The Effect of Smoking on Airway Permeability

The epithelium lining the surfaces of the lung provides a formidable protective barrier against foreign materials that are inhaled. While the nature of the lining cells and their surface coats is complex and quite variable between the trachea and alveolar surface, it is the junctions between the epithelial cells that seem to provide the greatest protective feature of the barrier. The fact that cigarette smoke can disrupt this barrier was first shown in animal experiments in which the tracer, horseradish peroxidase, broke through the airway epithelial junctions at all levels of the airways after guinea pigs were exposed to cigarette smoke. More recently Hulbert et al. reported that the epithelial disruption occurred early in the exudative phase of an inflammatory reaction and had returned to normal about 24 hours after the injury occurred.

Studies in humans by Jones and colleagues have also shown that those who smoke have an increased airway permeability to Tc DTPA and that this reverts toward normal with smoking cessation. In this issue of Chest, Mason and colleagues (see page 6) confirm and extend these findings by showing that while the abnormality in smokers is present throughout all lung regions, it is greatest in the upper lobes and reverses rapidly in all areas when the subjects stop smoking.

The fact that smoking causes a reversible leak in the normal airways barrier of both animals and man appears to be established. What remains to be determined is the nature of the disruption and whether it is an important factor in human disease. Since it seems likely that a great deal of data will be forthcoming in the years ahead, a little speculation is in order.

An interesting observation made by Mason et al is that the upper lobes appear to be more permeable. While this might be a technical problem related to a failure to correct for the tracer in the blood, it seems more likely to be due to the fact that the upper regions have an increased absorptive area because the pleural pressure gradient leads to greater expansion of these regions in upright man. Because the upper lobes suffer most from cancer and centrilobular emphysema, it is worth examining whether the permeability changes might be involved in the pathogenesis of these smoking-related diseases. The animal studies used a simple count of mitotic figures to measure the epithelial repair following the injury by cigarette smoke, and close examination of these data suggests that permeability was greatest just prior to the appearance of mitosis. This means that permeability would be most increased about the time of maximum DNA synthesis by the dividing cells. The possibility that a change in permeability provides the carcinogens in cigarette smoke easy access to the DNA of dividing epithelial cells therefore deserves to be considered in studies of the pathogenesis of lung cancer. The well-known interaction between asbestos exposure and cigarette smoking in the pathogenesis of lung cancer is pertinent. Is it possible that changes in permeability produced by smoking might enhance the penetration of the carcinogen in asbestos to the site of DNA synthesis in the cells participating in epithelial repair? Such a mechanism might provide some insight into the vexing problem of the greatly increased incidence of lung cancers in those who smoke and also work with asbestos.

The site of the lesion responsible for the increased airways permeability observed by Mason et al is a matter of some interest. I would predict that the leakage site is in membranous and respiratory bronchioles because these airways are susceptible to inflammation in smokers and have a sufficiently large surface area to provide for diffusion of the tracer across the barrier. Very recent information by Walker et al. suggests that the leaks develop at the corners where epithelial cells meet rather than along their lateral surface. These corners would occur in the greatest concentration in the distal portion of membranous bronchioles and in the portion of respiratory bronchioles covered by cuboidal epithelium, because areas covered by this type of cell will have the greatest number of corners per unit surface area. The alveolar surface and the ciliated surface of the more central airways have fewer corners per unit surface area because the cells have a greater free surface area in those locations. Since smoking causes inflammation of terminal and respiratory bronchioles, and the maximum leak occurs with the exudative phase of the inflammatory reaction, one might predict that the leak is associated with the repeated acute injury produced by cigarette smoke. Stopping smoking might allow the epithelium to repair so that the disrupted barrier would have a chance to recover. Again, the increased leak in the upper regions is of interest because
centrilobular emphysema, which results from destruction of the respiratory bronchioles (possibly from a proteolysis-antiproteolysis imbalance in the inflammatory reaction), is more common in the upper lobes.

Since the airways obstruction in COPD appears to be associated with the inflammatory reaction in the peripheral airways, \(^ {8,7}\) it seems reasonable to examine mechanisms that might amplify it. Whether an immune response to antigens either in the cigarette smoke or in other material in the inspired air could be important in amplifying this inflammatory reaction is a matter of some importance. Indeed, if such a mechanism existed, it might explain why a susceptible group of cigarette smokers develop severe obstructive lung disease while others can smoke heavily all their lives without apparent adverse result. Several population studies\(^ {14,15}\) have shown that smokers have an increased serum IgE concentration compared with nonsmokers, and one such study documented that this increased with age. This suggests that smoking is associated with a greater sensitization of the mucosal membrane, even though the precise mechanisms and antigens involved remain to be determined. The animal studies of Braley and associates\(^ {8,16}\) showed that immunization decreased the ability of antigens to penetrate the airway barrier and suggested that the metabolism of the test antigen may have been increased when the animals were immunized. The role of the immune response in limiting entry of antigens through the respiratory tract of smokers could be of interest in relation to the Dutch hypothesis\(^ {8}\) that the most rapid deterioration occurs in patients with COPD who are atopic and have reactive airways. Is it possible that those who are atopic amplify the inflammatory reaction in the airway by a chronic immunologic trigger that was designed to limit antigen entry?

The evidence that cigarette smoking is harmful to human health and that stopping smoking appears to reverse some of this adverse effect is substantial. The techniques reported by Mason et al in this issue and those reported elsewhere\(^ {31,32}\) may turn out to be very useful in investigating the mechanism of the early adverse effects of smoking.

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The Brain's Own Morphone and Cigarette Smoking: The Junkie in Disguise?

Opiate-like peptides are now recognized to be present in high concentrations in various areas of the body. \(\beta\) endorphin, a 31 aminoacid peptide, is stored in the anterior pituitary and can also be found in the circulation and CSF. The half life of this putative hormone is approximately 40 minutes. Methionine and leucine enkephalin are pentapeptides which are found in high concentration wherever opiate receptors are present and are believed to have half lives that are short (minutes).\(^ {1,4}\) Of interest to the chest physician is that opiate receptor sites and enkephalins are found in high concentrations in the solitary nuclei and area postrema of the medulla, areas that are thought to be important as relay stations for a variety of sensory and chemical stimuli that affect ventilation.\(^ {5}\)

In fetal and newborn animals, endogenous opioids do appear to play a role in ventilatory control.\(^ {4}\) The ventilatory response of fetal sheep to increased PaCO\(_2\) is markedly enhanced by naloxone, a drug which blocks opiate action by competing for opiate receptor sites.\(^ {6}\) In the neonatal rabbit, the ventilatory response to asphyxia is characterized by phases of hyperapnea,