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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Inhaled organic dusts may cause pulmonary disease in the airway, interstitial tissues, or both. We shall review examples of these diseases and the proposed mechanisms. The major mechanisms involved in these diseases are immunologic in nature, with the appropriate type of hypersensitivity reaction classified as in the Cell and Coombs classification. The inhaled dusts are generally inert except in the presence of an immune response generated by the host. To give an example of an inert protein capable of causing mild or serious asthma on an immunologic basis, the common problem of cat asthma may be used. The important agents in these inhalant dusts are generally proteins of animals or plants, although reactive chemicals used as plasticizers or chemicals used in the paint industry may cause mild or serious immunologic lung disease. Table 1 illustrates the Cell and Coombs classification of hypersensitivity reactions applied to lung diseases.

In certain exposures, more than one type of hypersensitivity reaction may result in an inflammatory reaction in the airways or the interstitium. Examples of such diseases with complex immunopathogenesis are shown in Table 2.

A concept that deserves major emphasis even in this summary is the formation of hapten-self-protein conjugates that serve as antigens. While the understanding of foreign proteins as inhaled antigens is not difficult, the concept of a reactive chemical, such as trimellitic anhydride, reacting to form a complex of trimellityl-self protein with new antigenic determinants is newer and more difficult. Such complexes are antigenic and cause 3 types of immunologic lung disease, and trimellitic anhydride serves as the model in all respects. The most clearly described allergic chemical asthma is due to IgE antibody against trimellityl-albumin with new antigenic determinants.

An even newer concept of great potential importance is that a reactive chemical, such as toluene disocyanate, can react with the cell surface or proteins bound to the cell surface of a highly reactive cell, such as a mast cell. In this circumstance, IgG antibody may generate an immediate-type reaction clinically analogous to an IgE-mediated reaction. The potential of this mechanism to define poorly understood inhalational disease is great.

Of major importance is that failure to diagnose these diseases may lead to serious progressive interstitial lung disease followed by fibrosis, which may be fatal. Some features of these diseases that are important in making a diagnosis are listed in Table 3. When a physician is aware of the disease, suspects the disease, finds a course compatible with the disease, and carries out appropriate diagnostic evaluations, the diagnosis can be made, and chronic progressive destructive lung disease may be avoided.

Appropriate serologic studies are an important aid in establishing the diagnosis. The presence of antibodies does not allow one to make a diagnosis. The physician makes the diagnosis by correlation of clinical and immunologic data. In some cases of hypersensitivity pneumonitis, specialized laboratories and occasionally research laboratories with special technology are necessary to perform appropriate studies. However, caution is necessary in selecting an appropriate laboratory. Some commercial laboratories may recommend inappropriate tests or are deficient in quality control of complex immunoassays, and results may be misleading. They may report false-positive or false-negative serologic results.

Examples of interstitial lung disease due to inhalation of materials generating an immune response with an inflammatory or destructive lung disease are listed in Table 4. This list is, of course, not inclusive, and many other exposures, particularly occupational, are listed in standard texts, such as reference 8.

The importance of these diseases is as follows: With the exception of allergic bronchopulmonary aspergillosis, which we estimate occurs in 1% to 2% of cases of asthma, these hypersensitivity lung diseases are uncommon. Because they are uncommon, the diagnosis of inhalational lung disease may not be suspected. For example, in the first case listed in Table 4, a child was not considered to have hypersensitivity pneumonitis until a lung biopsy was interpreted as consistent...
with that diagnosis. A search for the cause was then made, and exposure to bird droppings was identified. The second case\(^2\) in Table 4 was thought to be consistent with trimellitic anhydride lung disease; that diagnosis could not be established, but isocyanate lung disease was eventually diagnosed. If the diagnosis of inhalational lung disease is established, the disease can be controlled by avoidance of exposure. If significant lung damage has not occurred, further progressive lung damage may be prevented by environmental control.\(^3\) There may be significant reversal of disease and prevention of progression of allergic aspergillosis by judicious use of prednisone therapy.

In summary, pulmonary diseases due to inhaled organic dusts may be the result of a wide spectrum of occupational and other environmental exposures. The immunologic mechanisms involved and the antigens may vary widely. Early diagnosis is a major goal since prevention of progression to fibrotic lung disease may be achieved in almost all patients.

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**Cellular Processes in Lung Repair**

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Tissue response to injury entails the activation of repair mechanisms that promote removal of debris, granulation tissue formation, and tissue reorganization. This wound healing process is responsible for the restoration of normal tissue architecture and function after injury. In all tissues, wound healing is characterized by recruitment of mesenchymal cells into injured sites, angiogenesis, and reepithelialization. This is also true in lung, where the nature and extent of the injury, together with the ability of the host's repair mechanisms, will determine the final outcome. The extent to which these processes maintain the original architecture determines the recovery of lung function or the development of scar tissue.

Current knowledge of the events occurring during lung repair has been enhanced by new developments in separate areas of biomedical research. These include the study of growth factor expression and biologic activities, the discovery of a new family of cell surface receptors involved in cell recognition of extracellular matrices, a better understanding of the effects of extracellular matrices on cell behavior, and the studies of other systems, such as skin wound healing. The mechanisms discussed will pertain mostly to interstitial lung disease, although some overlap is likely with those of other entities, such as emphysema.

**Repair Mechanisms**

Acute lung injury is characterized by loss of normal architecture (Fig 1), with destruction of both epithelial and endothelial sides of the alveolus-capillary barrier. This results in the extravasation of fluid and cells into the interstitium and alveolar spaces.\(^*\) Once the insult has taken place, inflammatory cells are the first to appear at the

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**FIGURE 1.** Normal alveolar septum. (From Kuhn et al. Am Rev Respir Dis 1989; 140:1693-1703. Reproduced by permission.)

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