Editorial

What is pulmonary fibrosis?

The origin of the term fibrosis lies in the histological observation of abnormal accumulations of collagen and other fibrous material thought to be secondary to injury or inflammation. In the light of recent advances in our understanding of the structure and metabolism of lung collagens and other components of the extracellular matrix, what had been a straightforward definition of pulmonary fibrosis has begun to look less satisfactory. Recent reviewers have been careful to qualify their definitions of pulmonary fibrosis to accommodate some puzzling experimental data.

Idiopathic pulmonary fibrosis (or cryptogenic fibrosing alveolitis) is classified as a fibrotic lung disorder due to an apparent increase in fibrous tissue within the alveolar interstitium. Recent biochemical studies of lung tissue obtained at biopsy, however, showed no increase in the amount of lung collagen in these patients. On the basis of this and other metabolic data the authors concluded that it was altered "quality, form and location" rather than the amount of collagen that was important. This conclusion was probably inappropriate since there are methodological problems associated with studies of biopsy material and the specimens obtained may not be representative of the whole lung (see refs 4 and 5 for reviews). Two independent studies of a large number of patients showed significantly increased collagen deposition, whether expressed as a concentration or as total content, in the lungs of patients with idiopathic pulmonary fibrosis. The conclusion drawn from the study by Fulmer and colleague, that there is an inappropriate distribution of collagen, is nevertheless important since remodelling of matrix components with deposition of bands of collagen in parenchymal regions normally characterised by thin basement membrane is a key feature of fibrotic lung disorders.

The interpretation of biochemical and histological data has been complicated by recent developments in connective tissue biochemistry. For example, there are now known to be at least 11 genetically distinct types of collagen and these may be identified individually by biochemical and immunological fingerprints. It is questionable whether standard histochemical techniques can distinguish between even two types of collagen, and measurement is notoriously difficult with these techniques. Changes to matrix components other than the collagens, particularly the proteoglycans, may alter the quality and number of binding sites available to standard histochemical stains, and this may confuse the issue. Some progress has been made with immunohistochemical markers for collagen. In one study of idiopathic pulmonary fibrosis there was an increase in the ratio of type I to type III collagen whereas in a second study changes in the reverse direction were seen. These differences may in part reflect the stage of disease at which samples were taken. The increasing availability of monoclonal antibodies to the different types of collagen, plus the application of in situ hybridisation techniques with probes to individual collagen types, should allow further progress to be made in the histological assessment of collagen.

Further biochemical developments have improved our understanding of the dynamic nature of lung collagen and normal fibroblasts, and have led to an appreciation that both the rate of degradation of collagen and the synthesis rate and number of fibroblasts play an important part in the regulation of lung collagen mass. Collagen synthesis is complex, with eight or more processing steps once the precursor molecules have been synthesised, with widely differing rates of turnover for newly synthesised and for mature collagens (see ref 5). There are few data on normal synthesis rates for pulmonary collagen in man and no general agreement on how they should be measured. There is indirect evidence of enhanced synthesis rates in idiopathic pulmonary fibrosis in man, however, and synthesis rates are generally agreed to be increased in animal models of pulmonary fibrosis. Degradation is more difficult to measure and current evidence in man is contradictory. In animal models, where there is more information, the general pattern that has emerged suggests increased breakdown of extracellular collagen and decreased breakdown of newly synthesised collagen.

These findings highlight another impediment to progress: the absence of valid experimental models for interstitial lung disease, particularly idiopathic
pulmonary fibrosis. For some time research workers have relied on chemical injury induced by such agents as paraquat and bleomycin to mimic lung fibrosis in man, although the time course for the onset of such fibrosis is very short compared with the relatively slow, progressive course of most interstitial lung disorders seen in man. Radiation induced lung damage has a slower course in most species and may provide a better model, although even with this form of injury there appear to be differences in response, both quantitatively and qualitatively, between species and even strains.

Some progress has been made in understanding the relationships between different types of cells in the lung, particularly those concerned with connective tissue metabolism. The availability of cells from bronchoalveolar lavage in recent years has made it possible to study putative mediators that may affect matrix and fibroblast function. Cells such as lymphocytes and mast cells have been implicated as sources of mediators, and currently much attention is focused on the role of the alveolar macrophage as an important “effector” cell. Macrophages are capable of releasing at least two factors that may be relevant to the proliferation of mesenchymal cells observed in human interstitial lung disease—alveolar macrophage derived growth factor and platelet derived growth factor. Platelet derived growth factor has several actions, acting as a chemotactic factor for smooth muscle cells and fibroblasts and in addition as a “competence” factor, allowing various mesenchymal cells to respond to other “progression” factors, such as alveolar macrophage derived growth factor. In a study by Martinet et al, the spontaneous release of platelet derived growth factor by alveolar macrophages from patients with idiopathic pulmonary fibrosis was several times higher than that of control subjects, and this may explain the increased numbers of mesenchymal cells seen in idiopathic pulmonary fibrosis. The authors point out that platelet derived growth factor may be chemotactic for neutrophils, which are an important source of proteases and oxidants and are thought to be responsible for much of the destruction of parenchymal architecture. Other recent studies have suggested that clonal selection of mesenchymal cells might also operate. Clearly progress is being made in this complex area, largely as a result of the application of the techniques of modern cellular and molecular biology.

Yet for connective tissue biochemists at least the original question posed in the title remains unanswered. In the words of Lewis Thomas, we must “wait for science to come in . . . with the solid facts”, then perhaps we can frame a new definition of fibrosis. The metabolic intricacies of fibrosis may appear irrelevant from the strictly clinical point of view when the radiographic appearances suffice to determine further treatment. Further advances in antifibrotic treatment are unlikely, however, without a better understanding of the metabolic nature of this group of disorders. Current knowledge of collagen metabolism in normal lungs and in pulmonary fibrosis might lead us to conclude that “anti-collagen” strategies, designed to inhibit collagen accumulation by interfering with one or more of the many post-translational modifications required to produce the final mature fibril, is potentially hazardous, although this approach should still be pursued. Rapid advances in our understanding of cellular factors associated with injury, inflammation, and repair suggest that we should also consider taking several biochemical steps backward along the fibrotic pathway in our search for new therapeutic approaches.

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