid is maintained by the hydrostatic pressure in capillary beds and the opposing force of the transmural colloid osmotic pressure upheld by non-leaking plasma proteins. Inflammatory factors produce a dramatically increased vascular permeability to macromolecules by

airway tissue. During the 1980's several other authors have measured the total airway tissue amount of Evan's Blue dye in work suggesting that substance P or a similar tachykinin mediates neurogenic inflammation ("oedema", "plasma leak" etc.) in the airways of guinea-pigs and rats. However, it is not sufficient to measure the tissue dye content. The extravasated amount of plasma in the airway tissue can be assessed only if both the total amount and the intravascular plasma pool are known [14]. The first work that quantitated actual neurogenic extravasation in rodent airways was carried out by ERJEFÄLT [14, 20] and the experiments demonstrating neurogenic exudation of plasma into the airway lumen (guinea-pigs) were also carried out by ERJEFÄLT [4, 5]. The possibility that nerves mediate a mucosal exudation response is highly intriguing but its importance must be based on human observations.

The available data suggest that neurogenic tachykinin-mediated inflammatory exudation occurs exclusively in rodent and not in human airways [20, 21]. The latest addition to a series of negative results

in human subjects concerns nicotine, which is a potent exudative agent in guinea-pigs [21]. This neural stimulant, even in doses which cause significant pain, are without exudative effects in human airways [21]. The attraction of the hypothesis of neurogenic exudative inflammation in airway disease has clearly created an imbalance between belief and actual support of human data.

again reduced towards normal values, epithelial tight junctions would be re-established immediately (fig. 4). The following findings support the reasoning above: in guinea-pig isolated tracheal tubes a subepithelial hydrostatic pressure increase of only 5 cm H<sub>2</sub>O is sufficient to produce significant luminal entry of macromolecular tracers [7]. Such pressure-induced epithelial passages are reversible and reproducible [7]

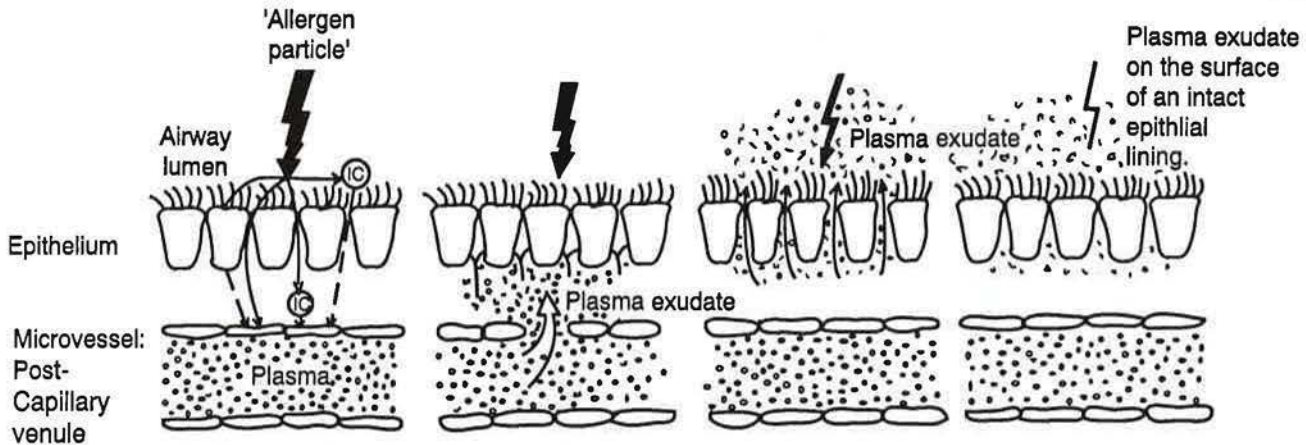


Fig. 4. - This scheme may illustrate how plasma is exuded through barriers in the airway microvasculature and mucosa. The inflammatory stimulus reversibly separates endothelial cells in the post capillary venules of the tracheobronchial microcirculation. Plasma is then extravasated through the ensuing holes in the venular wall. In the lamina propria the plasma protein systems are activated to produce peptide mediators. This process further increases the osmotic load and the accumulation of fluid in the subepithelium. A slightly increased hydrostatic pressure on the basolateral aspects of the epithelial cells creates paracellular pathways allowing entry of unfiltered plasma exudate into the airway lumen. After the mucosal exudation process the epithelial lining promptly resumes its tightness. IC: inflammatory cells.

#### Mediators of extravasation

A wide range of non-neural mediators and factors emerging from cells and the plasma itself may account for plasma exudation in human nasal and tracheobronchial airways [3]. Many mediators will affect both blood flow and extravasation. In theory, the plasma exudation response is regulated by blood flow in addition to the increased vascular permeability. However, the airway mucosa/submucosa seems so well perfused with blood that pharmacologically induced changes in blood flow may not have a great influence on the exudation process [14, 22]. Even a large dose of a topical vasoconstrictor, that would reduce mucosal blood flow by 50%, has not reduced inflammatory stimulus-induced airway exudation of plasma [22].

#### Increased subepithelial hydrostatic pressure may move plasma exudates across the mucosa

Plasma extravasated from the abundant subepithelial microvessels will multiply its solutes and expand in volume. It surrounds the basolateral aspects of the epithelial cells and, by increasing the hydrostatic pressure, the exudate may compress the sides of these cells (fig. 4). At a certain pressure the tight junctions at the apical pole of the epithelial cells would also separate. Thus an intercellular pathway may be created through which the plasma exudate can flow in bulk into the lumen. When the interstitial pressure is

as are the *in vivo* exudative responses. A further agreement with *in vivo* conditions is the finding that mucosal absorption *in vitro* is not increased during or after the luminal entry of macromolecules [8]. Hence, it is proposed that a hydrostatic-pressure regulated, valve-like epithelial mechanism is involved in mucosal exudation of plasma into the airways.

#### Epithelial effects of mediators and drugs may not be required

As discussed above, the luminal entry of plasma exudates *in vivo* appears to be an automatic consequence of subepithelial extravasation. Furthermore, in experiments with isolated tracheal tube preparations the presence of mediators or drugs on the mucosal surface did not alter the hydrostatic pressure-induced movement of macromolecules across the mucosa [7]. It is inferred from the collected *in vitro* and *in vivo* observations and from the proposed mechanism of the mucosal crossing that epithelial effects of mediators and drugs would not be required to bring about and prevent, respectively, the mucosal exudation of plasma. The current anti-inflammatory drugs used in asthma and rhinitis may not selectively prevent the luminal entry of plasma exudates [14]. Had this occurred the drugs would have caused mucosal oedema!

Anti-exudative drugs may directly tighten the venular holes as is evident from animal data [14, 19].

However, this action awaits confirmation in human airways. In complex disease conditions the important anti-exudative effect may rather reflect inhibition of earlier and crucial steps of the inflammatory process (fig. 5) than direct vascular actions.

#### Glucocorticoids inhibit airways plasma exudation

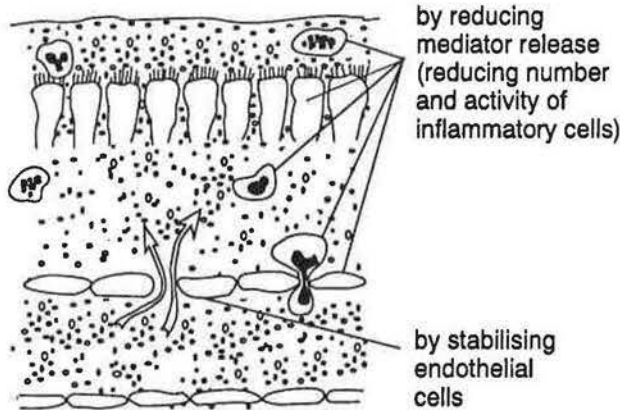


Fig. 5. - When glucocorticoids reduce plasma exudation in human airways this probably reflects inhibition of cellular mechanisms that fuel the inflammatory process (above) rather than a direct vascular anti-permeability effect (below).

#### Plasma exudates on the intact mucosa in airway defence

Plasma exudation across airway endothelial-epithelial barriers is largely an unfiltered flow of the various-sized plasma solutes. Hence, circulating immunoglobulins and other proteins with significant capacity to bind, catabolize, and neutralize offending factors will be abundant on the surface at the very site of mucosal provocation. This would be a major defence mechanism [20, 23, 24].

At exudation the plasma proteins come in contact with activating factors such as negatively charged surfaces and an abundance of potent plasma-derived peptides are produced. Accordingly, the exudation response would allow potent plasma protein systems (kinin-, complement-, coagulation-, fibrinolysis- etc.) to operate on mucosal surfaces at the sites where the challenge has occurred.

Newly formed peptides of the exudate will not only be potent mediators. By osmotic forces the increasing number of these molecules will attract fluid and make the plasma exudate significantly more voluminous after it has been extravasated. The subsequent flow of exudate into the lumen could wash away allergen and other factors which have penetrated between epithelial cells. A large volume of fluid may contribute significantly to humidification of inhaled dry air. When the demand is high, as during the hyperpnoea of exercise, the dry air may itself evoke mucosal exudation responses. The elimination of luminal

exudate would be by mucociliary transport and, if needed, coughing.

Inflammatory stimulus-induced plasma exudation usually goes on for only a few minutes, apparently because the mechanisms for closure of the vascular leak are strong. Even in the continuous presence of an inflammatory mediator a spontaneous closure takes place. In most instances the defence reaction will thus be a brief localized burst of plasma exudate into the lumen. However, when required the exudative defence is an 'inexhaustible' source of a potent armamentarium [20, 23, 24]. It seems unfortunate that the current literature on respiratory defence has ignored the possibility of a contribution of the mucosal exudation mechanism.

#### Plasma exudation into the lumen as an index of mucosal inflammation

Inflammatory cells may be in the airways for trivial or unknown reasons, and should be there for tissue repair. It is, therefore, difficult to accept the view that inflammation can be equated with the presence of these cells, unless it can also be demonstrated that they are fuelling an inflammatory process. Indeed, markers are needed to show to what extent the tissue itself is affected by active inflammation.

Airways inflammation may be associated with a great number of tissue responses. Most of these are nonspecific exaggerations of normal airway functions. Thus bronchial tone, secretions, mucociliary transport, cough/sneezes, blood flow, and blood pooling may be altered by both inflammatory and non-inflammatory stimuli. In contrast, the plasma exudation response is not an exaggeration of the normal capillary exchange of solutes but a specific defence/inflammatory response of subepithelial post-capillary venules. Particularly in human airways the exudative tissue response is not induced by irritant agents which merely evoke neurogenic actions [20, 21]. The plasma exudation response is graded in terms of the number of venular leaky sites and by the amount of exuded plasma per unit time [19]. The prompt and non-injurious luminal entry of the extravasated plasma indicates further that increased airways vascular permeability can be monitored just by sampling and analysing mucosal surface material [4, 5]. Animal tracheobronchial data thus show excellent correlation between luminal and tissue exudative indices for immediate, biphasic, and sustained airways inflammation and for dose-response to inflammatory challenges [5, 14].

The unfiltered nature of the mucosal exudate [4, 5, 10, 25] suggests that large proteins, which are not normally transuded or secreted, may be preferable surface indices of airways plasma exudation. This aspect seems particularly valid for bronchoalveolar lavage (BAL) studies. BAL harvests material which has accumulated for an unknown period of time on a mucosal surface area which cannot be well defined and which includes the alveolar lining. The small plasma

protein albumin is the dominating protein in normal alveolar and bronchial lining fluids. Hence, although it may be increased in asthma [26, 29] albumin may not be well suited as an exudative index in BAL fluid.

The distinction between pulmonary microvascular-alveolar indices and bronchial microvascular-mucosal indices is particularly important in studies of bronchial diseases such as asthma (fig 6). In accordance with the thought that the large plasma proteins may better reflect bronchial mucosal exudation, GRÖNNEBERG *et al.* [26] have demonstrated allergen-induced exudation of fibrinogen (MW 340000) rather than albumin (MW 69000) in BAL fluids from asthmatic subjects.

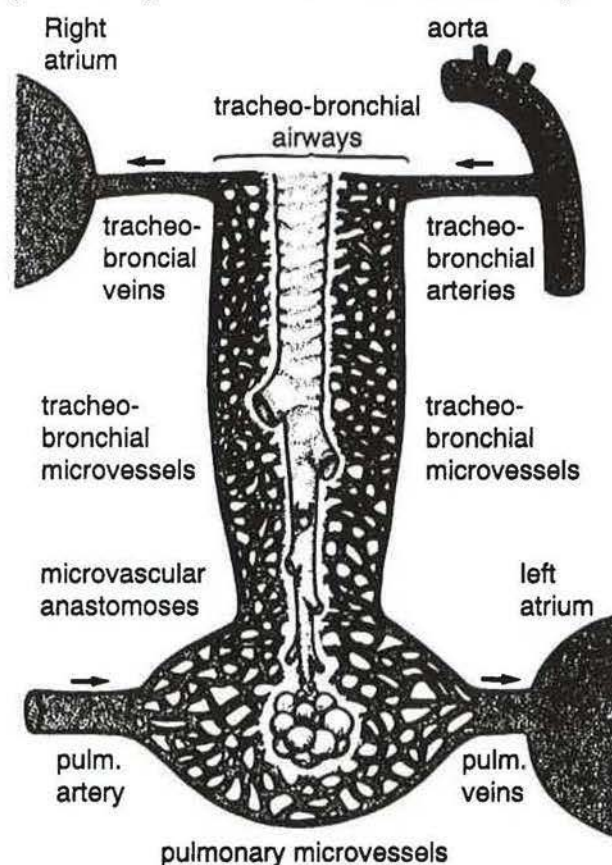


Fig. 6. - Asthma is a tracheobronchial and not a pulmonary disease. Hence, tracheobronchial and not pulmonary microvessels participate in asthma pathogenesis. The airways receive systemic blood from tracheobronchial arteries. Peripherally there are anastomoses between bronchial and pulmonary microvessels. The tracheobronchial microvessels react to a variety of inflammatory factors which do not affect the pulmonary microvessels. In particular, the pathophysiology and pharmacology of plasma exudation are distinctly different in the two systems (Fig. drawn by F. Kröll).

In BAL fluid obtained from symptomatic non-allergic asthma MATTOLI *et al.* [27] have demonstrated elevated levels of fibronectin (MW >400000) and VAN DE GRAAF *et al.* [28] have found reduced levels of large plasma proteins in BAL fluids obtained after prolonged treatment of asthmatic subjects with an inhaled glucocorticoid. Similarly, SVENSSON *et al.* [30] demonstrate glucocorticoid-induced inhibition of fibrinogen in allergic rhinitis. In the human nose, where prior

saline lavages can provide a low base-line and where airway specificity and distribution of the lavage fluid are well controlled, albumin is a useful exudative index along with fibrinogen,  $\alpha_2$ -macroglobulin and other large proteins.

### Conclusion

Inflammatory stimulus-induced plasma exudation into the airway lumen can occur as a brief and directed response that does not compromise the integrity of the epithelial lining as a barrier to luminal material. In co-operation with the mucociliary apparatus, exuded plasma protein systems thus act on the surface of the intact airway mucosa to neutralize offending factors.

The airways plasma exudation is induced by mediators which produce transient holes in the venular wall by actively separating endothelial cells. It appears that the plasma exudate itself, by increasing the hydrostatic pressure in the subepithelial space, creates pathways for its luminal entry. Anti-exudative drugs may act on the microvascular wall or they may inhibit earlier and crucial events in the inflammatory process. Glucocorticoids are potent anti-exudative agents in airway disease but this may only in a small part reflect direct effects on the vascular wall.

Exuded plasma containing an abundance of peptide mediators potentially contributes to several pathological and pathophysiological characteristics of the airway tissue and surface in inflammatory airway diseases [1-3]. However, the plasma exudation process is not necessarily associated with airway oedema, epithelial disruption, or increased mucosal absorption. This is important because plasma exudation may be a consistent feature of airways diseases such as asthma and rhinitis whereas the other three alterations are not.

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#### *Exsudation plasmatique dans les voies aériennes: mécanismes et fonction. C.G.A. Persson.*

Des provocations inflammatoires de la muqueuse trachéo-bronchique et nasale provoquent une extravasation rapide ou une exsudation du plasma à partir de la micro-circulation qui est bien développée immédiatement sous la membrane basale de l'épithélium. L'exsudation plasmatique n'est pas une exagération de l'échange normal de liquide capillaire et des solutés, mais une réponse inflammatoire spécifique des veinules post-capillaires. Le plasma exsudé peut ne pas produire d'œdème. Les exsudats plasmatiques traversent le revêtement muqueux au cours d'un processus rapide, unidirectionnel, non filtré et dès lors non lésionnel, pour apparaître à la surface de la voie aérienne au siège de la provocation. Les données *in vitro* suggèrent la possibilité qu'une pression hydrostatique légèrement accrue déplace l'exsudat à travers d'ouvertures du type valvulaire entre les cellules épithéliales. Par le mécanisme d'exsudation muqueuse au niveau des veinules, tous les systèmes protéiques puissants du plasma circulant agiront sur les défenses respiratoires à la surface d'une muqueuse intacte. Une conséquence ultérieure est que les indices exsudatifs obtenus à partir de la surface de la voie aérienne reflètent quantitativement l'intensité et le déroulement dans le temps du processus inflammatoire muqueux ou sous-muqueux. Et ceci se produit indépendamment du mécanisme cellulaire particulier qui intervient pour nourrir l'inflammation. L'exsudation muqueuse de plasma se produit de façon caractéristique dans l'asthme et la rhinite, même lorsqu'il n'y a pas d'œdème de la voie aérienne, pas de destruction épithéliale, et pas d'augmentation de la capacité d'absorption. Toutefois, l'exsudation plasmatique et ses peptides médiateurs dérivés contribuent potentiellement à la plupart, si pas à la totalité, des caractéristiques physiopathologiques et physico-pathologiques des maladies inflammatoires des voies aériennes.

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