VI. LUNG CONNECTIVE TISSUE IN PATHOLOGIC STATES

A. Emphysema

Emphysema is defined as dilation of air spaces with accompanying destruction of alveolar walls. The current concept of the pathogenesis of emphysema is generally referred to as the "protease-antiprotease theory". This concept holds that the lung is constantly exposed to a variety of proteases which are balanced by an antiprotease screen, the most important of which is α_1-antitrypsin. While this antiprotease screen is sufficient in most individuals, in certain circumstances it is ineffective or the protease burden is too great and lung tissue destruction results.

The evidence favoring this theory is overwhelming. Its most important support derives from the association of panacinar emphysema with α_1-antitrypsin deficiency and from the induction of emphysema by proteases in experimental animals. For details, the reader is referred to the chapter by Kuhn in this text as well as several other reviews;[191-199] we will concentrate on the changes in lung connective tissue content and metabolism in human and experimental emphysema.

Most interest in connective tissue abnormalities in emphysema has focused on the elastic fiber. There are several reasons for this, including

1. The characteristic physiologic abnormality of emphysema is loss of elastic recoil throughout the volume range (i.e., the static deflation volume-pressure curve is shifted to the left); this is consistent with a loss or break in the elastic fibers of the alveolar structures.
2. Light microscopic evaluation of human emphysematous lung demonstrates fragmentation of elastic fibers.
3. The best animal model of human emphysema results from the intratracheal instillation of elastase;[191] this model can be mimicked with other enzymes which must be capable of digesting elastin.[200]

It is important to realize, however, that no matter how compelling the indirect evidence that abnormalities in elastic fibers are central to the pathogenesis of emphysema, there are few human data that directly support this concept. There have been very few morphologic studies of emphysematous lung connective tissue at the ultrastructural level;[154,201] those that have been carried out report changes in collagen, but not elastic fibers. Most biochemical studies have failed to find alterations in elastin content in emphysematous lung.[202-206] The one exception is the study by Mandl et al.[55] in which lung elastin was diminished in the parenchyma of individuals with emphysema. It has been suggested that the elastin present in emphysematous lung may differ from normal lung elastin in amino acid content,[207-209] but such changes may reflect technical problems in isolating intact, purified elastin that is representative of the bulk of the elastic fibers present.

Although biochemical methodologies have not yielded direct evidence to support the concept that abnormalities of elastic fibers are central to the pathogenesis of this disease, this does not mean that the overall concept is incorrect. For example, derangement of elastic fiber organization might have profound effects on lung mechanical properties, yet would be very difficult to detect using current biochemical techniques.

Interestingly, morphologic observations of human emphysematous lung have suggested that alveolar interstitial collagen may be disorganized.[154] In addition, it has been hypothesized that abnormalities of proteoglycans are critical to the pathogenesis of this disorder.[210,211] However, as in the case of elastic fibers, studies of lung collagen and glycosaminoglycans in human emphysematous lungs have been inconclusive.[212]

Sequential studies of animal lungs following intratracheal administration of protease