Pathogenesis of Hypersensitivity Pneumonitis*

John E. Salvaggio, M.D., F.C.C.P.; and Richard D. deShazo, M.D.

The hypersensitivity pneumonitides include those alveolar filling and interstitial diseases resulting from intense or prolonged exposure to finely dispersed organic dusts of appropriate particle size. The inciting antigens include a wide range of vegetable and animal dusts, among which are thermophilic actinomycetes, other bacteria, true fungi, animal proteins, insect products, free living parasites, wood dusts, and even some simple inorganic chemicals. The traditional sources of antigen in the classic forms of this disease such as farmer's lung and bagassosis have been decaying actinomycete-laden composts, such as “moldy” hay and bagasse.

Seven years ago in a state of the art lecture on the same topic, it was pointed out that these diseases, although ill-defined, were characterized by several common features. These features, which still hold today, are as follows: (1) The diseases seem predominantly to involve the peripheral airways, and features such as hilar lymphadenopathy or systemic involvement as has been noted in sarcoidosis are not present. (2) Histologically the pulmonary lesions consist of mononuclear cell interstitial and alveolar infiltrates with T lymphocytes and macrophages being prominent. In many recovering cases, suppressor T cells are the most predominant T cell subtype. (3) Granuloma formation is often a prominent histologic feature, particularly in more chronic cases. (4) Alveolar macrophages present within the lesions are markedly activated. (5) The diseases are associated with high levels of serum precipitating antibodies against the offending organic dust antigens. (6) Although most of the etiologic agents can activate the complement system via the alternative pathway, the diseases are not associated with demonstrable changes in serum complement activity. (7) The diseases are associated with elevated serum and bronchial wash IgG, IgA, and IgM levels, but IgE levels are usually normal. (8) Evidence for lymphokine production is prominent in symptomatic patients, particularly locally within the lung.

Etiologic Agents

Although a wide range of agents may cause this disease, 4 points should be made concerning these substances: (1) It is important to realize that any organic dust of appropriate particle size likely can induce lesions given the right exposure conditions. This fact is of enormous importance to agriculture and industry. (2) Inhaled particulate antigens are usually necessary to induce lesions, since in man and experimental animal models organic particles of appropriate size or aggregated particulate protein antigens administered by the respiratory tract route will produce the characteristic lesions. Soluble antigens administered by the same route generally do not do so. (3) As in most cases of alveolar filling diseases, particle size is very important in producing an alveolitis. (4) Many of the antigens involved in production of these diseases are themselves immunologic adjuvants. For example, it has been clearly shown that the thermophilic actinomycetes that are members of the same order as Mycobacterium tuberculosis (i.e., the Actinomycetales) can have marked adjuvant effects on delayed hypersensitivity and antibody production.

Pathology

These diseases are virtually always characterized by mononuclear cell alveolar and interstitial pulmonary infiltrates. Furthermore, the lung is the major site of involvement, and there are no granulomatous lesions in other organs such as the liver and lymph nodes, bone and skin, as seen in sarcoidosis. Although there have been isolated reports of biopsy-proved vasculitis during the early stages of acute disease, pulmonary vasculitiss is not a consistent feature of this disease. The infiltrates consist of large numbers of lymphocytes, particularly T cells, as well as numerous activated alveolar macrophages. In subacute forms of the disease, noncaseating granulomas closely resembling those noted in sarcoidosis are often prominent. There may be marked involvement and narrowing of bronchial walls characteristic of bronchiolitis obliterans. With time, the pulmonary granulomatous lesions may persist or disappear. In recent experimental models of the disease, animals appropriately sensitized to antigen followed by antigen challenges, either by the IV or aerosol route, became "desensitized," with disappearance rather than progression of the mononuclear cell pulmonary infiltrates after repeated challenge. The explanation for this type of "desensitization" is unclear at this time. It may involve suppressor factors or suppressor cells; it does not, however, appear to involve classic immunologic tolerance, since it occurs even in the face of persistently increased levels of specific antibody.

Pathogenesis

The most intriguing studies of hypersensitivity pneumonitis continue to revolve around the area of disease pathogenesis. The antigens involved show several important biologic effects, including the ability nonspecifically to activate the alternative pathway of complement, activate alveolar macrophages, and act as immunologic adjuvants. With regard to the role of circulating antibody in production of symptoms, it does not appear to be as important as previously thought. For example, precipitating antibody against offending organic dust antigens is present in large percentage of exposed but asymptomatic subjects, and the histopathology of the lung lesions in most cases is substantially different from the vasculitis lesions of classic Arthus-, or "immune complex,"-mediated hypersensitivity. Furthermore, serum complement levels, which usually fall in acute immune complex-mediated disease, either remain within the normal range or increase following natural exposure or antigen bronchoprovocation challenge of these patients.
is thought that some of the early nonspecific pulmonary neutrophilic infiltrates in this disease are based on activation of the alternative pathway of complement,\textsuperscript{16} with subsequent production of chemotactic factors, and there is some evidence that certain of the antigenic components of organic dusts and animal protein-derived antigens can consume hemolytic complement via activation of the classic pathway. Yet the normal serum complement levels and lack of vasculitis in biopsy material provide strong evidence against an Arthus or immune-complex (type III) form of allergic tissue injury. Furthermore, in experimental animal models of the disease, attempts to reproduce lung lesions by passive transfer of hyperimmune serum followed by inhalation challenge with the antigen used for immunization have not reproduced the findings noted in human disease. Such exposures have generally produce minimal pulmonary lesions or lesions characterized by hemorrhage and neutrophilic infiltrates that do not resemble, or evolve into the mononuclear cell predominant (T-cell and macrophage) lesions noted in human hypersensitivity pneumonitis. Conversely, in the guinea pig and the rabbit, the transfer of specifically sensitized lymph node cells followed by antigen challenge via the respiratory route has produced lesions closely resembling those seen in human hypersensitivity pneumonitis,\textsuperscript{16,17} providing strong evidence for the delayed cell-mediated (type IV) hypersensitivity mechanisms in disease pathogenesis. Local lymphokine production in bronchoalveolar wash fluid (e.g., migration inhibition and blastogenic factors) has also been a prominent feature in experimental animal models of these diseases, further supporting this hypothesis.\textsuperscript{16} The presence of activated alveolar macrophages as well as strikingly prominent infiltrates of T lymphocytes provides additional morphologic evidence for this pathogenetic mechanism. Finally, in some experimental models of granulomatous pneumonitis, lesions can be inhibited by such procedures as neonatal thymectomy, administration of corticosteroids, or antimacrophage serum.\textsuperscript{16,17}

There have been several recent intriguing evaluations of patients in recovering phases of hypersensitivity pneumonitis studied by bronchoalveolar lavage (BAL). The pulmonary infiltrates, unlike those seen in sarcoidosis, were characterized by large numbers of suppressor rather than helper T cells.\textsuperscript{18,19} For example, in sarcoidosis the percentage of lymphocytes obtained from BAL is often in the range of 50%, and the helper/suppressor T-cell ratio is often 5:1 or greater. In hypersensitivity pneumonitis, however, the percentage of lymphocytes in BAL fluid is often 60–70%, and the number of suppressor/cytotoxic cells is often well above 40%.

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\caption{Lesions are initiated by inhalation of large amounts of particulate organic dust antigens containing endotoxin and enzymes and possessing adjuvant properties. Initial nonspecific activation of the alternative pathway of complement provides the necessary stimulus (split complement components) for increased vascular permeability and chemotactic recruitment of neutrophils. Alveolar macrophages are also activated, with release of enzymes and O2 metabolites, interleukin 1 and other monokines. This results in some acute tissue injury (enzymes and O2 metabolites) and expansion of lymphocyte populations (interleukin 2 production). Macrophage associated antigen is "presented" to lymphocytes. The specific "local" bronchoalveolar B-cell antibody response provides an additional stimulus in the form of immune complexes that also bind complement, and activate alveolar macrophages. Repeated exposure to antigen also results in development of intense T cell mediated (delayed) hypersensitivity. Sensitized T cells continue to release interleukin 2, with subsequent expansion of lymphocyte populations. Release of other lymphokines, such as macrophage migration inhibition factor, also further activates alveolar macrophages. Under the influence of as yet undefined genetic factors, populations of suppressor T cells (and possibly macrophages) and their products ultimately expand and dampen or modulate the degree of pulmonary T-cell-mediated granulomatous inflammation.}
\end{figure}
of the total lymphocyte population, with the number of helper cells ranging 30% or lower (ie, helper/suppressor ratios less than 1). The meaning of these findings is unclear, however, for several reasons. First, elevated number and percentages of suppressor/cytotoxic cells are present in lavage fluids of asymptomatic persons exposed to antigen as well as those exposed who develop clinical disease. Further, a recent investigation reported the presence of T lymphocytes bearing class II histocompatibility antigens (HLA-DR) and activated T-cell markers (MLR-I-3) in the BAL effluent of patients with hypersensitivity pneumonitis who had normal lavage helper/suppressor cell ratios. Since activation markers are not necessarily related to the regulatory or effector function of lymphocytes and can be detected on activated lymphocytes of either helper or suppressor/cytotoxic subclasses, it is possible that the presence of such activated cells in the BAL fluid of patients merely reflects an ongoing local immune process (probably type 4 cell-mediated hypersensitivity) and is not necessarily a marker of disease activity or progression.

**IMMUNOREGULATORY EVENTS**

Immunoregulatory events have recently assumed the forefront in animal models of hypersensitivity pneumonitis. Among the recent findings of these studies that have provided new insights are the following: (1) Certain immunosuppressive agents such as cyclophosphamide can actually enhance rather than suppress the development of granulomatous pneumonitis in certain strains of mice. (2) It appears that a cyclophosphamide-sensitive suppressor T-cell regulates the development of pulmonary granuloma formation in this species. (3) The intensity of pulmonary granuloma formation in this species appears to be genetically determined and is a dominant and polygenic trait, since inbreeding studies involving different strains reveal that the F-1 hybrids are responders, and the F-2 hybrids do not segregate into 2 distinct populations. (4) The degree of granuloma formation appears to be linked to the immunoglobulin heavy-chain locus (IgH), because inbreeding studies reveal that most high-responder mice inherit the IgH haplotype of the high-responder strains. (5) Anergy has also been shown to develop in a BCG-induced mouse model of hypersensitivity pneumonitis and appears to be a recessive and unigenic trait also linked to the IgH complex. The cells that mediate anergy are adherent cells and are thought to be macrophages. In man, some recent evidence from studies of so-called Japanese type, summer-type hypersensitivity pneumonitis also indicates that patients with active disease are anergic.

Thus, there is now increasing evidence that animals lacking high levels of antigen-specific suppressor cell activity can develop pulmonary granulomatous inflammation as a consequence of T-cell mediated hypersensitivity, while low-responder strains develop suppressor cells that modulate the degree of granulomatous inflammation. After granuloma development, anergy, which is also under genetic control by genes linked to the IgH allotype, appears and may be mediated via macrophages directed to be suppressive by T-lymphocyte-derived factors.

The previously mentioned animal models, in which short-term aerosol exposure to protein antigens results in granulomatous pulmonary inflammation, and chronic exposure leads to resolution of the pulmonary inflammation, may offer important clues to the incidence and clinical course of hypersensitivity pneumonitis in man. This type of modulation or desensitization appears, at least in the rabbit model, to be associated with the loss of expression of cell-mediated hypersensitivity by lung immunocompetent cells that remain in the lung. A long refractory period occurs after the modulation, during which reimmunization and aerosol challenge, even with unrelated antigens, does not result in the development of new pulmonary infiltrates. These data may explain the large numbers of T cells with suppressor/cytotoxic phenotypes in the lungs of patients exposed to antigen but without clinical disease. Furthermore, in pigeon breeders' disease, BAL fluid contains large numbers of lymphocytes that respond to phytohemagglutinin and antigen, while lavage fluids from asymptomatic pigeon breeders contain lymphocytes that do not respond. It is possible that a state of modulation exists in the latter group similar to that noted in the reported animal models.

Overall, these studies suggest that hypersensitivity pneumonitis in man develops as the result of a complex series of immunologically specific events. These likely involve sensitization, the development of granulomatous inflammation, and a series of genetically determined immunoregulatory events that result in either up- or down-regulation of local hypersensitivity (Fig 1). A better understanding of these mechanisms in man and in animal models of hypersensitivity pneumonitis may provide important information that can help us understand the mechanisms of other chronic granulomatous diseases, including sarcoidosis.

**REFERENCES**

Clinical Features of Hypersensitivity Pneumonitis*

Jordan N. Fink, M.D.

Hypersensitivity pneumonitis (HP) is an immunologic lung disease due to the sensitization and recurrent exposure to any of a wide variety of inhaled organic dusts. The disease occurs as a diffuse, mononuclear infiltration of the lung parenchyma which may organize into granulomas and fibrosis. While most individuals who develop HP are exposed to offending organic dusts during their occupation, sensitization can occur from contaminated forced-air heating, humidification, or air-conditioning systems.

No clinical feature or laboratory test is diagnostic of HP; diagnosis of the disease should be made from a combination of history with characteristic symptoms, physical findings, x-ray abnormalities, pulmonary function and immunologic features. The demonstration of precipitating antibodies to the suspected inhaled antigen is particularly helpful, and the reproduction of the clinical features by inhalation challenge can be confirmatory. Occasionally, lung biopsy is needed to clarify the diagnosis.

Clinical Features of HP

The diagnosis of HP should be considered in patients exposed to possible offending antigens who have a recurrent influenza-like illness or interstitial lung disease. The clinical and laboratory abnormalities tend to disappear when the offending antigen is avoided, but continued exposure may result in irreversible pulmonary damage with progressive impairment. In some patients, progression may continue even after avoidance of exposure is practiced.

The onset of HP may be acute or insidious. With intermittent exposure, the symptoms begin 4 and 6 hours following inhalation of the antigen. Fever, chills, malaise, dry cough, and dyspnea occur, subsiding over 12 to 18 hours. With repeated episodes, anorexia accompanied by weight loss is common.

When exposure is continuous and less intense, chills and fever may not always occur. Cough with mucopurulent sputum, exertional dyspnea, easy fatigue, anorexia, and weight loss occur frequently; an acute episode is rare. In the chronic form of HP, the symptoms are largely respiratory with progressive shortness of breath, leading to pulmonary disability. There may be associated anorexia and weight loss with mucopurulent sputum; acute episodes are rare.

End-inspiratory bibasilar rales are the characteristic physical findings of the acute episode and may last for weeks after exposure is terminated. Repeated exposure to antigen or chronic low-level exposure may lead to progressive and irreversible respiratory symptoms. Patients with farmer's lung have had such a progressive course even after avoidance of the offending antigen.

Antigens Causing HP

Hypersensitivity pneumonitis is due to inhalation and subsequent sensitization of a wide variety of organic dust antigens. The offending agents may be bacterial (thermophilic actinomycetes), fungal (Alternaria, Aspergillus), serum proteins (avian proteins), chemical (anhydrides), or yet undefined (coffee dust).

The major occupations and industries associated with HP are those in which moldy vegetable compost contaminated with thermophilic actinomycetes can be inhaled. Farmers, sugar cane workers, and mushroom compost handlers are at risk, as are individuals living or working in environments...