disease progression and therapeutic responsiveness may occur over prolonged periods of time, a multifarious analysis is an objective quantitative assessment of the clinical course of patients with IPF. Several investigators have devised multifarious scoring systems that combine the results of different studies into a single parameter that can be used to monitor disease progression. Watters and colleagues formulated the clinical, radiographic, and physiologic score from 7 variables: dyspnea, chest roentgenographic appearance, spirometric results, lung volumes, diffusing capacity, resting P(A-a)O2, and exercise oxygen saturation. That score correlates with the histopathologic abnormalities in open lung biopsy specimens better than any single component of the score. Thus, this type of analysis is superior to the usual methods and provides a useful means of longitudinal quantitative assessment of the clinical impairment in these patients.

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Pharmacologic and Other Chemical Causes of Interstitial Lung Disease*
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Drug-induced lung disease is an increasingly frequent problem facing the practicing clinician. Adverse lung reactions from various pharmacologic and toxic agents may have diverse clinical presentations, which are often difficult to distinguish from complications related to an underlying disease process. Clinicians are frequently confronted with drug-induced lung disease as an important aspect of the differential diagnosis in a given case. Unfortunately, the best diagnostic approach in these cases is often unclear since the disease process is often of a nonspecific nature and the various clinical tests provide supportive but not diagnostic information. In part, this diagnostic and therapeutic dilemma is related to our poor understanding of the mechanism of drug-induced lung disease. Although the specific mechanisms of drug-induced adverse reactions in the lung are

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often as diverse as the drugs themselves, there is increasing evidence that some drugs injure the lung in a somewhat stereotypical fashion and likely serve as an example of how a class of drugs or toxic agents may result in significant lung disease.

**BLEOMYCIN**

Bleomycin is a cancer chemotherapeutic agent, which is derived from *Streptomyces verticillus* and represents a mixture of glycopeptides. Bleomycin kills neoplastic cells by inducing strand scission in DNA and interfering with DNA synthesis. Recent studies indicate that the toxic effect of bleomycin on cancer cells is mediated by $O_2^-$-derived radicals via an iron-mediated mechanism. The iron-drug complex facilitates single electron transfers to electrophilic molecules such as $O_2$ and initiates a cascade of toxic $O_2^-$ radicals within cancer cells.

It is likely that bleomycin pulmonary toxicity is also related to the generation of toxic $O_2^-$-derived radicals within the lung by the bleomycin-iron complex. For example, it is known that high $O_2^-$ concentrations significantly increase the risk of bleomycin pulmonary toxicity in human subjects and, conversely, that low $O_2^-$ concentrations significantly reduce the toxicity. It is also known that depletion of iron by either dietary means or use of deferoxamine, an iron chelator, decreases the risk of bleomycin pulmonary toxicity in animal models. Finally, pulmonary endothelial cells in culture can be directly injured by bleomycin, and this injury is exacerbated in the presence of hypoxia and prevented by removal of iron with the use of deferoxamine. Thus, bleomycin likely causes pulmonary toxicity by the same mechanism by which it is cytotoxic to cancer cells, that is, the generation of toxic $O_2^-$-derived radicals. The lung may be a common site for bleomycin toxicity because lung parenchymal cells are exposed to higher concentrations of $O_2$ than any other cell population in the body. Furthermore, the activity of bleomycin hydrolase, an enzyme that inactivates bleomycin, is deficient within certain types of lung cells and may contribute to the susceptibility of the lung to damage by this drug.

**NITROFURANTOIN**

Nitrofurantoin is a urinary antiseptic, which has been associated with serious and sometimes fatal lung reactions for more than 2 decades. Despite the relatively infrequent use of nitrofurantoin in clinical practice, this drug continues to be one of the most commonly reported causes of drug reactions that cause significant lung toxicity. Although acute hypersensitivity reactions have been reported with nitrofurantoin, the most serious type of lung toxicity is related to the development of an insidious, progressive pulmonary fibrosis.

Nitrofurantoin undergoes cyclic reduction/oxidation within the cell in a fashion similar to the toxic herbicide paraquat. Under anaerobic conditions, nitrofurantoin forms an anion-free radical detectable by electron spin resonance; in contrast, under aerobic conditions nitrofurantoin reoxidizes to the parent compound, liberating a free electron and generating toxic $O_2^-$-derived radicals. Although nitrofurantoin generates $O_2^-$ radicals by a different mechanism than bleomycin, cells are damaged in a remarkably similar fashion, with hypoxia accelerating toxicity and antioxidants protecting from nitrofurantoin toxicity.

Nitrofurantoin toxicity serves as an excellent model of oxidant-mediated lung damage, such as may occur with agents like paraquat or oxygen. Our current understanding of drug-induced lung disease from oxidant-generating drugs indicates that great caution must be used with supplemental oxygen in these patients. Similarly, it is possible that future novel therapies augmenting endogenous antioxidant levels within the lung or using therapeutic exogenous antioxidants may reduce the toxicity from these drugs.

**AMIODARONE**

Amiodarone is a new and potent antidysrhythmic agent, which is associated with a high incidence of serious and potentially fatal lung reactions. Like many drugs, amiodarone has been associated with adverse drug reactions thought to result from both direct toxic effects of the drug and indirect toxic effects related to activation of inflammatory or immune mechanisms. In this section, further discussion of amiodarone pulmonary toxicity will be confined to its role as a drug associated with a "hypersensitivity reaction" in the lung.

Several drugs have been reported to be associated with a hypersensitivity reaction in the lung, including amiodarone, nitrofurantoin, and gold. Venet and co-workers first reported that amiodarone pulmonary toxicity in 5 subjects was associated with a marked increase in both polymorphonuclear leukocytes and lymphocytes in the bronchoalveolar lavage fluid of these patients. The increase in lymphocytes was due to a specific increase in the T-suppressor/cytotoxic subclass of lymphocytes (CD8+ lymphocytes), a finding previously reported in classic hypersensitivity pneumonitis occurring with farmer’s lung disease and pigeon breeder’s disease.

Although some authors believe that all cases of amiodarone pulmonary toxicity are related to a hypersensitivity reaction, it is likely that this represents only a subset of patients with amiodarone pulmonary toxicity occurring in 30% to 50% of the patients with documented pulmonary toxicity. It is not clear what role CD8+ lymphocytes play in the pathogenesis of amiodarone pulmonary toxicity, but in patients receiving amiodarone, this finding in the bronchoalveolar lavage fluid may represent one of the best diagnostic markers for the toxic reaction. Similarly, the finding of CD8 lymphocytosis in the bronchoalveolar lavage fluid of patients receiving other drugs, such as gold, nitrofurantoin, and methotrexate, may serve as one of the few useful diagnostic tests documenting an adverse drug reaction.

**SUMMARY**

A drug-induced lung reaction remains a clinical diagnosis. The clinician must first recognize that a drug the patient is receiving may be implicated in causing the new pulmonary findings. Where appropriate, the clinician must gather all available information to either confirm or deny that an adverse drug reaction has occurred. Our current understanding of drug-induced lung disease is improving as better models of drug-induced lung disease develop and as our...
awareness of risk factors associated with adverse drug reactions improves. There is little information currently available that indicates why specific individuals are susceptible to a given toxic reaction; however, as our understanding of the mechanism of drug-induced lung disease improves, it is likely that insight will be gained into this challenging problem of individual susceptibility. Furthermore, as mechanisms are better delineated, it is likely that both our diagnostic and therapeutic approaches to these patients will improve, resulting in earlier diagnosis and more timely therapeutic intervention.

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Interstitial Lung Disease Due to Inhaled Organic Dusts*

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