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Treatment of IPF
What Does the Future Hold?

In this issue of CHEST (see page 848), Goldstein and Fine present a well-conceived and thoughtful review of new approaches to the treatment of fibrotic lung diseases, primarily idiopathic pulmonary fibrosis (IPF). Last summer, a workshop sponsored by the Division of Lung Diseases, National Heart, Lung and Blood Institute was convened to consider novel approaches for the treatment of IPF. The impetus for these two publications is the acknowledged ineffectiveness of present therapeutic regimens for a uniformly fatal disease as well as the accumulation, over the past 25 years, of experimental data detailing the potential inflammatory pathways resulting from various lung injuries which in turn could progress to irreversible fibrosis.

Although there is no question that new modifying therapies are needed for IPF and other diseases which result in lung fibrosis, it seems unlikely that there is a common fibrotic pathway that follows dissimilar inflammatory responses. Consider the distinct histologic
entities of organizing pneumonia, lymphocytic interstitial pneumonia, eosinophilic pneumonia, pulmonary capillaritis, some diffuse alveolar damage, and cellular interstitial pneumonia which if unchecked may lead to irreversible fibrosis. However, all of the aforementioned inflammatory reactions which have multiple etiologies are quite responsive to corticosteroid treatment occasionally requiring the addition of an immunosuppressive cytotoxic agent. A prominent component of organizing pneumonia is fibroelastic proliferation within the distal air spaces resulting in the deposition of new connective tissue. This is a potentially completely reversible lesion after corticosteroid therapy. The determining factors are early institution of treatment, the tolerance of the patient to corticosteroid drugs, and the limitation of the inciting injury. For example, the idiopathic variety of bronchiolitis obliterans organizing pneumonia has a better prognosis than the same lesion when complicating a collagen vascular disease.

IPF remains a perplexing disease with a variable course and an elusive etiology, but in most cases, a rather typical clinical, radiographic, and histologic picture evolves. Five years postdiagnosis, approximately 50% of the subjects are alive and as many as 30% survive for up to 10 years. We know from review of prior chest radiographs that the disease is often present years before the onset of troublesome symptoms and the establishment of the eventual diagnosis. It is unusual for pulmonologists to see "early" potentially treatable cellular as opposed to fibrotic IPF. Once a diagnosis is established, in most cases it is difficult to predict which patients will have stable disease, although prolonged survival is sometimes afforded to younger patients and those who respond to initial treatment. It is clear that IPF is a fatal disease but it is also a regional disease, i.e., there will be areas of advanced fibrosis intermixed with lymphoplasmocytic infiltration of alveolar walls as well as normal-appearing lung. New therapies should be directed toward these islands of regional inflammation with the purpose of protecting the uninvolved lung since it is unlikely that drug treatment will readily reverse the already excess mature collagen deposition.

The pathogenic sequence that leads to IPF is unknown. I am skeptical of equating the pathogenic sequence proposed for acute lung injury as occurs in human ARDS or in animal models, which utilizes intratracheal bleomycin, paraquat, or hyperoxia to IPF, a point also made by Goldstein and Fine. These injuries cause fibrosis in days as opposed to years. There is no experimental model that simulates IPF. Similarly, utilizing isolated cell cultures (fibroblasts, type 2 epithelial cells) to assign the biologic effects of various inflammatory and fibrotic modifiers does not necessarily equate to their function in an intact biological system where there are several types of paranchymal and inflammatory cells and multiple mediators in the milieu.

In the past 25 years, information concerning inflammation and fibrosis has exploded with the description and functional analysis of multiple cytokines, growth factors, adhesion molecules, oxidants, and proteases. It is naive to think that blocking the action of a single or even several biologic modifiers such as II-1, TNF, IL-8, TGF-B all having been implicated in the pathogenesis of IPF, via antibodies or soluble receptors will cause disease improvement or stabilization. Several compounds have been identified that reportedly prevent fibrosis. A major problem is the inability to identify the initiating injury. As suggested by others, perhaps there is a genetic predisposition, i.e., altered expression of a normal gene which may be turned on by immune, environmental or possibly viral factors. There is also the unresolved issue of an individual's inability to turn off the inflammatory fibrotic response, for example failure of programmed cell death (apoptosis). After reviewing the present article by Goldstein and Fine and previous article by Hunninghake and Kalica, one becomes overwhelmed by the numerous potential therapies suggested. While there appears to be scientific rationale for many of these interventions, at some point we are going to have to "bite the bullet" and begin by being imperative in our choice of treatments. In spite of our inability to "nail down" the pathogenic sequence of IPF, it is time to get started. These trials will have to involve multiple centers, and criteria must be established to assure the diagnosis of IPF in the enrolled patients.

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Vo2max: The Gold Standard?

Assessment of maximum exercise tolerance is a critical part of candidate selection for heart or lung transplantation. To best quantitate maximum exercise tolerance, physicians traditionally have measured maximal oxygen consumption (Vo2max), although the accuracy and reproducibility of this measurement is